# Excess Synchrony in Motor Cortical Neurons Provides Redundant Direction Information With That From Coarse Temporal Measures

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**Oram, Mike W., Nicholas G. Hatsopoulos, Barry J. Richmond, and John P. Donoghue.** Excess synchrony in motor cortical neurons provides redundant direction information with that from coarse temporal measures. *J Neurophysiol* 86: 1700–1716, 2001. Previous studies have shown that measures of fine temporal correlation, such as synchronous spikes, across responses of motor cortical neurons carries more directional information than that predicted from statistically independent neurons. It is also known, however, that the coarse temporal measures of responses, such as spike count, are not independent. We therefore examined whether the information carried by coincident firing was related to that of coarsely defined spike counts and their correlation. Synchronous spikes were counted in the responses from 94 pairs of simultaneously recorded neurons in primary motor cortex (MI) while monkeys performed arm movement tasks. Direct measurement of the movement-related information indicated that the coincident spikes (1- to 5-ms precision) carry ~10% of the information carried by a code of the two spike counts. Inclusion of the numbers of synchronous spikes did not add information to that available from the spike counts and their coarse temporal correlation. To assess the significance of the numbers of coincident spikes, we extended the stochastic spike count matched (SCM) model to include correlations between spike counts of the individual neural responses and slow temporal dependencies within neural responses (~30 Hz bandwidth). The extended SCM model underestimated the numbers of synchronous spikes. Therefore as with previous studies, we found that there were more synchronous spikes in the neural data than could be accounted for by this stochastic model. However, the SCM model accounts for most ($R^2 = 0.93 \pm 0.05$, mean ± SE) of the differences in the observed number of synchronous spikes to different directions of arm movement, indicating that synchronous spiking is directly related to spike counts and their broad correlation. Further, this model supports the information theoretic analysis that the synchronous spikes do not provide directional information beyond that available from the firing rates of the same pool of directionally tuned MI neurons. These results show that detection of precisely timed spike patterns above chance levels does not imply that those spike patterns carry information unavailable from coarser population codes but leaves open the possibility that excess synchrony carries other forms of information or serves other roles in cortical information processing not studied here.

## INTRODUCTION

The study of neural responses has concentrated, in general, on how the number of spikes varies with input stimulus, motor output, or the conjunction of both signals. More recently, precise spike timing has been proposed as a mechanism to represent information not available from coarse temporal response measures (Abeles 1991; Rieke et al. 1996; Singer and Gray 1995). The idea that the nervous system could use the precise times as well as the number of spikes is compelling. Neural spike trains have the potential to carry substantially more information than that available from spike count if timing (approximately millisecond accuracy) between neurons is considered (Abeles 1991; Buracas and Albright 1999; Rieke et al. 1996). Temporal correlation at fine scales could underlie aspects of higher cognitive process such as binding, motor coordination, and even consciousness because they could signal relationships among neurons carrying separate codes in their coarse temporal response measures (Abeles 1991; Engel et al. 1992; von der Malsburg 1995; von der Malsburg and Schneider 1986).

Studies of precisely timed spike patterns from cortical areas related to motor function have shown that the number of precisely timed spike patterns, including synchronous spikes, carries information about the occurrence, initiation, and direction of limb movement unavailable from chance, under the assumption of statistical independence of each of the engaged neurons (Hatsopoulos et al. 1998b; Riehle et al. 1997; Vaadia et al. 1995). Further study showed that the correlation between the spike counts of cells assessed over extended intervals (100's of milliseconds) also carries information unavailable from consideration of independent spike counts (Maynard et al. 1999). Given that correlation of coarse temporal response measures almost always increases the information carried by spike count (Abbott and Dayan 1999; Deneve et al. 1999; Maynard et al. 1999; Oram et al. 1998; Snippe and Koenderink 1992), we examined whether the information carried by synchronous spikes between responses of motor cortical neurons is completely explained by the information carried by the number of spikes in the neuron pair and their coarse temporal correlation (>20-ms time scale).

We find that, when the coarse temporal statistics within and between motor cortical responses are included, both information theoretic and modeling methods indicate that synchronous spikes do not carry information unavailable from the spike count pairs. Despite the observation that they carry no unique directional information, the synchronous spikes occur at a rate higher than expected from two independent stochastic processes, leaving open the possibility that synchrony may have

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other roles. The difference between observed and predicted numbers of synchronous spikes may be explained by postulating a common input or some other form of functional connectivity.

## METHODS

### *Task*

Two monkeys (*macacca fascicularis*) were operantly trained to move a cursor on a computer monitor whose position was controlled by a handle connected to a two-joint mechanical arm. Each monkey was required to move the cursor from a center target to one of eight possible targets positioned radially from the center. Each trial was composed of four different epochs: *1*) a 500-ms hold period beginning with the start of trial event during which the monkey had to keep the cursor over the center target, *2*) a variable 1–1.5 s instructed delay period beginning with the appearance of one of the eight radially positioned targets (instruction trigger), *3*) the reaction time period beginning with the go signal (which was indicated by the blinking of the radially positioned target), and *4*) a movement period beginning with the onset of movement defined as the moment at which the cursor left the center target. Because each radially positioned target could appear with equal probability, this task was fully specified by three bits of information (see Hatsopoulos et al. 1998a,b for more details regarding this task). One of two monkeys was also trained on a second task that involved generating a two-segment sequential movement. Because there were two sequences that were possible under two conditions (either preplanned or not), the conditions were specified by two bits (N. G. Hatsopoulos, L. Paninski, and J. P. Donoghue, unpublished observations).

### *Recordings*

An array of 100 microelectrodes was implanted in the MI arm representation, as described in earlier publications (Maynard et al. 1999). Of the total array, only 22 and 11 were connected in the 2 animals, respectively, and thus available for recording, The microelectrode arrays (Bionic Technologies, Salt Lake City, UT) consisted of 100, 1.5-mm-long platinized tip, silicon probes arranged in a square grid (400 $\mu$m on center). All surgical procedures conducted for this study were in accordance with Brown University IACUC-approved protocols and the Guide for the Care and Use of Laboratory Animals (National Institute of Health publication no. 85-23, revised 1985).

### *Assessment of coarse temporal response measures (>20-ms resolution)*

The number of spikes were counted in ±50-, 100-, 200-, 500-, and 1,000-ms sample periods centered on each of the four event triggers (as the monkey's behavior is not controlled for before the start of trial trigger, we only examined data after the start of trial trigger). The mean and variance of firing rate were calculated and the fano factor (variance/mean) evaluated from data in the ±1,000-ms sample period using sliding windows of 20, 50, 100, 200, and 500 ms. To evaluate the independence of the responses over time, correlation of spike counts between these sliding windows was also assessed for each arm movement direction for individual cells. Statistical comparison of the correlation for each cell in each sliding window against independence ($r = 0$) was performed using the Fisher transform of the correlation coefficient (Snedecor and Cochran 1980) from each arm movement direction to ensure normality of the distributions.

Coarse temporal correlation between the responses of different neurons was calculated for each direction of arm movement using the spike counts from the sample periods ±50, 100, 200, 500, and 1,000 ms centered on the triggers. The correlation across all directions was calculated by transforming each set of responses to each direction $d$, $r_d$, into its $z$-score $r_z = (r_d - \bar{r}_d)/\sigma_d$, where $\bar{r}_d$ is the mean and $\sigma_d$ is the standard deviation of the responses to direction $d$. The overall correlation is therefore the correlation of the normalized response variability and does not reflect correlation of the signal, nor is it biased toward those directions with greater absolute response variability.

### *Assessment of synchronous spikes*

The spike times were binned (i.e., rounded) to a temporal accuracy of 1 ms. "Synchrony" was defined at three different temporal resolutions: 1, 3, and 5 ms counted for each trial. That is, spikes in one neuron were considered synchronous if they occurred at 0, ±1, or ±2 ms, relative to spikes in the second neuron, respectively. We used the number of synchronous spikes to form our measure of a precise temporal code for the information theoretic analysis in the different sample windows. Results based on 3- and 5-ms temporal resolutions were qualitatively similar to those observed at a 1-ms resolution and for conciseness are not included.

### *Measuring the information content of neural codes*

Transmitted information is a statistical measure quantifying, in the present situation, how well different directions of arm movement can be distinguished from each other using the responses of the neurons. The amount of information carried by a neuron's response depends on the code used to interpret the response (e.g., spike count). If precisely timed spikes play a special role by encoding unique information (Abeles 1991; Engel et al. 1992; Lestienne and Strehler 1987; Vaadia et al. 1995; von der Malsburg and Schneider 1986), then some of the information they carry should be unavailable from considering the pair of spike counts alone. We were therefore interested in how much information was carried by the number of synchronous spikes and second whether the synchronous spikes together with the paired spike count carried more information than that carried by the paired spike count code alone.

Details of information theory can be found elsewhere (Cover and Thomas 1991; Golomb et al. 1997; Shannon 1948) In brief, we asked how well the responses of single or populations of neurons could, in principle, tell us which direction of arm movement was performed. Mutual information is defined as

$$I_{(D;R)} = \sum_D \sum_R \left\{ p(r)p(d|r) \log_2 \left[ \frac{p(d|r)}{p(d)} \right] \right\} \quad (1)$$

where $I_{(D;R)}$ is the information transmitted about the set of arm movement directions $D$. The outer sum ranges over all the directions, $D$. The inner sum ranges over the set of all observed responses, $R$. For the terms of the inner product, $p(r)$ is the probability of observing response $r$ independent of the direction of arm movement. $p(d|r)$ is the probability of direction $d$ being the motor output having observed response $r$. $p(d)$ is the a priori probability of direction $d$, which is determined by the frequency with which the monkey moved its arm in direction $d$ in the experiment.

While $p(d)$ is determined exactly from the experiment, $p(r)$ and $p(d|r)$ must be estimated from the neuronal data. Because of limited sample size $p(r)$ and especially $p(d|r)$ are subject to misestimation (Kjaer et al. 1994; Optican et al. 1991). Several methods have been developed to correct for limited sample size (e.g., Kjaer et al. 1994; Victor and Purpura 1996; for review see Golomb et al. 1997). We chose the method of Kjaer et al. (1994) because it does not require us to make assumptions (e.g., Gaussian) to incorporate the distributions of the response measures and their possibly nonlinear covariation.

The method of Kjaer et al. (1994) uses a back-propagation neural network that performs nonlinear regression of the selected neural code on the direction of arm movement. The response measures were used as inputs to the neural network, and the directions of arm movement were used as target outputs (Kjaer et al. 1994). After training, the

outputs represent $p(d|r)$. The network was trained on three-quarters of the data and tested on the remaining quarter, preventing over-fitting that leads to the overestimates of the information (Kjaer et al. 1994). We used the spike count, the number of synchronous spikes, or the conjoint code of spike count and number of synchronous spikes as response measures for input to the network of Kjaer et al. (1994). This method provides a good estimate of $I_{(D;R)}$ (Golomb et al. 1997; Heller et al. 1995; Kjaer et al. 1994). Statistical analysis of the information measures was performed after transforming to ensure homogeneity of variance.

