Using a single cell model to explain oxytocin neurons ability to reliably report absolute long term levels of gut peptides involved in satiety.

Jorge Maícas Royo, Duncan J. MacGregor and Gareth Leng

Centre for Integrative Physiology, University of Edinburgh, UK

Introduction

In analysing the firing patterns of oxytocin cells in the supraoptic nucleus (SON) we noticed an unexpected feature: the mean firing rate at large binwidths is much less variable than expected from the variability at small binwidths, implying a structure in their activity that "smooths out" perturbations in activity. We have used computational modelling to determine whether this can be explained by the after-hyperpolarising potential (AHP), and if the AHP role in oxytocin cells is thus to help produce a relatively stable firing rate. However, a model of oxytocin neurons with an AHP and hyperpolarising after-potential (HAP) was not able to match both this behaviour and the interspike interval distribution. Our new model solves this by adding equations for a depolarising after potential (DAP). To test the role of the AHP with this new model, we matched recordings of five oxytocin cells exposed to apamin, a blocker of the AHP, at two concentrations. With the new model we obtain good matches for the five cells by varying only the AHP amplitude and the synaptic input rate.

Fig. 1. Oxytocin cell recording. To be sensitive to small changes, oxytocin cells will respond to almost everything that comes. They also respond to the noise that is always present in the brain. In fact, oxytocin spike activity seems at first sight quite irregular.

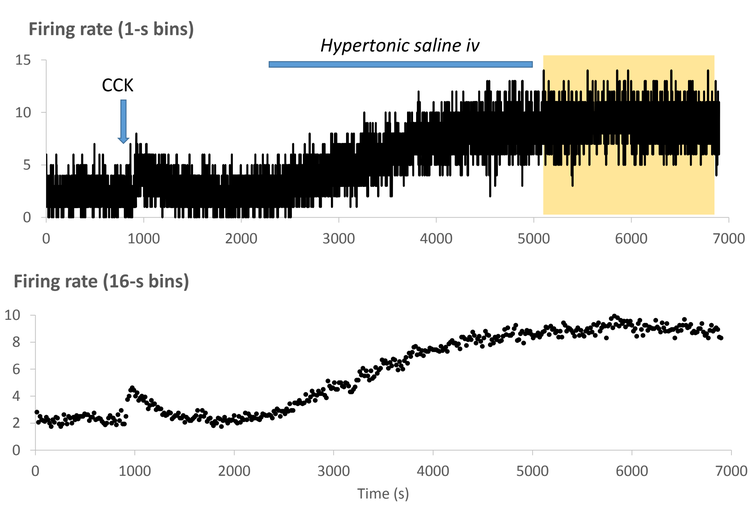


Fig. 2. These two images both represent the same oxytocin cell recording. During that recording, the gut peptide CCK, and hypertonic saline were injected intravenously. The only difference between the graphs is that, in the top one we are averaging the firing rate of the cell every second. In the bottom graph we are taking the average every 16s. We can see how noisy the first one is, and how clearly the second one shows the underlying signal: how the firing rate changes in response to the CCK and the saline.

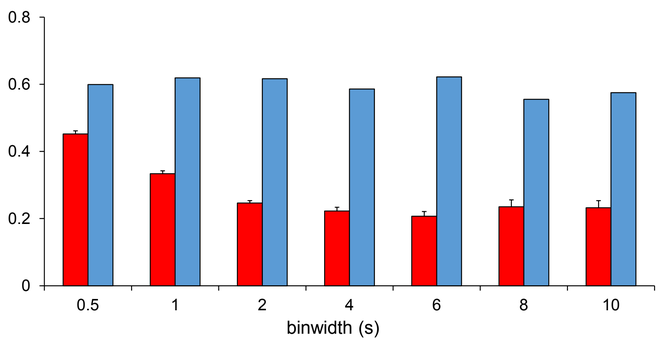
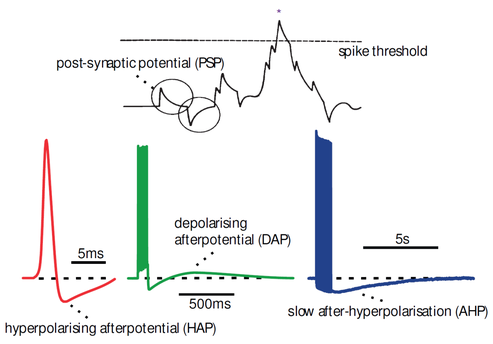


Fig 3. The index of dispersion measures variability. For random events it equals 1 and is independent of bin width. The data here uses 3000s of recording of the same cell firing at 12.9 spikes/s after the end of infusion (yellow shaded area in Fig. 2). The index of dispersion was measured every 250s at different binwidths (0.5,1,2,4,6,8,10 s), and the blue bars show the mean (SE) index of dispersion at each binwidth (n=12). The blue bars show the index of dispersion for shuffled data from this cell: the intervals recorded over each 3000s period were randomly shuffled, and the index calculated for the shuffled data. At all binwidths, the index of dispersion for the raw data is lower than that for the shuffled data, and it declines with increasing binwidth

The Model

Our models seek to match data from oxytocin cells in vivo. Oxytocin membrane potential depends on the contributions, excitatory or inhibitory, of the synaptic afferences the cell receives.



