Using a network model to explain oscillatory spike firing patterns and study signal processing in the ventro-medial nucleus of the hypothalamus

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Introduction

The ventromedial nucleus (VMN) of the hypothalamus is one of the main regulators of feeding and sexual behaviour. The neurons respond to several different signals including ghrelin, leptin, cholecystokinin (CCK), and glucose. The VMN contains a heterogeneous neuronal population, of differing biochemical and electrophysiological identities.

Investigation by recording the *in vivo* firing activity, and examining spike patterning using inter-spike interval (ISI) histograms and hazard functions has identified approximately eight different subtypes. The most intriguing of these show a distinct 3Hz oscillation, detected as a series of ~300ms spaced modes in the ISI histogram. The current project develops a simple network model to show how such a pattern might be generated. We then use the model to test the signal processing properties of these neurons that might relate spike patterning to physiological function.

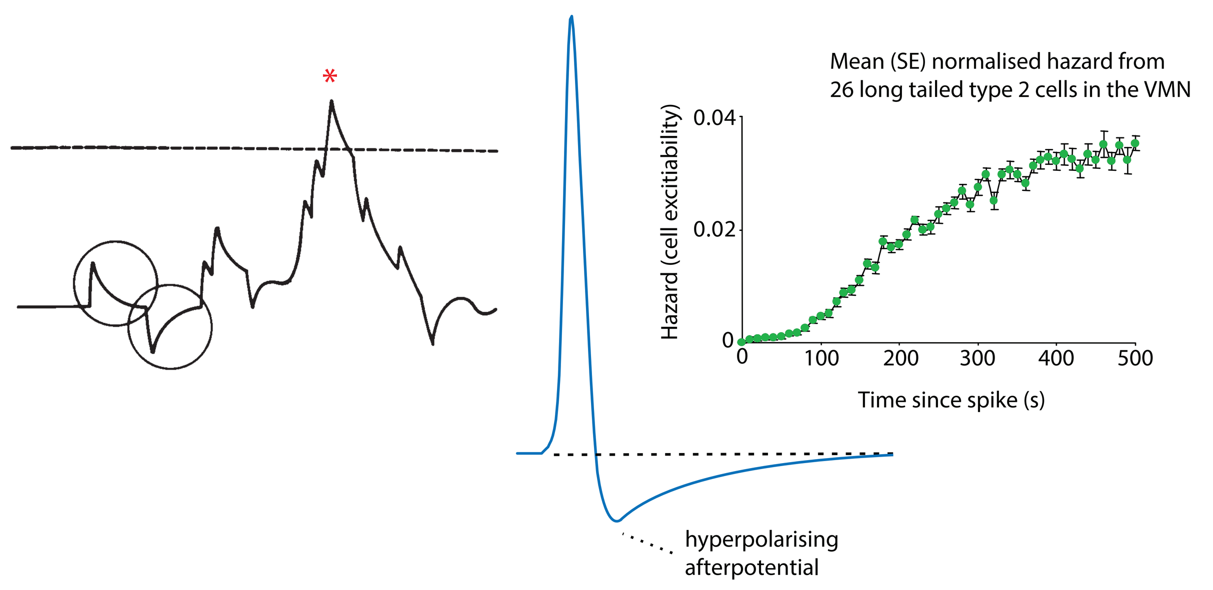

Figure 1 : Model simulated excitatory and inhibitory PSPs summate and trigger a spike when the sum (the membrane potential) crosses the spike threshold (left). Following the spike an HAP is simulated by a decaying exponential (middle). Here we show a particularly slow one, sufficient to match the long (> 300ms) refractory period observed in some of the VMN neurons (right).