### *Assessment of the statistical significance of the numbers of synchronous spikes*

We were also interested in estimating the number of synchronous spikes expected by chance. Any synchronous spikes above chance levels, even if they do not carry information, would indicate that there was some level of functional connectivity between the neurons. Such connectivity between neurons has been examined using the precise temporal structure of responses in visually responsive cortical areas (e.g., Gochin et al. 1991). The spike density function captures coarse (<30-Hz bandwidth, >20-ms time scale) temporal structure in the responses and is known to influence expected numbers of precise response structures (Abeles and Gerstein 1988; Aertsen et al. 1989; Dayhoff and Gerstein 1983a,b; Lestienne and Strehler 1987; Lestienne and Tuckwell 1998; Victor and Purpura 1996). We therefore calculated the spike density function (SDF) for each cell to each stimulus by convolution of individual responses with a Gaussian (SD = 5 ms) (Richmond et al. 1987).

We extended the spike count matched model (Oram et al. 1999) to examine the number of precisely timed spikes expected from an underlying stochastic mechanism. Briefly, for each cell in the pair, the SDF is transformed into a cumulative spike density function (CSDF) for each stimulus at each time point $t \left[ \sum_{i=1}^{t} SDF(i) \right]$. Normalization by the value at the end of the sample period ($t = T$) gives the cumulative spike probability function $\mathrm{CSPF}(t) = CSDF(t)/CSDF(T)$. The spike times of each artificial trial are found by applying the inverse of the cumulative probability distribution to random numbers in the interval (0,1), $R_{[0..1]}$. The time bin (width $\delta t$) in which a spike occurs, $t_{\mathrm{spike}}$, is such that $t_{\mathrm{spike}}$ satisfies $\mathrm{CSPF}(k) \leq R_{[0..1]} < \mathrm{CSPF}(k+1)$, the time of the $k$th bin being $k\delta t - (k+1)\delta t$.

Each pair of spike count distributions and their correlation are preserved by stepping through the experimental data trial by trial and forcing each simulated trial to have the same number of spikes as the corresponding experimental trial. The extended SCM model therefore incorporates the slow variation in firing rate and the distribution of spike counts generated by individual neurons as well as the coarse temporal correlation of the spike counts and the correlation between the SDFs (i.e., correlation between the slow variation in firing rate of the individual neurons over time: the possible tendency for the spike density functions of different neurons to rise and fall together). The numbers of synchronous spikes were counted and compared with the experimental data using standard regression and ANOVA methods.

## RESULTS

For the present study it was critical to have well-isolated single neurons. To avoid potential distortion of the spike numbers and times from interference between spikes, we only accepted data from the activity of the optimal single neuron on an electrode. This also means that our analysis always compared pairs of cells recorded at least 400 $\mu$m apart. The analysis required sufficient data for each experimental condition to perform the information theoretic analysis (see Golomb et al. 1997). We therefore required each direction of arm movement to be repeated at least 15 times (typically ~30–50, range 17–156, mean 58.7; total numbers of spikes: range 538–36,482, mean 5,753.9). The data from 28 motor cortical neurons were examined from 2 monkeys (see also Hatsopoulos et al. 1998b; Maynard et al. 1999). The cells were simultaneously recorded in groups of 4, 6, 8, and 10 cells, giving 94 pairs in total (6, 15, 28, and 45 pairs from the respective recording session). For the pairs, the mean number of trials was 252.6 (range 188–337), and the mean number of spikes was 24,729.5 (range 4,905–69,169).

We are primarily interested in the potential for spike trains to convey two independent messages: one message in the coarse temporal response properties and one using fine temporal response properties. Most previous studies have estimated the number of precisely timed spike patterns using models that assume a spike count distribution based on a Poisson process. As any deviation from a Poisson distribution of spike count will necessarily influence the number of precisely timed spike patterns expected by chance (Oram et al. 1999), we begin with a detailed examination of the coarse temporal response statistics of single motor cortical neurons (Figs. 1–6). We then examine the occurrence of precisely timed patterns of pairs of spikes between neurons and show that synchronous spikes occur at a rate higher than expected by chance (Figs. 7–9). However, an information theoretic analysis indicates that information obtained from synchronous spikes is redundant with the information from the spike counts (Fig. 10). Examination of the relationship between the coarse and fine temporal response characteristics using a statistical model (Figs. 11–13) suggests the most parsimonious explanation of the excess synchrony is that of fixed, common input related to the firing rates of both neurons in the pair.

### *Coarse temporal response statistics of single motor cortical neurons*

Given the strong relationship between the coarse temporal response statistics of single neurons and the expected fine temporal structure both within and between neurons (Aertsen and Gerstein 1985; Dayhoff and Gerstein 1983a; Lestienne and Tuckwell 1998; Oram et al. 1999), it is essential to incorporate the relevant statistics in any assessment of the possible functional significance of precisely timed spike patterns. While the non-Poisson nature of the responses can be known from the interspike interval (ISI) histograms, the effect of changes in response variability is more influential on the numbers of precisely timed spike patterns than is deviation of the ISI from that expected from a Poisson process (Oram et al. 1999). We therefore begin by examining the variability of the responses of motor cortical neurons.

### *The fano factor*

Figure 1 shows the fano factor (variance/mean) assessed using a short (20 ms, Fig. 1, *top*) and long (500 ms, Fig. 1, *bottom*) sliding window of the data from one cell over the ±1,000-ms sample period. The fano factor using the small time window is <1 and becomes larger than one when longer time windows are used (compare Fig. 1, *top* and *bottom*). The result of a fano factor different from 1 demonstrates that the responses of this cell are not consistent with a Poisson firing

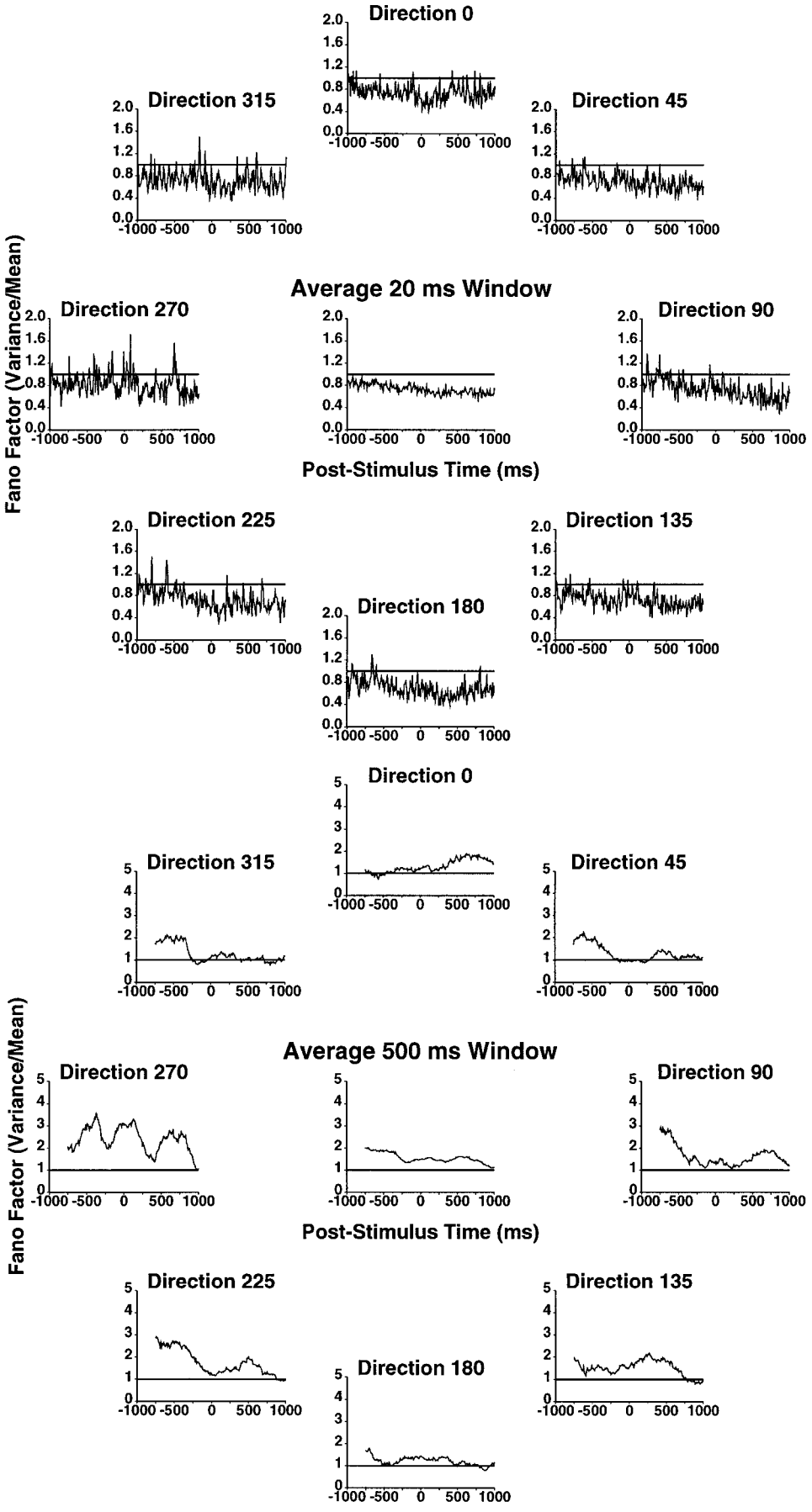


FIG. 1. Fano factor of 1 cell during the task to the 8 movement directions. The responses were aligned to the onset of arm movement and the fano factor (the ratio of variance to the mean spike count) was calculated using 20-ms (*top*) and 500-ms (*bottom*) sample windows. The *middle panel* shows the average of the fano factors. Note that the fano factor for short intervals is typically below 1, whereas it is >1 for the longer time windows.

process. Figure 2 shows the average fano factor for the motor cortical cells assessed using different sample windows starting at each of the four triggers. For the 20- and 50-ms sample windows, the variance is less than the mean firing rate taken around all triggers ($P < 0.001$ each comparison), indicating that at short sample windows there is less variability between neural responses to single directions of movement than would be expected from a Poisson process. For the 100-ms sample window, the fano factor is less than one taken from the instruction trigger ($P < 0.001$). The variance is, on average, numerically larger than the mean when windows longer than 100 ms are considered for the start of trial, go and start of arm movement triggers and for the 500-ms window for the instruction trigger ($P < 0.0005$ each comparison), indicating that at long sample windows there is greater variability between neural responses than would be expected from a Poisson process. In summary, the fano factor is significantly smaller than 1 with short sample windows and significantly greater than 1 with longer windows. Thus the responses of motor cortical neurons are not consistent with random samples from a Poisson process (see also Baker and Lemon 2000; Lee et al. 1998).