When the membrane potential reaches a threshold, a spike is produced, and the oxytocin cell reacts to the spike with 3 different kinds of currents* (Fig 4).

In our new model a DAP has been added.

Fig 4. Oxytocin membrane currents. The hyperpolarising afterpotential is the quickest and strongest. After a spike, it makes the membrane unable to fire again for tens of milliseconds. The depolarising afterpotential has the opposite effect, but it needs the contribution of several spikes to occur. When that happens, it increases excitability for around half a second, encouraging bursting. Lastly, is another hyperpolarising current, the AHP. This is the slowest one and it needs the contribution of many spikes happening close to each other to have a noticeable effect. It is this one that may have the explanation for why oxytocin cells are so regular at longer bin widths.

The tools

To test if the model matches the recordings we use statistical tools applied to the spike activity recorded in vivo (Fig. 5).

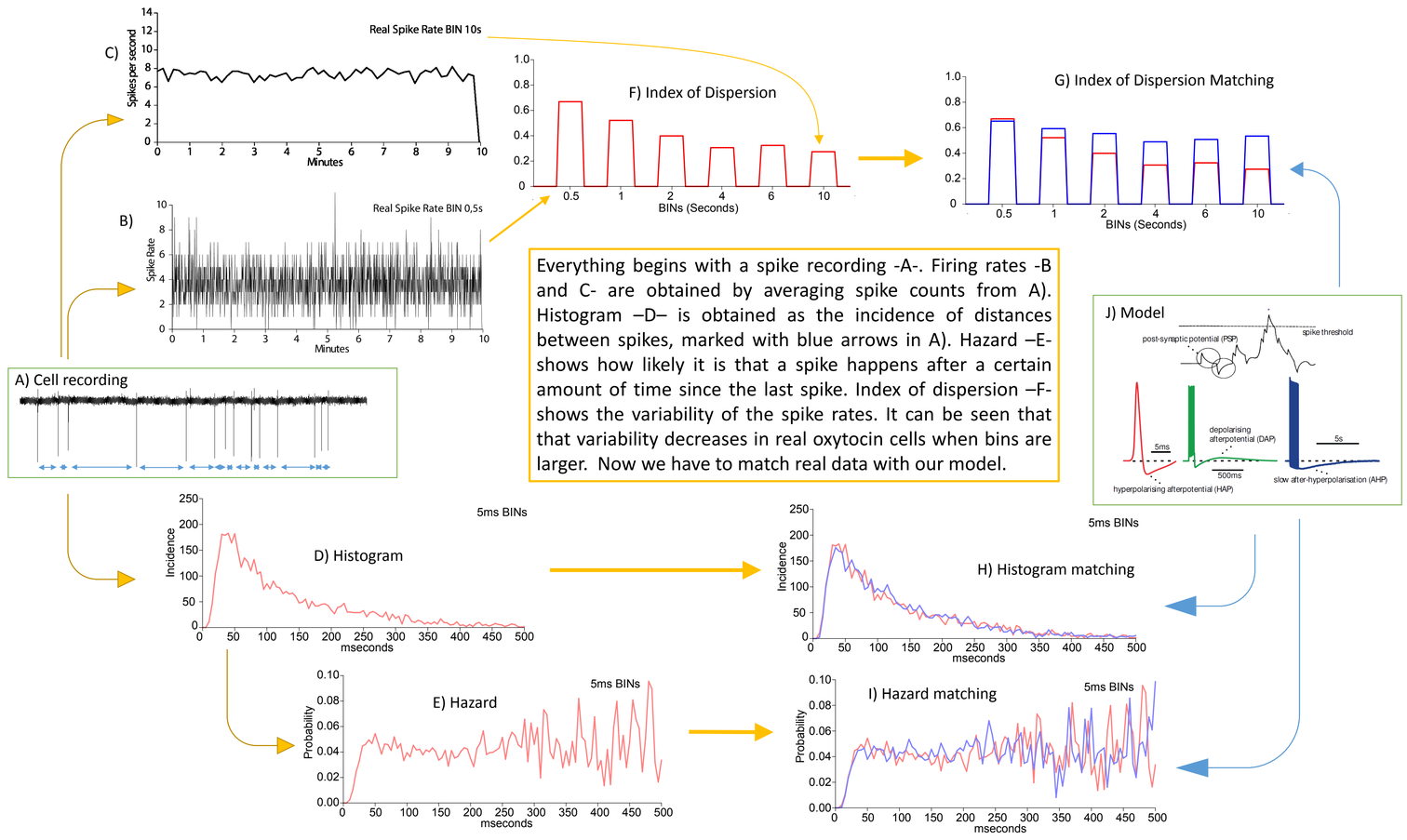


Fig. 5. From our model -J-, that integrates the currents shown in Fig .4, we generate modelled spike times. From them, we obtain –in blue- modelled Index of Dispersion -G-, Histogram –H- and Hazard -I- matching them with the real ones. Note how the matching is good except for the Indexes of Dispersion. That is because we were trying the match with the previous model, without DAP.