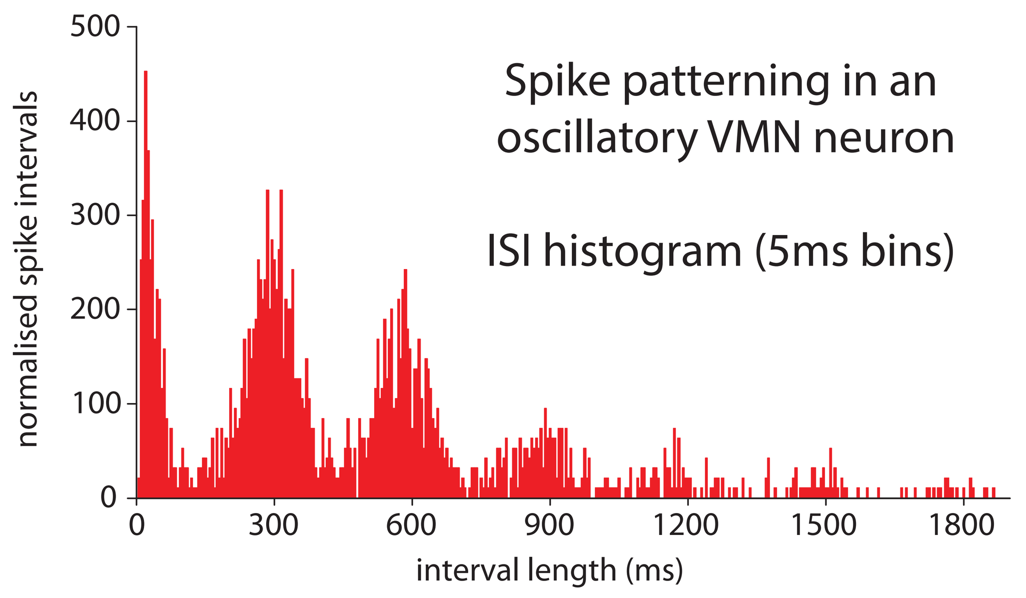

Figure 2 : An example oscillatory VMN neuron (Sabatier and Leng 2008). The ISI histogram shows a distinct series of peaks at ~300ms intervals suggesting an underlying 3Hz rhythm. The early very short interval peak may correspond to the doublet firing observed in other non-oscillatory VMN neurons. The well defined peaks suggest a rhythmic input which is necessary but not sufficient to trigger spike firing.

Modelling the Network

The model uses a network of modified 'integrate and fire' neurons. These produce a series of spikes comparable to the *in vivo* extracellular recordings, and simulate post-spike potentials such as the hyperpolarising afterpotential (HAP). Such models can already match the firing patterns of vasopressin and oxytocin neurons very closely (MacGregor et al 2009). External input is a random series of mixed excitatory and inhibitory post synaptic potentials (PSPs), modelled as exponentially decaying perturbations to the membrane potential.

The network is generated by allowing each neuron a chance to form a synapse with each of the others, using some defined probability (usually 0.6). When a neuron fires it has a chance to generate an input PSP at each of the neurons it connects to, controlled by a synaptic transmission probability (usually 0.5). Two distinct cell types use a slow and a fast HAP, based on types detected *in vivo*. Neurons thus vary both in the input they receive, and in their intrinsic excitability.