### *Sequential correlation within responses*

A second method of assessing whether the neural response can be characterized as a Poisson process is to examine temporal correlation within the responses of a single neuron. Correlation between time points within single responses indicates a non-Poisson process and is another influence on the expected numbers and types of precisely timed spike patterns. While a certain amount of correlation is implied by deviation of the response variability from that expected from a Poisson process, other sources of correlation are also possible. Note that the correlation between time periods of the response measures the deviations about the mean response at those time periods and is not therefore related to the time course (spike density function) of the response. Figure 3, *top*, shows the correlation of spike count between successive 20-ms time windows of one cell over the ±1,000-ms sample period. There is some evidence of negative correlation before the start of arm movement with a short time window for the responses of this cell, but little sign of correlation of spike count after the start of arm movement (Fig. 3, *top*). The *bottom section* of Fig. 3 shows the correlation of successive 500-ms windows of the responses from the same cell, showing positive correlation for most of the sample windows. Figure 4 illustrates the mean ± SE strength of mean correlation across neurons between successive time windows centered about each of the four triggers for each of the sample windows (20, 50, 100, 200, and 500 ms). Overall, it can be seen that as the window size increases the correlation between successive windows increases, changing from $r \approx 0$ at the shortest window (20 ms) to positive correlation of spike count between 50 ms or longer windows. The correlation is significantly different from 0 for all triggers at all sample windows >20 ms ($P < 0.005$ each comparison) and for the instruction trigger at 20-ms window ($P < 0.0005$). These results also demonstrate that the responses of motor cortical cells cannot be adequately described as Poisson processes.

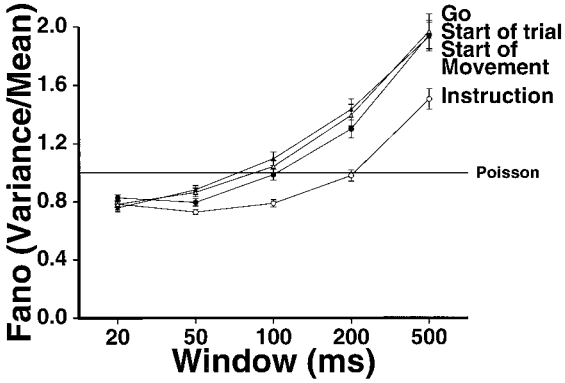


FIG. 2. Average fano factor of motor cortical cells. The fano factor (mean ± SE) is shown for each of the 5 time windows for the 4 different triggers. ●, start of trial trigger; ○, instruction trigger; ▲, go signal; △, start of movement. Overall ANOVA: Trigger $F_{[3,405]} = 12.0$, $P < 0.00005$; Window $F_{[4,540]} = 215.8$, $P < 0.00005$; Cell/Direction Estimate $F_{[135,1620]} = 12.1$, $P < 0.00005$; Trigger by Window $F_{[12,1620]} = 7.4$, $P < 0.00005$; Trigger by Estimate $F_{[405,1620]} = 4.8$, $P < 0.00005$; Window by Estimate $F_{[540,1620]} = 2.7$, $P < 0.00005$.

### *ISI distribution*

Finally, a third potentially independent influence on the expected number of precisely timed spike pattern is the distribution of the ISIs. In a Poisson process the occurrences of events (spikes) are statistically independent. This implies an exponential distribution of ISIs for a constant-rate process. Even with variable firing rate, the ISI distribution would be a sum of exponentials showing a monotonic decline. The *top panel* of Fig. 5 shows the ISI distribution for the cell in Fig. 1. The *bottom panel* of Fig. 5 shows the ISI distributions of a second cell recorded simultaneously with the cell in the *top panel*. The ISI distribution does not have the exponential shape expected of a Poisson process (Kolmogorov-Smirnov test, $P < 0.05$; exponential estimated by least-squares fit) in either of these examples, nor in any of the 28 recorded neurons. There is no reason to believe these are cells that are damaged. First, it is well established that certain cortical neurons exhibit bursts of spikes with short ISIs. These so-called intrinsic bursting cortical neurons bursters are usually pyramidal neurons and have somata that lie in layers IV and V, which is likely from where we are recording (Connors and Gutnick 1990). Second, the recorded cells exhibit normal movement-related modulation that begins several hundred milliseconds before movement onset typical of cells in primary motor cortex.

### *Coarse temporal correlation between responses of neuron pairs*

When the spike counts between different neurons were compared in ±500-ms sample period around the start of arm movement, many cell pairs showed significant correlation (Fig. 6). Note that the correlation could be either negative (Fig. 6, *top*) or positive (Fig. 6, *bottom*). Thirteen percent (1,061/8,080) of the pairs of responses over all of the individual movement directions at all sample windows and all triggers showed significant ($P < 0.05$) correlation. Forty-five percent (850/1,880) of the cell pairs showed significant correlation between responses ($P < 0.05$, after Bonferroni correction for multiple comparisons) for at least one of the individual movement directions assessed over all time windows and all triggers. A significant proportion (average over triggers 37%, Table 1) of pairs showed correlation of response variability either of the

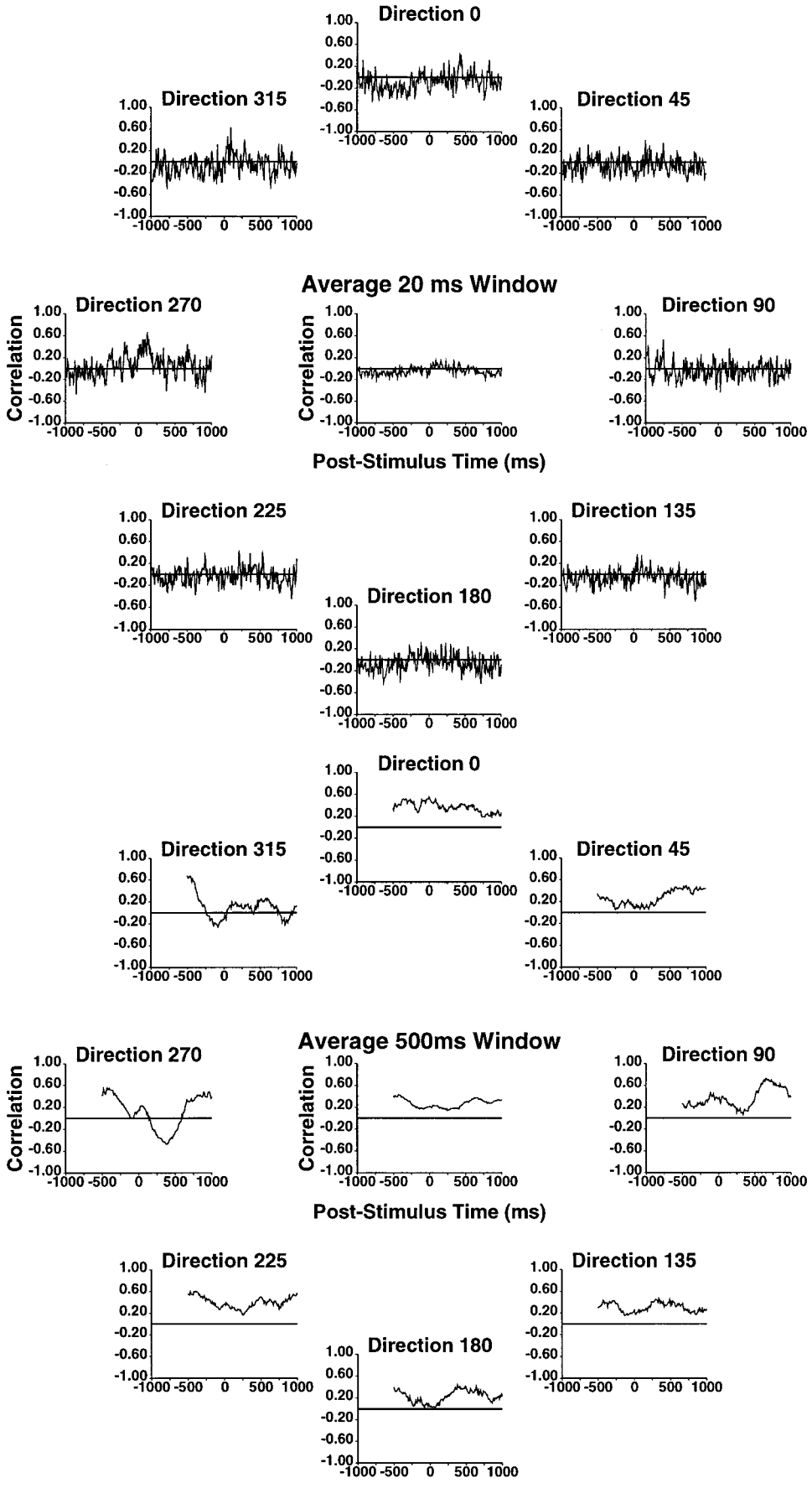


FIG. 3. Temporal correlation between time periods for the 8 movement directions. The responses were aligned to the onset of arm movement, and the correlation of successive time windows was calculated. *Top*: 20-ms sample window. *Bottom*: 500-ms sample window. The horizontal line in each panel indicates zero correlation (independence). Each of the 8 *outer panels* represents the correlation for the responses to 1 arm movement direction. The *middle panel* is the average correlation.

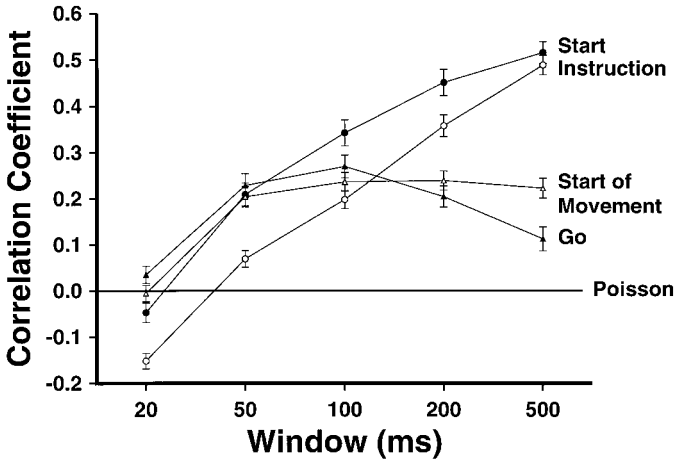


FIG. 4. Average correlation between successive time windows for motor cortical neural responses. The mean correlation coefficient (±SE) across neurons is plotted for each of the time windows and for each of the event triggers. The correlation coefficient was *z*-transformed (see Snedecor and Cochran 1980) for statistical analysis. The inverse transform was applied prior to plotting the values. The correlation between successive time windows increases with increasing sample window. Overall ANOVA: Trigger $F_{[3,405]} = 21.0$, $P < 0.00005$; Window $F_{[4,540]} = 283.0$, $P < 0.00005$; Cell/Direction Estimate $F_{[135,1620]} = 10.3$, $P < 0.00005$; Trigger by Window $F_{[12,1620]} = 62.1$, $P < 0.00005$; Trigger by Estimate $F_{[405,1620]} = 4.1$, $P < 0.00005$; Window by Estimate $F_{[540,1620]} = 1.5$, $P < 0.00005$.

combined responses (see METHODS) or for one of the movement directions in sample periods as short as ±50 ms. The majority (~60%, Table 1) of the recorded pairs of cells showed at least one significant correlation value at longer sample periods (±500 and ±1,000 ms).

