LETTER

Reply from C. L. Witham and S. N. Baker

We thank Drs Schouten and Campfens for their interest in our paper. We are more optimistic about the practical capabilities of directed coherence than the position they adopt in their letter, but we would also emphasise the need for caution in using these methods.

At the basis of directed coherence (Granger causality) methods is an autoregressive model of the signals of interest. For the bivariate case, this can be expressed as:

$$x_i(t) = \sum_{n=1}^{N} \sum_{j=1}^{z} A_{ij}(n) x_j(t-n) + \varepsilon_i(t)$$

Where $x_i(t)$ is signal i measured at time index t. The matrix A, which varies as a function of time lag n, represents the ability of the past history of each signal to predict the present values. A_{11} measures how well x_1 is predicted by its own past history – this will be influenced by any periodicity in the signal (its autocorrelation). A_{12} tells us how much better we can predict the current value of x_1, if we know not just its own past history, but also that of signal x_2. Measures of directed coherence use the A_{12} coefficients – suitably transformed to the frequency domain, and normalized – to estimate whether there is a causal influence from x_2 to x_1. The term 'causal' is used because we analyse only the ability of the past history of the two signals to predict the present value. Finally, the term ε_i represents the component of x_i which cannot be predicted from any previous values. In the autoregressive literature, ε is sometimes referred to as the *innovation* – that component of x which is novel (i.e. unexpected given its past).

Schouten and Campfens are formally correct when they point out that the transfer functions determined from directed coherence will refer to the closed loop case, and are not necessarily applicable to the open loop condition. As so often in physiology, the complexity of the systems we study forces us to use analytical methods outside their formal realm of applicability. Rather than give up on quantitative analysis altogether, we believe it is reasonable to use methods in circumstances which are less than ideal; however, it is then beholden on the experimenter to keep a keen eye on what types of errors might result.

How will the existence of a closed loop system modify the transfer function extracted by directed coherence? To examine this, we modelled the simple system illustrated in Fig. 1*A*. Signal 1 was a mixture of signal 2 (delayed by 20 ms) and a white noise source. Signal 2 was a mixture of signal 1 (also after a 20 ms delay) and a second white noise source (independent from the noise source contributing to 1). By adjusting the weights $k_{1\to2}$ and $k_{2\to1}$, we could modify the strength of coupling in each direction around this loop. The expressions giving the relative weighting of the noise and feedback were chosen to make the directed coherences equal to the corresponding weights k.

Figure 1*B* shows the directed coherence and associated phase in the 1→2 direction, in the situation where $k_{1\to2} = 0.1$, and $k_{2\to1} = 0$; this is the open loop condition. As expected, the calculated directed coherence was close to 0.1 at all frequencies. Directed coherence for the 2→1 direction (not shown) was close to zero. The phase–frequency plot showed a linear relationship; the regression fit yielded a slope indicating a delay of 19.8 ms, close to the true value of 20 ms.

We next ran a simulation for the symmetric closed loop system $k_{1\to2} = k_{2\to1} = 0.1$; directed coherence and the associated phase are shown in Fig. 1*C*. The results seem little affected by the presence of the closed loop situation; once again the directed coherence was approximately 0.1; the linear fit to the phase–frequency relationship indicated a delay of 19.8 ms. By eye a very slight systematic deviation from linearity was visible, although this had negligible impact on the r^2 statistic (0.9996 *versus* 0.9999 for Fig. 1*B*).

The analysis began to yield subtly different results if we increased the strength of feedback; Fig. 1*D* presents analysis for $k_{1\to2} = k_{2\to1} = 0.5$. Although the directed coherence correctly identified the strength of the coupling, the phase showed marked deviations from a linear relationship. The periodicity in the phase–frequency relationship reflects oscillations of different frequencies undergoing positive or negative feedback (resonance or cancellation) around the closed loop. Despite this, it was striking that a linear fit to the phases – however ill-warranted it might appear from the data points – yielded a delay estimate of 19.4 ms, once again in close agreement with the true value.

The directed coherence phase departed even more strongly from a linear dependence on frequency in a simulation where $k_{1\to2} = k_{2\to1} = 0.9$ (Fig. 1*E*), although again a linear fit produced a delay estimate quite close to the actual value (18.9 ms).