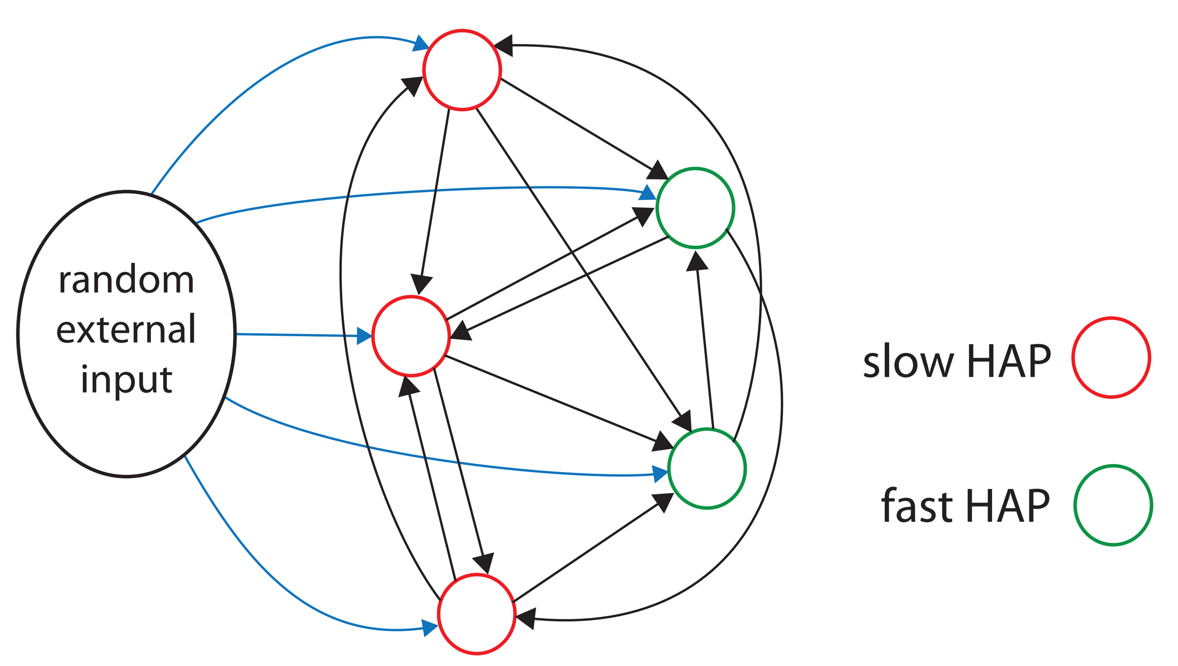

Figure 3 : Schematic of the network model. The neurons form a network with random sparse excitatory connections and also receive a random external input. The model uses two distinct cell types, one with a slow and the other with a fast HAP. The slow HAP cells synchronise to generate a 3Hz rhythm. This forms an input to the fast HAP cells which produce a pattern matching the *in vivo* oscillatory cells in response.

A Two Cell Type Network

The slow HAP cells are required to generate the 3Hz oscillation, but they can't match the short interval peak observed in the oscillatory cell, and so we use a second cell type with a fast HAP that takes the 3Hz signal as input. These fast HAP cells then show a good match to the oscillatory cell. This also removes the need for random variation in cell parameters. Synaptic noise is added (random transmission latency and failure) to make the network less tightly synchronised with more sinusoidal activity.