### *Number and distribution of synchronous spikes*

Figure 7 shows the cross-correlogram of one pair of the motor cortical neurons. Each point indicates the correlation coefficient for the offset delay between the pair of neurons. This value is the number of times that spikes were observed to occur in the responses of both cells at each delay scaled to account for the firing rates. We examined the cross-correlograms for patterns ranging from −100- to 100-ms delay. A single pair showed a clear peak indicative of a monosynaptic connection between the two neurons: all other significant peaks were at or centered near the zero delay bin (synchrony). The existence of sharp synchrony exhibited in Fig. 7 has been observed before: Hatsopoulos et al. (1998b) estimated that 36% of all cell pairs that exhibited significant synchrony showed cross-correlation peaks with widths at half height of 1–3 ms. The majority of cell pairs (64%) showed broader peaks with widths ranging from 10 to 15 ms at half height. The cross-correlogram illustrates two points. First, the correlation is low, peaking at 0.02, indicating that at best, knowledge of a spike at one time point accounts for only 0.0004 of the variability in whether a spike is going to occur at a given offset in the response of the second cell. The correlation gives an indication of the potential power of the signal carried by synchronous spikes; if a high correlation was observed it would imply many synchronous spikes above chance levels and hence the possibility of a strong signal that was unavailable from spike count. However, the low observed correlation suggests that the potential information carried by synchronous spikes unavailable from spike count is limited. If synchronous spikes were to carry direction information unavailable from spike count, the cross-correlation at 0 ms delay would be high relative to the other delays for some but not all directions of arm movement. Indeed, the correlation at the fine temporal scale varies with direction of arm movement, suggesting that it may act as a neural code independent of the spike counts. The low correlation values suggest that the code would, however, be relatively weak.

The peak in the cross-correlogram at a delay of 0 ms is clearest when all trials for a pair of cells are considered, regardless of the particular direction of arm movement (Fig. 7, *middle panel*, calculated from pooling all trials across all directions of arm movement). Thus the result suggests the amount of synchrony varies continuously with direction. This was further examined by ranking the cross-correlation over delays −55 to +55 ms for each direction and each cell pair. The $R^2$ of the correlation of the ranks between directions at the 0-ms delay (synchronous spikes) was 0.19, compared with 0.02–0.09 (mean = 0.05) for delays between 5 and 55 ms. This indicates that knowledge of the cross-correlation at 0-ms delay of one direction of arm movement allows some prediction of the cross-correlation at 0-ms delay (but not other delays) to the other directions of arm movement. This confirms that if a peak at 0-ms delay is present in one direction, then a peak is likely for other directions, and if a pair does not show a peak in the cross-correlogram for one direction, peaks will tend not be found in other directions. Note that this does not indicate whether the information about direction carried by synchronous spikes is independent of spike count. If the distribution of synchronous spikes changes across direction in a way that can be related to the coarse temporal response measures, then the information they carry will be redundant with the information carried by those coarse temporal response measures.

The number of synchronous spikes for a pair of neurons varies from trial to trial, even when the spike counts are comparable across trials. Figure 8 shows the number of synchronous spikes observed for one pair of neural responses. The *middle panel* shows the summed distributions. The numbers of synchronous spikes to each direction of arm movement varies considerably, and the distributions show appreciable overlap. This also suggests that when considering pairs of neurons the numbers of synchronous spikes will carry relatively little information related to direction of arm movement.

The relationship between the number of spikes and the number of synchronous spikes was investigated because a nonlinear relationship implies that the exact rather than assumed distribution of spike counts needs to be incorporated into models used to estimate the expected numbers of precisely timed spikes (Oram et al. 1999). The numbers of synchronous spikes from all cell pairs and all directions of arm movement have been combined and plotted as a function of the pair of spike counts in Fig. 9, *top*. The nonlinearity is illustrated in the *bottom section* of Fig. 9, where the observed number of synchronous spikes along the diagonal of the *top section* is plotted as a function of the response strength (number of spikes, responses of both neurons having the same number of spikes). The regression curves show that the nonlinear (quadratic) function fits the data more closely than a simple linear function. The nonlinearity was confirmed across all spike count pairs using regression of a linear plane on the data and com-

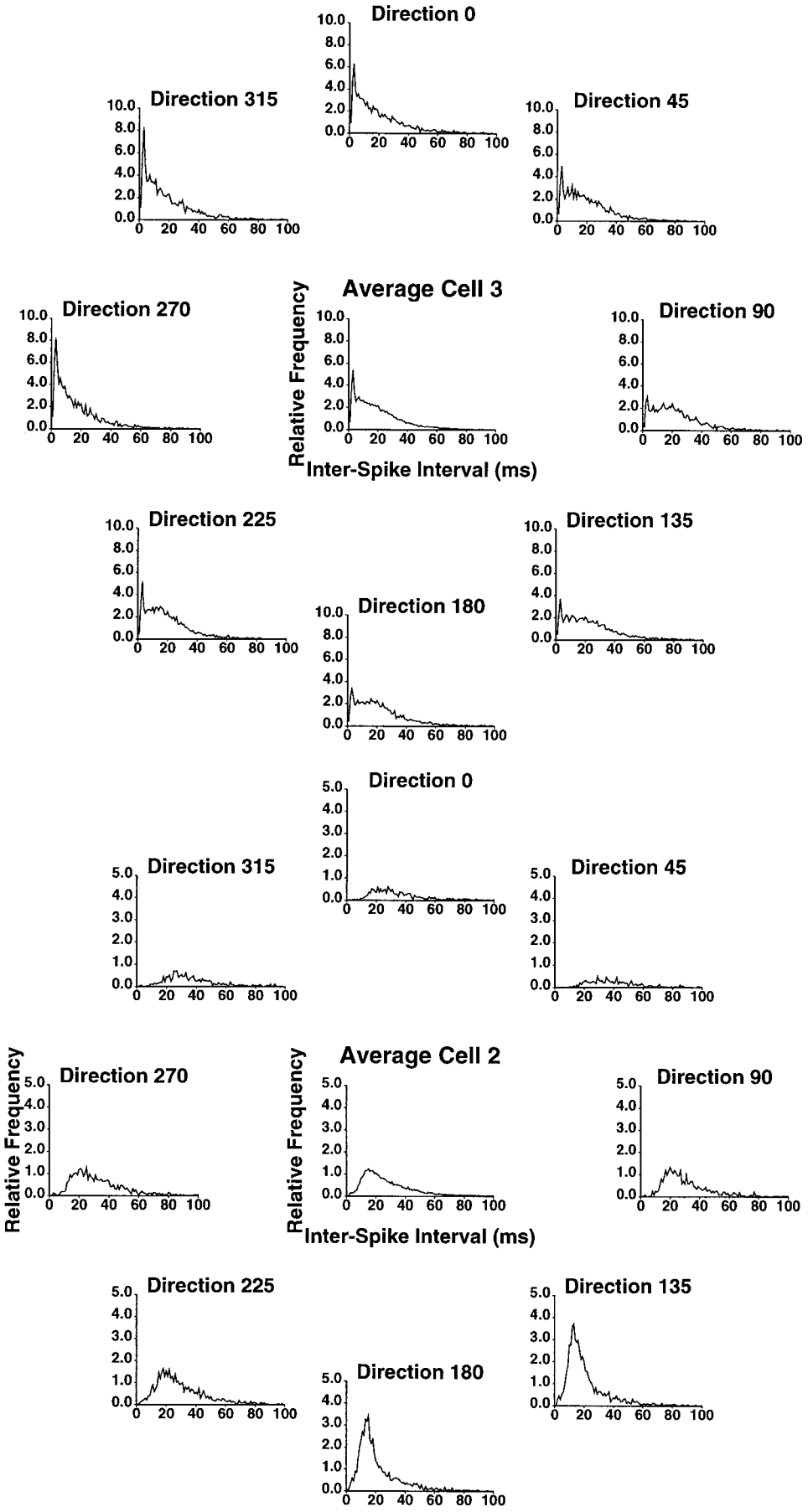


FIG. 5. Distribution of interspike intervals (ISIs) of 2 cells. The ISIs of the responses aligned to the onset of arm movement were found. The outer ring of panels are the ISI distributions for each of the 8 movement directions (0, 45, 90, 135, 180, 225, 270, and 315°). The *middle panel* shows the ISI distribution from the combined data of all 8 directions. Number of trials: direction 0° = 45, 45° = 44, 90° = 37, 135° = 49, 180° = 48, 225° = 46, 270° = 34, 315° = 34, Combined = 337. *Top*: ISI distribution of *cell T1052897-3* aligned to the start of movement. Number of spikes: direction 0° = 4,190, 45° = 3,881, 90° = 2,891, 135° = 3,865, 180° = 3,892, 225° = 4,102, 270° = 3,456, 315° = 3,445, Combined = 29,722. *Bottom*: ISI distribution from a 2nd cell (*T1052897-2*) with data aligned to the start of movement. Number of spikes: direction 0° = 799, 45° = 655, 90° = 1,227, 135° = 2,945, 180° = 2,715, 225° = 2,080, 270° = 1,281, 315° = 666, Combined = 12,368.

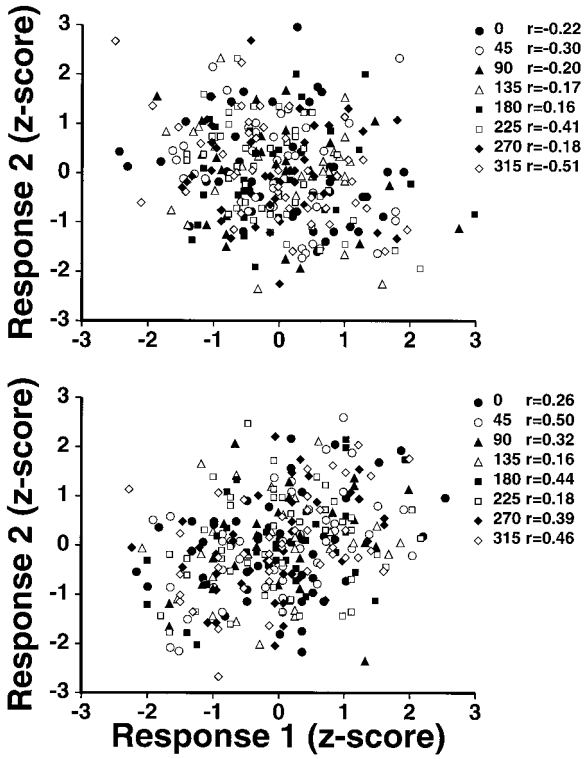


FIG. 6. Correlation exists between responses of different motor cortical neurons. *Top*: negative correlation between responses of a single pair of neurons assessed with response alignment on the start of arm movement. Each plot point is the paired *z*-scores of an individual response from the pair of neurons. The different symbols correspond to responses collected during different directions of arm movement (0, 45, 90, 135, 180, 225, 270, 315). For this pair of cells, significant correlation was observed for 7 of the 8 directions of arm movement as well as across all responses. *Bottom*: positive correlation between responses of a single pair of neurons. Significant correlation was observed in 6 of the 8 directions of arm movement as well as across all responses.

paring it with the regression of a surface defined by the sum of the individual spike counts and their product. For all sample periods, the increase in $R^2$ when including the product of the two spike counts in the regression was significant ($P < 0.05$; see Table 2).

### *Information carried by synchronous spikes is redundant with that carried by spike count*

The observation of precisely timed synchrony between the firing of two neurons does not in and of itself indicate that the synchrony is separable from the coarse temporal characteristics of the responses. We use information theoretic analysis to directly assess whether the synchrony can form a separable code from the coarse temporal characteristics. Although the analyses were performed using all four trigger points, we present data from all cell pairs primarily for the analyses around the go signal and start of arm movement because these are the only time periods where significant information related to direction of arm movement was found. The three response measures used in the calculation of the information were *1*) the dual spike counts (1 spike count from each neuron), *2*) the number of synchronous spikes, and *3*) the conjoint code of the dual spike counts and the number of synchronous spikes (see METHODS for further details).