The reason why the effects of closed loop feedback depend on loop gain are easily grasped intuitively. The presence of a closed loop offers the potential for 'echoes'. A given noise innovation in signal 1 will contribute to signal 2 directly with strength $k_{1\to2}$; but it will also influence 2 indirectly via its first echo around the loop (1→2→1→2) with a magnitude $k_{1\to2}{}^2\ k_{2\to1}$. The relative contribution of the first echo compared with the direct effect will hence be $k_{1\to2}k_{2\to1}$. In a situation where the directed coherence in each direction is 0.1, the echo will have only 1% of the impact of the direct connection. This is so close to the open loop condition as to be practically indistinguishable (Fig. 1*C*). Only when the coupling coefficient becomes quite large can the effect of the closed loop be discerned. In our application of directed coherence to corticomuscular coupling, values of directed coherence were almost all <0.1. Any echoes would be predicted to be <0.001; in comparison the significance limit on the directed coherence was usually in the range of 0.005 to 0.01. Concerns about the validity of our results based on the presence of closed loop feedback therefore seem unjustified.

Schouten and Campfens suggest that the delays which we estimated from directed coherence were larger than expected based on results from stimulation. However, our previous computational modelling showed that delays estimated from the coupling of endogenous oscillations should not be directly comparable with those measured by the onset latency of stimulus-evoked effects (Williams & Baker, 2009*a*), even for an open loop. In human subjects using non-invasive EEG recordings, our delay estimates agree well with what we would expect from the known conduction times given these considerations (Witham *et al.* 2011). By contrast, our previous publication using invasive local field potential (LFP) recordings in monkeys estimated substantially longer delays than expected

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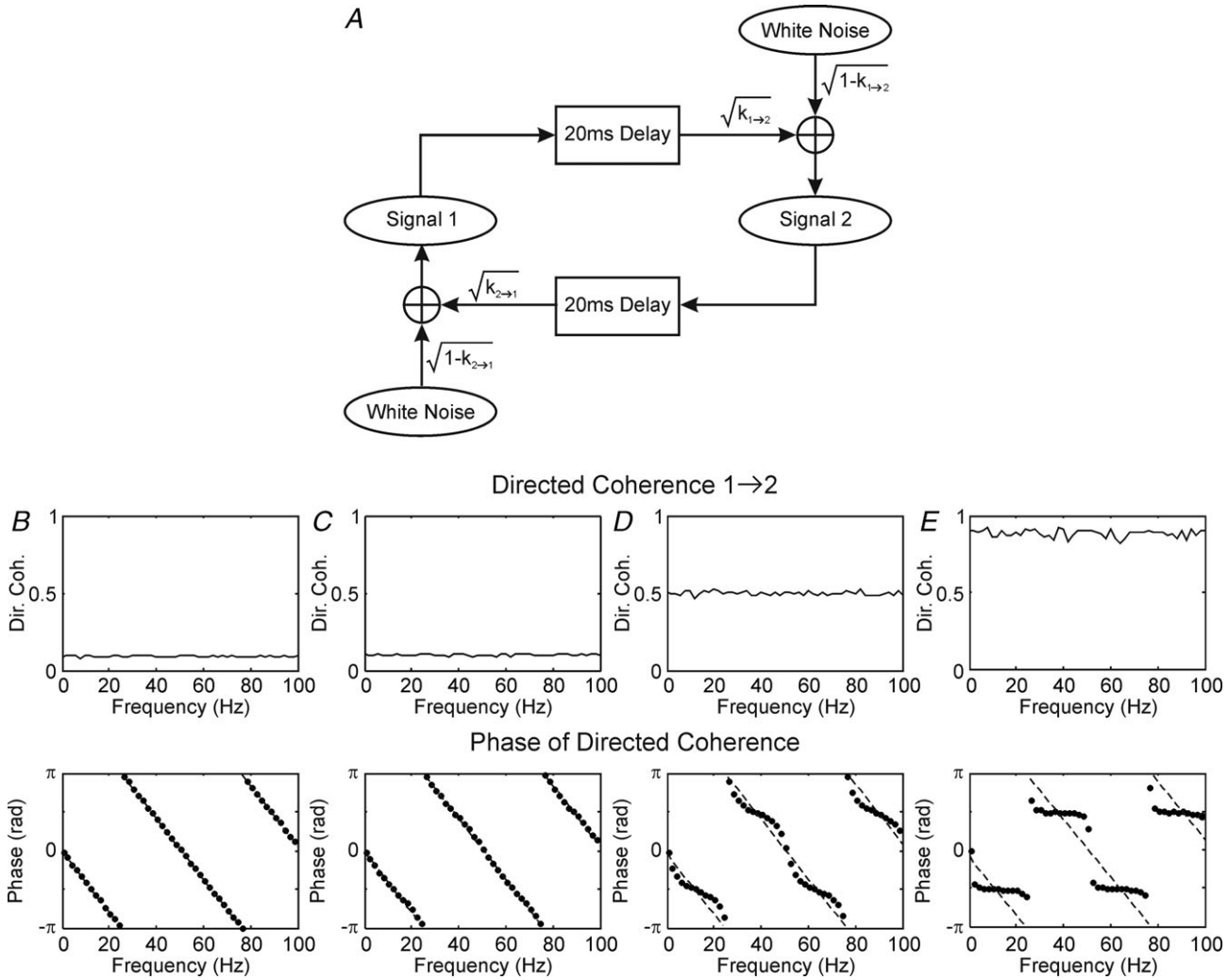