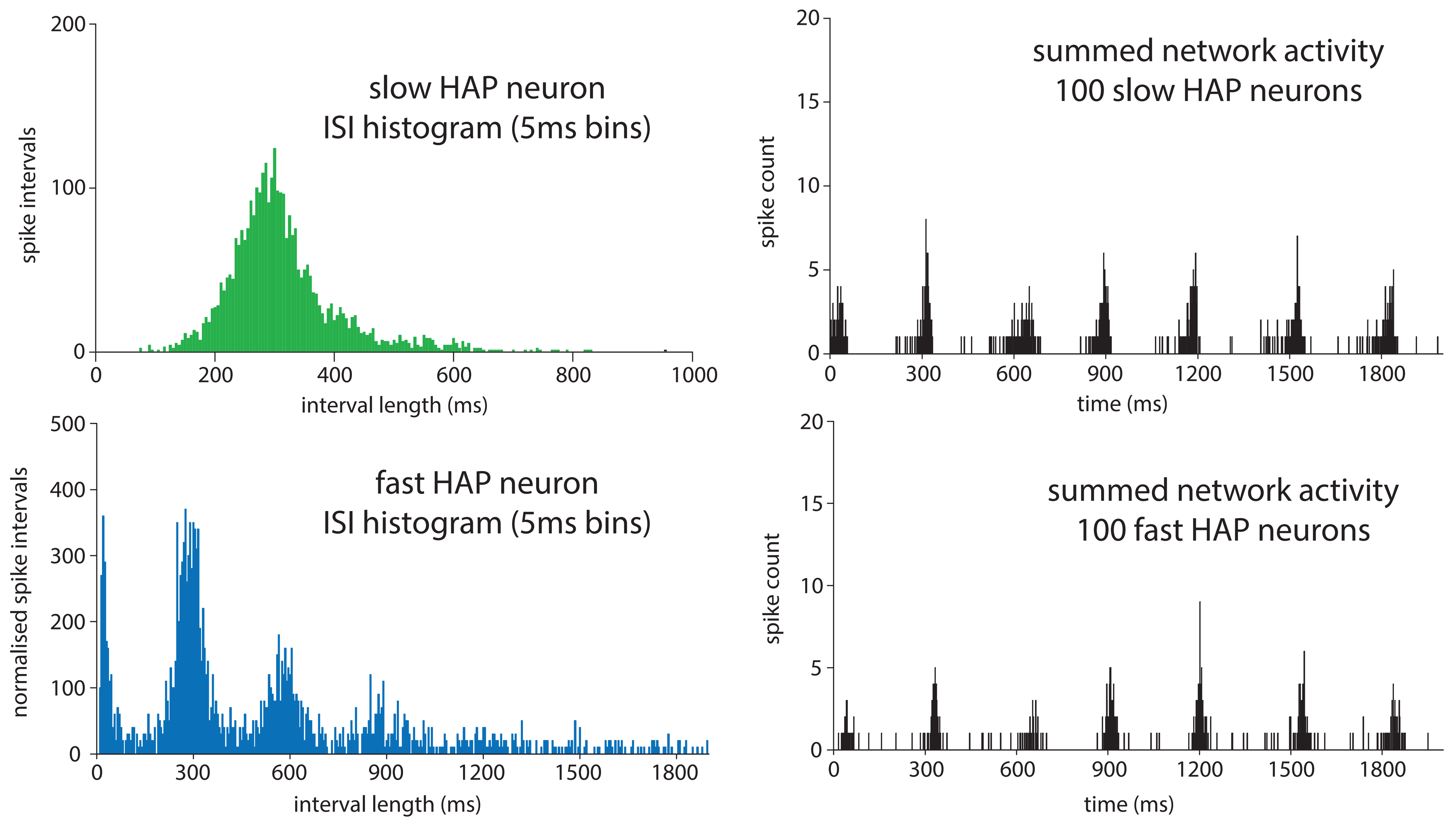

Figure 4 : 3Hz rhythm generated intrinsically by a mixed cell type sparsely connected network. This uses a mixture of slow HAP (mean 60ms half life, 100 neurons) and fast HAP (5ms half life, 100 neurons). The neurons are randomly connected (0.1 to 0.7 chance of forming a synapse). The ISI histogram for the fast HAP neurons shows similar 300ms spaced peaks to the recorded oscillatory neuron. The slow HAP neurons (not shown) show a similar histogram to other types of recorded cell. The summed network activity over the slow HAP neurons shows a wavelike synchronisation similar to a sinusoidal input.

Signal Processing - Network Input-Output Response

The response of cells in the network which are receiving the majority of their input from within the network is dependent on synchronisation as well as frequency. The duration of the slow HAP sets an optimal input rate for synchronisation. We explored this by adding a third cell type (simulating some cell receiving the output of this network as input), with the same parameters as the fast HAP cells, receiving the oscillatory fast HAP cell activity as input. We tested the firing rate response to a range of input rates applied to the slow HAP cells, assuming that these cells receive the external input signal.