The information from synchronous spikes obtained from single pairs of cells is much less than that available from considering the spike count code of that same pair (Fig. 10, *top*, and Table 3). Synchronous spikes carry an average 7.9 ± 1.06% of the information carried by spike count (0.029 ± 0.001 bits vs. 0.325 ± 0.006 bits). However, the information per synchronous spike pair is larger than the information per individual spike (overall average 0.0115 ± 0.001 vs. 0.0010 ± 0.0007 bits per event). Adding the number of synchronous spikes to the spike count code adds no further information to that already available from knowing the two spike counts (compared for all pairs in Fig. 10, *bottom*), demonstrating that no additional information about movement direction is added by synchronous events ($P > 0.05$). Note that the lack of additional information about movement direction provided by synchronous events holds for all 96 pairs (Fig. 10, *bottom*), including those pairs with the greatest absolute numbers of synchronous spikes and those pairs with the greatest excess of synchronous spikes above chance levels. This result was found at all window periods.

To investigate further whether the synchronous spikes carried information unavailable from spike counts and the coarse correlation, an ANOVA was performed using code and cell as factors. Information values were log transformed to ensure homogeneity of variance. This analysis also revealed no effect of code (dual spike count 0.3247 ± 0.006 bits, addition of synchronous spikes 0.3252 ± 0.006 bits, $F_{[1,93]} = 0.184$, $P > 0.5$). The power of the analysis was such that changes of a few 100th of bits (±0.02 bits) would have been deemed significant, so the result is not due to lack of sensitivity of the test. The addition of synchronous spikes did not interact with neural pair ($F_{[93,5408]} = 0.78$, $P > 0.5$), indicating that synchronous spikes did not add information above that carried by spike counts for

TABLE 1. *Prevalence of response correlation*

| Trigger | Measure | Sample Window ±50 ms | ±100 ms | ±200 ms | ±500 ms | ±1,000 ms |
|---|---|---|---|---|---|---|
| Start trial | | | | | | |
| | Individual | 28 | 29 | 43 | 52 | 48 |
| | Combined | 36 | 37 | 51 | 60 | 59 |
| | Overall | 42 (45) | 43 (46) | 56 (60) | 63 (67) | 64 (68) |
| Instruction | | | | | | |
| | Individual | 13 | 23 | 34 | 40 | 43 |
| | Combined | 23 | 35 | 42 | 54 | 57 |
| | Overall | 29 (31) | 37 (39) | 47 (50) | 56 (60) | 57 (61) |
| Go signal | | | | | | |
| | Individual | 26 | 33 | 37 | 38 | 42 |
| | Combined | 30 | 42 | 49 | 48 | 48 |
| | Overall | 36 (38) | 52 (55) | 55 (59) | 52 (55) | 55 (59) |
| Start move | | | | | | |
| | Individual | 18 | 28 | 31 | 44 | 38 |
| | Combined | 27 | 34 | 31 | 47 | 42 |
| | Overall | 32 (34) | 41 (44) | 41 (44) | 54 (57) | 50 (53) |

Numbers of neuron pairs showing significant correlation between spike counts. Numbers in parentheses are percentages. The number of the 94 cell pairs showing statistically significant correlation ($P < 0.05$) between the pairs of spike counts for each of the 4 trigger points for each of the 5 sample windows are shown. Individual: a significant correlation between the spike counts was found in at least 1 of the individual directions of arm movement. Combined: a significant correlation between the spike counts from the combined data set (all spike counts transformed to their *z*-scores). Overall: either an individual direction or the combined data set showed significant correlation between the spike counts.

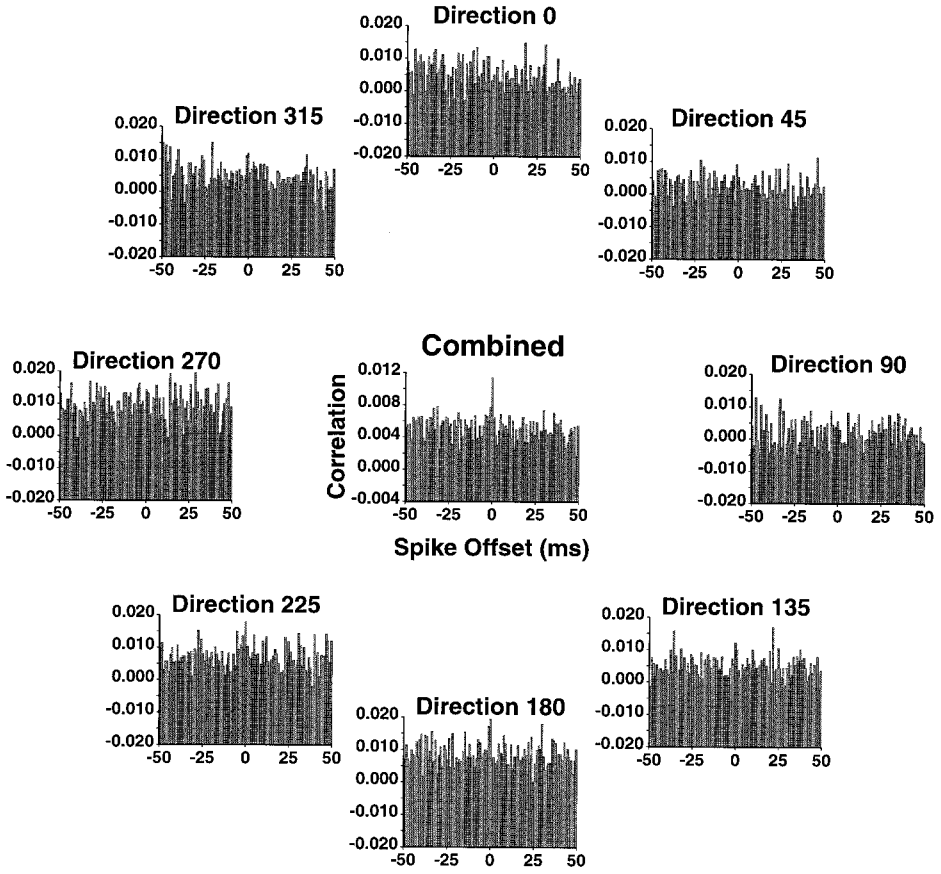


FIG. 7. Structure of fine temporal cross-correlation between responses of 2 cells. The correlation coefficient between the responses of 2 cells at temporal offsets of −50 to 50 ms are shown. The *outer circle* shows the correlation coefficients for each of the 8 directions of arm movement. The *middle panel* shows the correlation coefficient calculated from all trials. Number of trials: direction 0° = 45, 45° = 44, 90° = 37, 135° = 49, 180° = 48, 225° = 46, 270° = 34, 315° = 34, Combined = 337. Number of spikes: (*cell a*) direction 0° = 4,190, 45° = 3,881, 90° = 2,891, 135° = 3,865, 180° = 3,892, 225° = 4,102, 270° = 3,456, 315° = 3,445, Combined = 29,722; (*cell b*) 0° = 799, 45° = 655, 90° = 1,227, 135° = 2,945, 180° = 2,715, 225° = 2,080, 270° = 1,281, 315° = 666, Combined = 12,368.

any of the 94 pairs (see also Fig. 10, *bottom*). Note again that this includes those pairs with the greatest absolute numbers of synchronous spikes and those pairs with the greatest excess of synchronous spikes above chance levels. This effect did not vary with trigger point ($F_{[1,93]} = 3.7$, $P > 0.05$). The lack of extra information carried by synchronous spikes was robust across the sizes of sample windows ($F_{[4,372]} = 0.73$, $P > 0.5$), for all pairs at all sample periods ($F_{[372,5408]} = 0.48$, $P > 0.5$) and for all pairs at both trigger points ($F_{[93,5408]} = 0.303$, $P > 0.5$). In summary, despite extensive examination, there was no evidence that the synchronous spikes between the responses of cell pairs carried information beyond that available from a code that includes spike counts and their coarse temporal correlations.

### *Scaling the SCM model to predict the numbers of synchronous spikes*

The information theoretic analyses showed that a relationship exists between the coarse temporal response characteristics and the precisely timed synchrony. Excess synchrony would be expected to carry information redundant with the coarse temporal characteristics if simple (e.g., linear) relationships exist between the predicted and observed numbers of synchronous spikes. For example, local network properties can give rise to synchronous firing (Bush and Sejnowski 1996; Engel et al. 1991a,b; Hansel 1996; White et al. 1998). The simplest source of excess synchrony is to postulate a direct common input from either a single neuron or a small population of neurons. The source of excess synchrony could be independent of the particular arm direction: this would give rise to excess synchrony that was equal across all directions of arm movement. Alternatively the common input could form part of the driving inputs, predicting excess synchrony that rose in proportion to the chance numbers of synchronous spikes.

Figure 11 shows the regressions of the number of synchronous spikes predicted by the SCM model against the number of synchronous spikes found in six pairs from the motor cortical data. The $R^2$ values indicate the proportion of the variance in the number of synchronous spikes seen in the neural data that can be accounted for by a linear transformation of the SCM estimate. The range of $R^2$ values is generally high. However, when the range of observed numbers of synchronous spikes is low (<1, pair 1 and 4), the $R^2$ value becomes low for some pairs. The regression slopes are <1, demonstrating that there is an excess of synchronous spikes for these cell pairs. Thus the SCM model does not predict the absolute number of synchronous spikes. For those cases with high $R^2$, a simple scaling of the numbers of synchronous spikes from the model would produce nearly perfect predictions. For those cases where the $R^2$ is low, there are two possibilities. Either the synchronous spikes observed in the neural data are not predictable from the spike counts and the coarse temporal correlation, or the low $R^2$ values are simply due to a small range in the mean number of synchronous spikes and the high variability in the individual distributions of the synchronous spikes (Fig. 8). We tested which of these possibilities is more likely by examining the relationship between the results from the regressions and the range of the mean number of synchronous spikes found for the different directions of arm movement.