Figure 1.
A, model system used to test effects of a closed loop on directed coherence measurements. *B–E*, directed coherence in the 1→2 direction, and the associated coherence phase, for different simulations of the model in *A*. *B*, $k_{1\to2} = 0.1$, $k_{2\to1} = 0$. *C*, $k_{1\to2} = k_{2\to1} = 0.1$. *D*, $k_{1\to2} = k_{2\to1} = 0.5$. *E*, $k_{1\to2} = k_{2\to1} = 0.9$. All simulations were run with a time step of 5 ms (200 Hz sampling rate) for a duration of 2500 s. Dashed lines superimposed on the phase plots represent regression lines, fitted to the unwrapped phase values.

(Witham *et al.* 2010). The reason for this discrepancy remains unknown, although we did speculate on a possible explanation in Witham *et al.* (2011).

There is thus reason to be optimistic that directed coherence will find a useful place in the analytical armoury of neurophysiologists interested in closed loop systems, where overall loop gains are typically low. However, results from this complex method must never be taken at face value without careful consideration of alternative explanations. Schouten and Campfens state that these methods at least allow us to disentangle causality. In some situations, even this does not work as expected. For example, in our previous study using monkey (Witham *et al.* 2010), we showed significant directed coherence between LFP from primary somatosensory cortex (S1) and EMG. Was this evidence for motor output from S1? Probably not. We also showed that S1 received input from primary motor cortex (M1), at shorter delays than the delay from M1 to EMG. LFP from S1 would therefore contain information on fluctuations in M1 activity, at a sufficiently short time scale to allow prediction of EMG based on the past history of S1 LFP. Significant Granger causality doesn't always indicate causality in the accepted scientific sense.

A second concern with autoregressive methods relates to the assumption that the system under study is linear. Our knowledge of the underlying biology of the nervous system assures us that this is not the case: the central unit of information transfer within the brain is the action potential, generated by thresholding synaptic inputs – a highly non-linear process. As we have argued previously (p. 12, Witham *et al.* 2010), bivariate methods such as coherence or directed coherence are probably less affected by non-linearities. If a connection is identified between two signals, this is very likely to exist, although we may misjudge the strength of coupling (Baker *et al.* 2003). By contrast, multivariate methods such as partial directed coherence rely explicitly on connection strength

estimates for further calculation; this may lead to erroneous conclusions when the assumption of linearity is not met.

Schouten and Campfens end their letter with the hope that new experimental methods may allow assessment of the open loop transfer functions. Their suggestion to use controlled external perturbations is indeed a possibility. We have also recently taken a similar approach, delivering electrical stimuli to peripheral nerves as Poisson processes, and analysing the response of the monkey cuneate nucleus using coherence (Witham & Baker, 2011). The method has been previously used to investigate Renshaw cell responses to motor axon stimulation, also an important closed loop within the motor system (Laouris & Windhorst, 1989). Although applying external stimulation may be an improvement on using correlative measures of endogenous activity, it should be emphasised that responses measured by such techniques will still be closed loop responses. As described above, given the low loop gain this practically makes little difference. Analysing responses in situations where one of the component pathways has been lesioned is the only experimental way to measure pure open loop transfer functions. An alternative, which can yield considerable insight, is to simulate realistic computational models, in which feedback loops can be opened at will (Williams & Baker, 2009*a*,*b*).

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