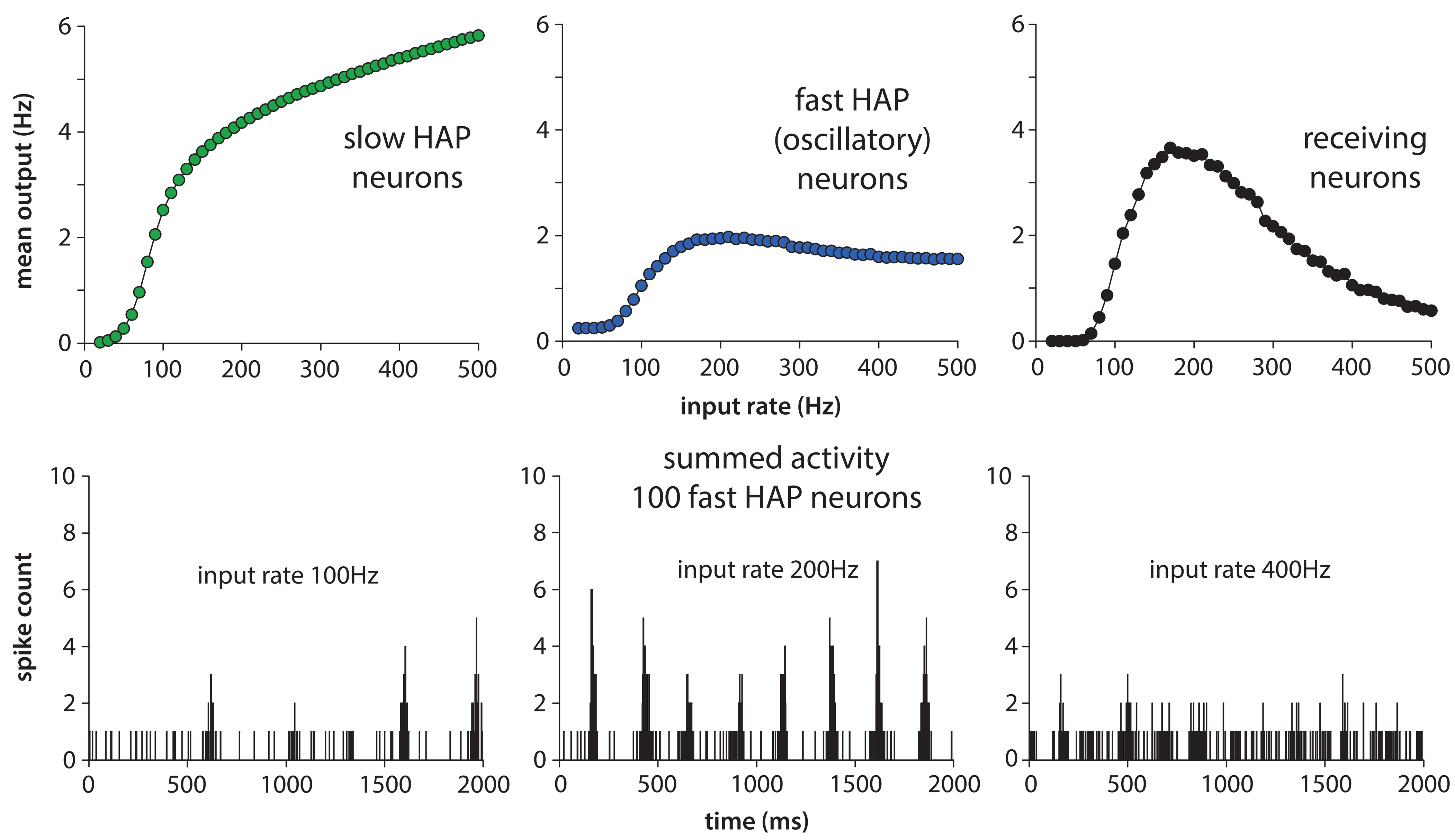

Figure 5 : The top row shows the mean output rate in response to increasing rates of input for the slow HAP neurons, the oscillatory fast HAP neurons, and neurons receiving oscillatory cell output as input, using a network with 100 neurons of eavch type. The bottom row shows example summed activity in the oscillatory neurons, forming the input to the receivinbg neurons. The increased synchronisation at 200Hz input produces the peak response.

Conclusion

The 3Hz oscillatory firing pattern can be generated by a mixed network of slow HAP neurons (synchronising to generate the 3Hz rhythm) and fast HAP neurons (taking the rhythmic activity as input to produce the oscillatory peaks). The input rate dependent synchronisation produces varied signal responses between cell types. The summed output from the oscillatory cells produces a highly biphasic response in receiving cells.

References

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Sabatier N., and Leng G. (2008) Spontaneous discharge characteristic of neurons in the ventromedial nucleus of the rat hypothalamus *in vivo*. European Journal of Neuroscience **28**: 693-706