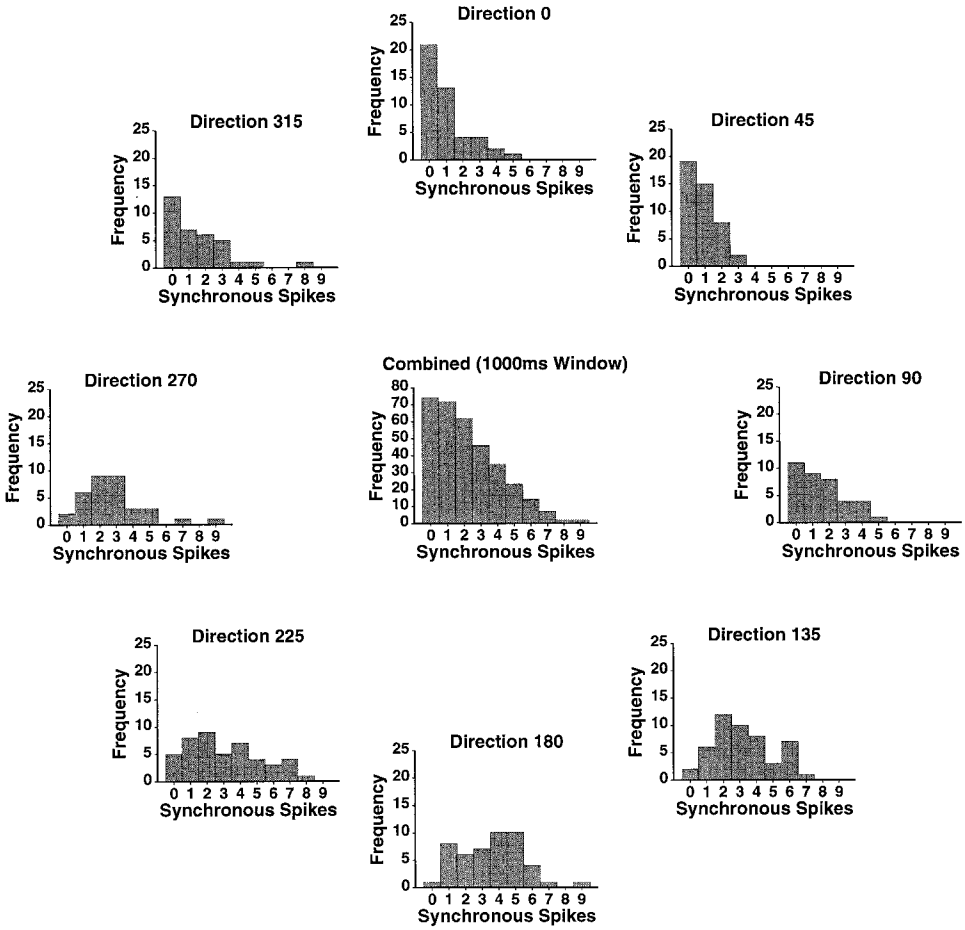


FIG. 8. Number and distribution of synchronous spikes. The numbers of synchronous spikes between 2 cells were noted for each trial. The distribution of the number is shown for each of the 8 movement directions and the overall distribution (*middle panel*). Data from the trials aligned to the start of arm movement, sample window −1,000 to 1,000 ms.

The *top section* of Fig. 12 shows the distribution of the $R^2$ for all 94 pairs of motor cortical neurons from all the 5 different sample periods (±50, 100, 200, 500, and 1,000 ms). When the range of the observed number of synchronous spikes is small, the $R^2$ value is evenly distributed across the entire range (0–1). This is to be expected. With small ranges, different samples from a single distribution would give rise to small differences in the mean number of synchronous spikes. Under these circumstances, the observed variability in the numbers of synchronous spikes would be due to sample bias and not a systematic variation. Thus the observed variability in the number of synchronous spikes simply reflects the statistics of small sample sizes, so no additional explanation for this variability is necessary. As the range of the mean numbers of synchronous spikes to different movement directions increases, only high values of $R^2$ values are seen. This shows that when significant variation is observed in the range of the number of synchronous spikes, the SCM model explains a high proportion of the variance (>80%). The *bottom section* of Fig. 12 shows the slope of the regressions between the numbers of synchronous spikes predicted by the SCM model and the number observed in the neural data. As all intercepts of the regressions were at or near to zero, a slope of 1 corresponds to equality between the SCM model and the motor cortical data. The slopes were variable when the range of the numbers of synchronous spikes was small. When the range of synchronous spikes was higher, the slopes showed more consistent values, clustering in the range 0.75–0.85. However, it is noteworthy that the slopes varied across cell pairs, so that a different constant had to be added to the model for each cell pair to account for the fit between the predicted number of synchronous spikes and the number obtained from the data. This individuality means that excess synchrony cannot be reduced to a simple global feature of rate modulation for all pairs, but the excess can, nevertheless, be related to rate modulation on a pair by pair basis.

The correlation coefficient associated with each $R^2$ can be transformed to account for its limits (−1 and 1) and the average taken (see METHODS) (Snedecor and Cochran 1980). Taking all data values, including those with the expected $R^2 = 0.0$ (i.e., little variation in the neural data), the reverse transform of the mean suggests the average $r = 0.874$ giving an $R^2$ of 0.76 ± 0.03 (mean ± SE). Thus a scaled version of the SCM model accounts for approximately three-quarters of the variance in the observed number of synchronous spikes even when including pairs of neurons where there is no meaningful variation in the number of synchronous spikes between directions. The *top section* of Fig. 13 shows the average $R^2$ calculated for each of the time windows from those window/pair combinations that had a range of at least 0.5 synchronous spikes/trial or more over different movement directions. As there was no significant difference between the time windows ($F_{[4,176]} = 0.93$, $P > 0.4$) the estimates were combined. When the values are taken from all sample window/neural pair combinations that showed a difference of 0.5 synchronous spikes/trial or more between different arm movements, $R^2$ was 0.93 ± 0.05 (mean ± SE). This suggests that when there is true variation in

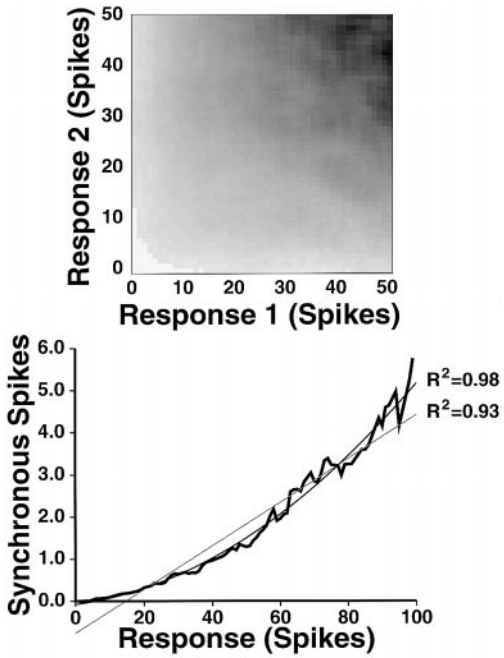


FIG. 9. Number of synchronous spikes is nonlinearly related to the 2 spike counts. The *top plot* shows the number of synchronous spikes as a function of the spike counts averaged across all cell pairs. The mean number of synchronous spikes seen in spike trains with total spike counts given on the *x*- and *y*-axes is plotted using the gray scale. The mean was calculated over all 94 pairs and all directions of arm movements. The *bottom plot* shows the number of synchronous spikes along diagonal of the *top plot* (thick line) as a function of the spike count (count from *neuron 1* = count from *neuron 2*). The resultant regression lines assumes a linear (thin line) or quadratic (medium line) relationship between the spike count pair and the number of synchronous spikes (see Table 2 for the results of the regressions of planar and quadratic surfaces).

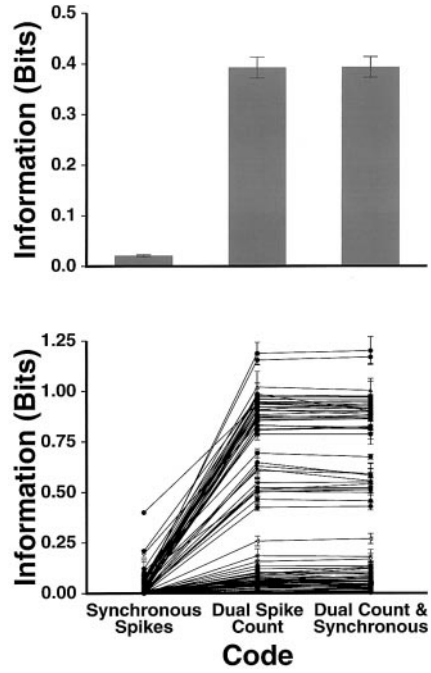


FIG. 10. Information content of spike count and synchronous spikes. Data from the trials aligned to the start of movement from the 94 pairs. Sample window −1,000 to 1,000 ms. Information from the spike counts of the 2 cells, synchronous spikes, a dual code of the 2 spike counts and the triple code of 2 spike counts and the number of synchronous spikes. *Top*: mean ± SE information from the 94 pairs. *Bottom*: information for each of the 94 pairs.

the neural data (rather than sample error), the SCM model typically accounts for >90% of the variance in the number of synchronous spikes.

While the SCM model accurately predicts the variability in the number of synchronous spikes, the model consistently underestimates the absolute numbers. The high $R^2$ values indicate that applying a scaling factor to the numbers of synchronous spikes obtained from the SCM model would bring those numbers into line with those observed in the neural data. The appropriate scale factor for each pair is given by 1/slope of the regression. Across all pairs and sample windows the average slope was 0.65 ± 0.051 (mean ± SE). When the estimates of the slope were taken from those neural pairs that showed a difference of 0.5 synchronous spikes/trial or more between different arm movements, the average slope was to 0.78 ± 0.015 (Fig. 13, *bottom*), giving a mean scale factor of 1.41 ± 0.05.

TABLE 2. *Nonlinear relationship between spike counts and synchronous spikes*

| Sample Period, ms | Linear $R^2$ | Linear + Product $R^2$ | Significance of Adding Product |
|---|---|---|---|
| ±50 | 0.703 | 0.874 | $F_{[1,407]} = 549.6$, $P < 0.0005$ |
| ±100 | 0.701 | 0.854 | $F_{[1,943]} = 989.6$, $P < 0.0005$ |
| ±200 | 0.720 | 0.866 | $F_{[1,2529]} = 2{,}746.0$, $P < 0.0005$ |
| ±500 | 0.727 | 0.898 | $F_{[1,9433]} = 15{,}754.1$, $P < 0.0005$ |
| ±1,000 | 0.724 | 0.900 | $F_{[1,30051]} = 53{,}074.5$, $P < 0.0005$ |

$R^2$ of the regression of the number of synchronous spikes against spike count. The number of synchronous spikes from all cell pairs was regressed against the spike count pairs independent of the direction of arm movement using either a linear combination of the spike counts (the plane) defined by Sync = $b_1$*Spk1 + $b_2$*Spk2, or using the curved surface defined by Sync = $b_1$Spk1 + $b_2$Spk2 + $b_3$Spk1*Spk2. For all window sizes the $R^2$ of the curved surface indicated a significantly improved fit.

TABLE 3. *Information by code*

| Go Trigger | Synchronous Spikes | Dual Spike Count | Dual Count and Synchronous Spikes |
|---|---|---|---|
| | *Sample period* | | |
| ±50 ms | 0.004 | 0.087 | 0.091 |
| ±100 ms | 0.008 | 0.125 | 0.126 |
| ±200 ms | 0.012 | 0.174 | 0.173 |
| ±500 ms | 0.025 | 0.309 | 0.306 |
| ±1,000 ms | 0.053 | 0.416 | 0.420 |
| | *Start of movement* | | |
| ±50 ms | 0.011 | 0.327 | 0.324 |
| ±100 ms | 0.020 | 0.393 | 0.394 |
| ±200 ms | 0.037 | 0.457 | 0.455 |
| ±500 ms | 0.060 | 0.518 | 0.517 |
| ±1,000 ms | 0.060 | 0.482 | 0.482 |

The directional information carried by synchronous spikes is redundant with the information carried by the spike counts and their correlation. The mean information is shown for each of the 5 sample window sizes for each of the 3 chosen measures of the neural responses (number of synchronous spikes, dual spike count pair, and the conjoint code of spike counts and number of synchronous spikes). The analysis was performed for response alignment at both the onset of the go signal and the start of arm movement. The directional information from the number of synchronous spikes is ~0.1 of the information carried by the dual spike code (compare Synchronous Spikes with Dual Spike Count). The information carried by the number of synchronous spikes did not provide any more information than was available from the dual spike count code alone (compare Dual Spike Count with Dual Count and Synchronous Spikes).

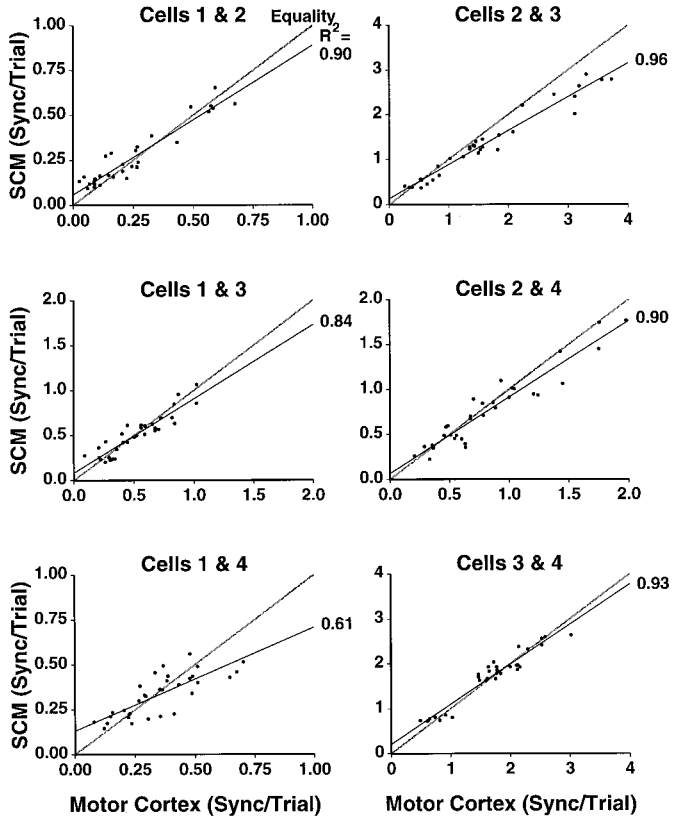


FIG. 11. Regression of predicted and observed numbers of synchronous spikes. The regressions from 6 pairs are shown. The gray lines indicate equality. The $R^2$ value is given at the top of each regression line. Note that the worst regression still explains over 60% of the variance in the numbers of synchronous spikes, with typically >90% of the variance being explained by the spike count matched (SCM) model. As the range in the observed number of synchronous spikes increase, so does the $R^2$ value, suggesting the poor $R^2$ values are due to sample error more than inadequacies of the model.

## DISCUSSION

Correlation between the spike counts of motor cortical neurons has been shown to exist (Lee et al. 1998; Maynard et al. 1999), and incorporating them into models improves the discrimination of movement direction (Maynard et al. 1999). Broad temporal correlation therefore needs to be considered when measuring information carried by populations of spike counts (Abbott and Dayan 1999; Oram et al. 1998). It is also essential to consider broad correlations to provide an accurate estimate of the information carried by synchronous spikes. The ability to obtain simultaneous recording of many MI neurons now makes it possible to examine directly whether or not synchronous spikes added to the information available from the spike counts plus their broad correlations across different cells. As with previous studies, we found ~10–20% of cell pairs showed levels of synchrony that were significantly ($P < 0.05$) above chance (Baker et al. 2001; Hatsopoulos et al. 1998b). Unlike most previous studies, we could extend the examination of cell pair characteristics beyond those recorded on the same electrode to neurons that were separated by 400 $\mu$m or more in the cortex. Thus our study is novel in that we provide an analysis of a simultaneously acting neuron populations acting over several square millimeters of cortex.

Our results show that there is an excess of synchronous spikes in MI neuron pairs. However, this excess provides no additional information about movement direction beyond that provided by the spike count and broad covariance of the same cell pair. Others have examined the responses of motor cortical responses for more complex patterns of precisely timed spikes (Baker and Lemon 2000). The existence of an excess number of synchronous spikes (see RESULTS) (Baker et al. 2001; Hatsopoulos et al. 1998b) indicates greater than expected numbers of any complex patterns of spikes that incorporates synchronous spikes. While the numbers of repeating triplets of spikes within a single neuron (Oram et al. 1999) are predicted almost exactly by the SCM model (unpublished observation), the excess synchrony is spread across all the complex spike patterns involving synchrony and does not therefore appear to be above chance levels for any particular complex spike pattern. Thus the analysis we performed was aimed to examine the excess synchrony (delay 0 ms): delays up to $\pm$100 ms were not found to be significant, and, with the proviso given above, we found no evidence for more complex spike patterns to be above chance levels (see also Baker and Lemon 2000). Of course, this analysis is restricted to spike patterns across pairs of neurons and does not address other possible patterns involving more than two neurons.

### *Response statistics of single motor cortical neurons and fine temporal structure*

The responses of single MI neurons cannot be characterized by a Poisson process because *1*) the variance/mean of the responses is less than that expected from a Poisson process (1.0) at short intervals and >1.0 at long sample periods (Figs.

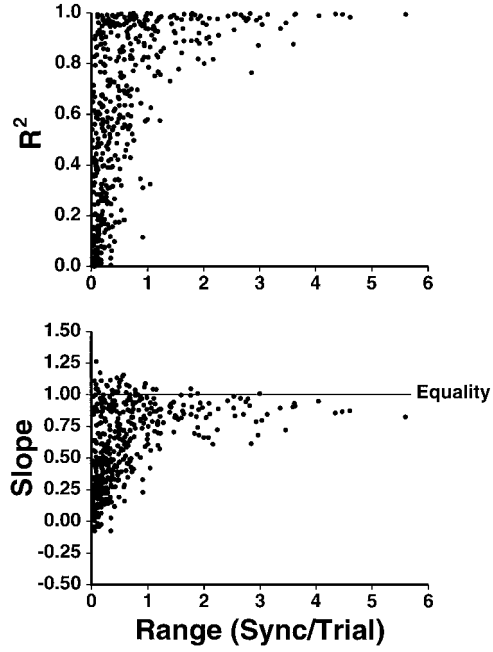


FIG. 12. Accuracy of the extended SCM model in predicting the synchronous spikes. Regression of the number of synchronous spikes predicted from the SCM model against the number observed in the neural data. *Top*: distribution of the $R^2$ values as a function of the range of the observed number of synchronous spikes to different directions of arm movement. As expected from simple statistical considerations, the $R^2$ values were higher when the range of synchronous spikes was higher. *Bottom*: distribution of the slopes of the regression as a function of observed range. A slope of 1.0 indicates that the number of synchronous spikes in the SCM model data are the same as that in the motor cortical data.

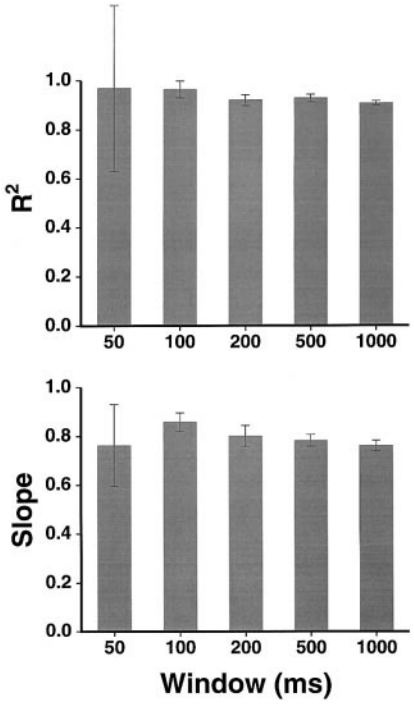


FIG. 13. Summary of the predicted number of synchronous spikes using the extended SCM model. Accuracy of the extended SCM model in predicting the number of synchronous spikes at different time windows. *Top*: mean ± SE of the $R^2$ values from the regressions for sample windows of ±50, 100, 200, 500, and 1,000 ms centered in start of movement. For all window sizes, the SCM model explained, on average, more than 90% of variability in the observed number of synchronous spikes between directions of arm movement. *Bottom*: mean ± SE of the slopes the individual regressions for sample windows of ±50, 100, 200, 500, and 1,000 ms centered in start of movement. The mean slope was below 1.0 for all window sizes, indicating that the neural data contained more synchronous spikes than expected by chance.

1 and 2) (see also Lee et al. 1998), and *2*) significant sequential correlation was found (Figs. 3 and 4). (Note that the sequential correlation is over and above the correlation between successive points of the average response profile.) As any deviation of the spike count distribution of responses from Poisson indicates that correlations must exist within the responses of the cells (Oram et al. 1999), it was necessary to include the observed spike count distribution when assessing the expected number of synchronous spikes.

The ISI distribution deviates significantly from a monotonic distribution for the first 15-ms intervals or so (Fig. 5). Studies of the responses of retinal ganglion cells have shown that the ISIs also have an influence on the expected fine temporal structure of responses (Berry and Meister 1998). The ISI distribution of responses from LGN and striate cortical neurons require adjustment to the first and second intervals to match that seen in the data (Oram et al. 1999). It was therefore necessary to include the observed ISI distributions as well as the observed distributions of the spike counts to properly assess the statistical significance of synchrony.

### *Coarse temporal correlation in spike count between neurons and synchrony*

The responses between pairs of MI neurons are significantly correlated at coarse temporal scales (Fig. 6 and Table 1). Previous studies have shown similar correlation between the spike counts of motor cortical neurons (Lee et al. 1998; Maynard et al. 1999). Moreover, these broad correlations add additional information about movement direction (Maynard et al. 1999). Such correlation needs to be included when calculating numbers of synchronous spikes occurring by chance on a fine time scale (Brody 1999a,b), because these factors markedly effect their numbers.

The observed positive correlation of spike counts between neuron pairs means there will be more instances with both counts being high or both being low than if the responses were independent. The nonlinear relationship between the pair of spike counts and the number of synchronous spikes (Fig. 9 and Table 2) implies that a decrease in synchronous spikes in low spike count trials is more than offset by an increase in synchronous spikes in high spike count trials. Thus the expected number of synchronous spikes is sensitive to the coarse temporal correlation of spike count (Brody 1999a–c). A misestimate of the distribution or failure to account accurately for any coarse temporal correlation will therefore necessarily lead to a misestimate of the expected number of synchronous spikes.

### *Information carried by spike counts and synchronous spikes*

We incorporated the observed spike count distributions and the coarse temporal correlation when examining the information carried by synchronous spikes using the method of Kjaer (Kjaer et al. 1994). The amount of information provided by a single synchronous spike pair was ~12-fold larger than that from a single spike, but the total information available in time windows from ±50 to ±1,000 ms was only ~1/12 of that available from the number of spikes. Further, the information carried by the synchronous spikes was redundant with that carried by the spike counts (Fig. 10), so that the synchronous firing of a pair of cells provided no new information about the direction of arm movement. Within a given time window the reverse is not true: spike counts provide information about direction that is not available from synchronous spikes. Previous analysis demonstrated that the synchronous spike carried directional information above that available from coincidences from statistically independent responses (Hatsopoulos et al. 1998b). The present analysis shows that this directional information is the same as or part of the information carried by the correlation of the coarse response measures. Thus under the present experimental conditions, synchronous spikes do not code directional information that is separate from that coded by the spike counts and their coarse temporal statistics. Our experimental paradigm, however, does not allow us to determine whether the observed synchronous spikes between neurons (or indeed spike counts) of the individual neurons are actually being used by the nervous system. Both these signals contain directional information, and they may be used in separate ways to "tag" movement direction for subsequent or ongoing processing. It is clear that the postsynaptic impact of synchronously arriving events is considerably more powerful than spikes that are temporally dispersed. The synchrony we observed may be more significant physiologically in directional coding than the firing rates of individual neurons. Therefore one cannot equate the redundancy in the abstract information sense with physiological relevance. Indeed, it is possible that synchrony we observed is created to increase the functional impact of the elevated firing rates. The synchrony (as measured

by the number of spikes within ±0, 1, 2, or 5 ms) does not, however, add information that is unavailable from the firing rates (the spike counts from each of the neurons in the pair) assessed from windows ranging from 50 to 1,000 ms.

### *Modeling synchronous spikes between motor cortical responses*

We predicted numbers of synchronous spikes using the coarse temporal statistics within and between individual MI neurons. To do this we extended the spike count matched model (Oram et al. 1999) to include the responses of a pair of neurons. The extended SCM model incorporates the observed spike count distribution of the individual cells and thereby includes the within response correlation induced by deviation from a Poisson process (see Oram et al. 1999 for discussion). By matching the spike counts of each recorded pair of responses on a trial-by-trial basis, the extended SCM model implicitly includes both linear and nonlinear coarse temporal correlation between the spike counts of the individual neurons. While we could have calculated the standard co-variance measure and assumed a multidimensional Gaussian distribution of spike count, the method adopted makes fewer assumptions about the coarse temporal statistics and was therefore more appropriate for assessing relationships between observed coarse and fine response statistics. It is also known that the numbers of synchronous spikes depends on the "shape" or profile of responses (Aertsen and Gerstein 1985; Lestienne and Tuckwell 1998; Oram et al. 1999). The SCM model incorporates the response profiles of each neuron by using the SDF (Oram et al. 1999), and the extended SCM model used here incorporates not only each SDF but also any co-variation between the two SDFs.

With inclusion of a linear adjustment, the SCM model generally predicted the mean number of synchronous spikes for all directions. The variability in the synchronous spikes is large compared with the range (Fig. 8), and therefore the differences in mean spike counts over different directions when the range is small is likely due to noise. Thus those cases where the model did not predict the mean number of synchronous spikes can be attributed to the effects of the high variability in the trial-by-trial numbers of synchronous spikes (Fig. 12). Thus a parsimonious explanation of these data are that the synchronous spikes above chance levels are directly related to the spike counts and their correlation. The model does, however, require a different scaling factor for each cell pair. The variability in the number of synchronous spikes with direction of arm movement (Figs. 7 and 8) indicates the presence of a "tuning curve" for the synchronous spikes with direction. In predicting the variability in the number of synchronous spikes, the SCM model generates the correctly shaped tuning curve: all that is missing is the amplitude of the tuning curve. The SCM model therefore can be thought of as providing a normalized tuning curve. Thus while the absolute numbers of synchronous spikes are not accounted for by the model, the variation in the numbers of synchronous spikes between different directions are directly related to the firing rates and their correlation. As the variation in numbers of synchronous spikes with direction is predictable from the coarse temporal characteristics of the responses, the number of synchronous spikes cannot carry any information about the direction that is not present in the coarse temporal characteristics of the responses. While the excess of synchrony could be used to provide a code giving information about aspects of behavior not studied here, it will be essential to incorporate concurrent changes in the coarse temporal characteristics of the responses for these conditions.

### *Excess synchronous spikes and information*

Despite incorporating the coarse temporal correlation between and within the responses, the extended spike count matched model consistently underestimated the number of synchronous spikes found in the neural data (Fig. 11). Closer examination revealed that the SCM model underestimated the observed number of synchronous spikes by a scale factor that was constant across directions of movement (Fig. 13). Had we examined data from just two directions, we would have noted that the excess synchronous spikes depended on the particular direction but could not have observed that the excess was in proportion to the expected number. The scaling factor suggested that the numbers of synchronous spikes in the neural data were approximately 1.4 times the number expected by chance for all directions of arm movement.

The observed excess of synchronous spikes does not, by itself, support the hypothesis that synchronous spikes have a special role in directional coding. When a constant scaling factor for each neural pair is incorporated, the extended SCM model accounted for >90% of the variability on average ($R^2 = 0.93 \pm 0.05$, mean ± SE) in the absolute numbers of synchronous spikes to different arm movement directions (Fig. 13). Thus there is a small amount of total variability (<10%) in the number of synchronous spikes that is not explained by the differences in spike counts between directions of arm movement. It is only this residual variability that could carry directional information unavailable from spike count. Hence it is not surprising that the information theoretical analysis indicated that the directional information carried by synchronous spikes was redundant with the information carried by spike count (Fig. 10). The lack of additional information about movement direction added by synchronous events was found for all pairs and therefore holds for those pairs with both small and large numbers of synchronous spikes, both in terms of absolute numbers of synchronous spikes and in terms of the excess of synchronous spikes above chance levels. This, combined with the sensitivity of the measure (a change of 0.02 bits being deemed significant) leads us to conclude that our findings are not a "false-negative" but reflect a genuine lack of a unique role for most or all synchronously occurring spikes in coding directional information.

### *Excess synchronous spikes and functional connectivity*

It is natural to consider possible structural or anatomical explanations for this mismatch between the observed synchrony and that predicted by the statistical SCM model. In general, the mechanism driving the excess of synchronous spikes seen in the neural data increases its effectiveness with increasing expected numbers of synchronous spikes (Fig. 11). [In those cases where the model does not predict the variability in the numbers of synchronous spikes, there is little variation present and the low $R^2$ value can likely be attributed to sampling error (Fig. 12).] As the number of synchronous spikes

increases with the spike count (Fig. 9 and Table 2), the mechanism driving the excess of synchronous spikes rises with the spike counts. In other words, for most of the cell pairs it is not possible to distinguish between the inputs driving the neural activity and the mechanism that gives rise to the synchronous spikes above the number expected by chance. We note that the presence of a single scaling factor from the SCM model for each neural pair shows that a variable amount of excess in the numbers of synchronous spikes with direction does not necessarily imply changes in the relationships between the neurons. We have shown here that data from several conditions is needed before being able to conclude that an excess of synchronous spikes, or indeed any precisely timed spike pattern, reflects dynamic changes in the relationships between neurons.

One possible explanation for the observed excess in synchrony may be that it is a natural consequence of a network of mutually interconnected neurons. There is anatomical evidence that neurons in motor cortex are highly interconnected via horizontal connections (Donoghue et al. 1996; Huntley and Jones 1991). Moreover, functional studies have shown that motor cortex, unlike primary sensory cortices, exhibit distributed patterns of activation with very little somatotopy (Sanes et al. 1995; Schieber and Hibbard 1993), consistent with the anatomically demonstrated extensive interconnectivity (Huntley and Jones 1991). A number of neural modeling studies have shown that neurons with mutual interconnections can engage in synchronous firing, particularly if one or more of the component cells are oscillatory (Bush and Sejnowski 1996; Engel et al. 1991a,b; Hansel 1996; White et al. 1998). However, such networks engage in synchronous firing patterns in ways that do not necessarily predict a linear increase in the excess synchrony with the background firing rate.

Another possible explanation for the excess of synchronous spikes is common driving input from a cell or population of cells. Consider a pair of neurons, each with their own set of inputs, and a further neuron (or population) that is connected directly to each of the pair. Assuming this input represents the entire source of synchronous spikes above chance levels and that the synaptic strength of this input is constant within the experimental period, it follows that the excess of synchronous spikes above chance levels will be determined solely by the activity of this input. The more active this input neuron is, the greater the excess of synchronous spikes. This would give rise to the excess over chance levels rising with the number of observed synchronous spikes and is precisely what was observed (Figs. 11–13). This argument explains our data only if the postulated common input mechanism co-varied with the other inputs to the cells. It is possible to imagine two cells with common preferred directions (say 90°) and common input being greatest for another direction of arm movement (say 270°). The largest number of synchronous spikes could then occur at 90° because of the high activity of both cells, but the greatest number of unexpected synchronous spikes would be at 270°. This was not seen in our data. Hence the argument based on common input with fixed functional connectivity that covaries with the other inputs is consistent with the data. A puzzling aspect of the "common input" hypothesis, however, is that pairs of cells at a distance from each other almost always show a zero lag correlation. That is, there is little evidence of cross-correlations between distant cortical cells with short lags indicative of monosynaptic driving of one cell onto another.

Recent computational studies provide further insight into how a fixed functional connectivity between neurons and neural populations could give rise to the results we observed. Chawla and colleagues (Chawla et al. 1999) have shown, using both integrate and fire models and models based on Hodgkin-Huxley equations, that changes *1*) in the strength or number of inhibitory connections, *2*) the strength or numbers of excitatory connections, or *3*) changes in the time course of the synaptic connections can all influence the relationship between the numbers of synchronous spikes and firing rate. Changes or variation in these parameters with experimental condition would therefore allow information unavailable from the spike count to be carried by the synchronous spikes. For constant values relating to *1–3* above, they found their models indicated that the number of synchronous spikes above chance levels increased with increasing firing rates of the interconnected populations, but the synchronous spikes could not carry information beyond that available from the spike count and coarse temporal correlation (Chawla et al. 1999). The analysis of our motor cortical data also shows that the number of synchronous spikes above chance levels typically increased with increasing firing rates and that the synchronous spikes did not carry information beyond that available from the spike count and coarse temporal correlation. Thus our data are consistent with a network that, under the experimental variations used (see METHODS), showed *1*) no change in in the strength or number of inhibitory connections, *2*) no change in the strength or numbers of excitatory connections, or *3*) no change in the dynamics of the synaptic connections.

### *Summary*

In summary, because the responses of individual motor cortical neurons are not well described by a Poisson process, they must contain temporal structure (correlation). Furthermore, the responses between different neurons assessed at coarse time scale are correlated. Even though we included these sources of correlation in our calculations, there was a clear excess of synchronous spikes seen in our data. However, we found no evidence that the synchronous spikes carried information related to direction of arm movement above that available from the spike counts and their correlation. These issues highlight the difficulties in interpretation of cross-correlograms from nonstationary data. It is important to note that current methods make it practical only to examine synchrony among cell pairs. There is no reason to believe that there is particular significance of our randomly selected cell pairs; the cortex may operate using very large numbers of cooperating elements. These may create synchrony occurring across various collections of cells that we have inadequately sampled. Our experiments do not rule out the possibility that larger groups of cells provide considerable information about direction or other aspects of movement, beyond that found in rate alone. Despite these caveats, our results show conclusively that detection of an excess of synchronous spikes above chance levels does not imply that the synchronous spikes carry information unavailable from spike count. It remains to be seen whether synchrony or any

other relational code among motor cortical neurons carries information about other aspects of movement planning and execution.

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