Testing the new model

The hypothesis is that the AHP prevents oxytocin cells from bursting for long periods. To test that, we analyse some recordings of oxytocin cells that have been exposed to apamin (Fig. 6). This apitoxin (bee venom) blocks slow conductance (SK) channels, a type of Ca^{2+} activated K^{+} channels which are responsible for the AHP.

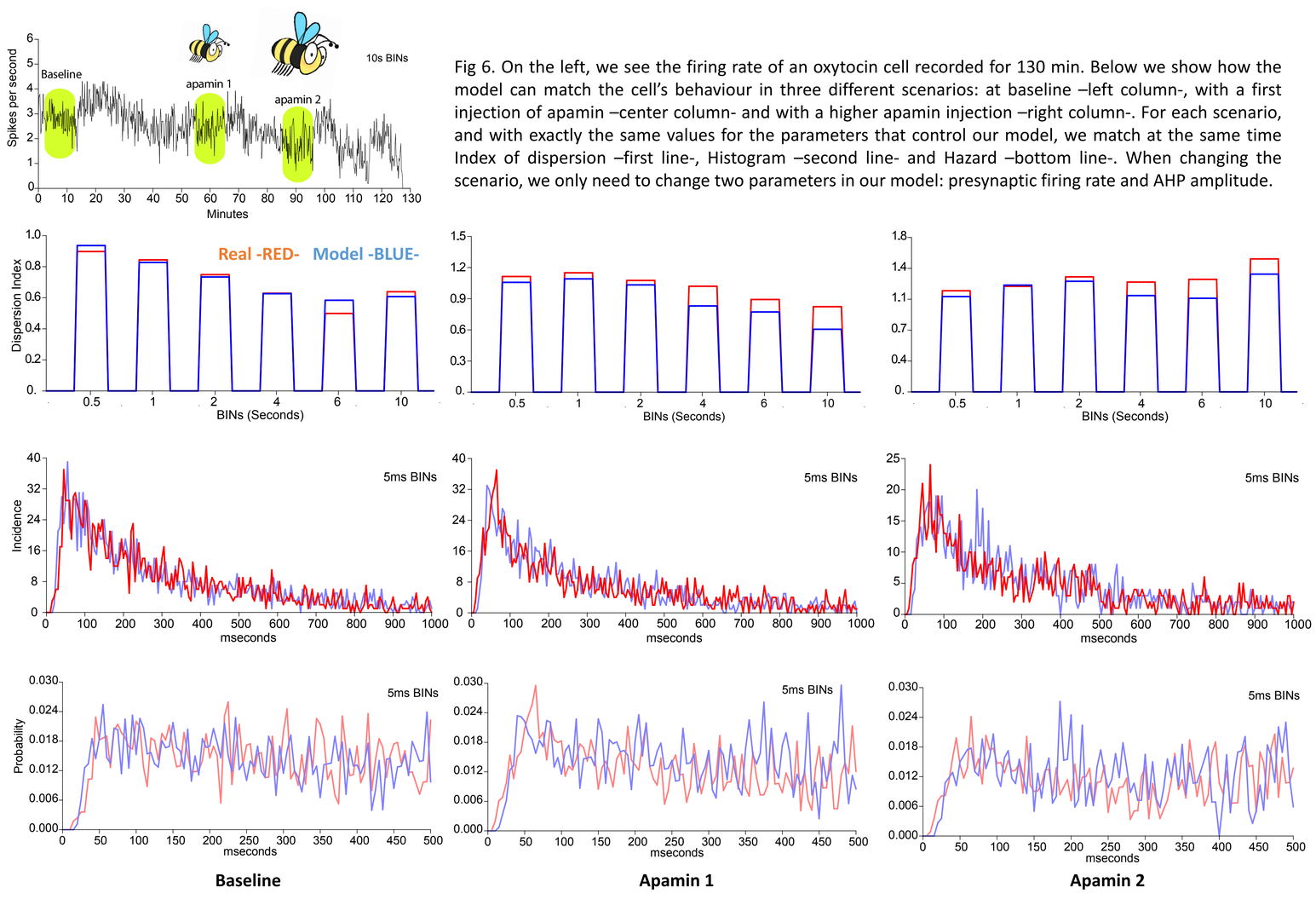


Fig 6. On the left, we see the firing rate of an oxytocin cell recorded for 130 min. Below we show how the model can match the cell's behaviour in three different scenarios: at baseline –left column-, with a first injection of apamin –center column- and with a higher apamin injection –right column-. For each scenario, and with exactly the same values for the parameters that control our model, we match at the same time Index of dispersion –first line-, Histogram –second line- and Hazard –bottom line-. When changing the scenario, we only need to change two parameters in our model: presynaptic firing rate and AHP amplitude.

When present, the AHP reduces the variability of the oxytocin response in the long term. Also it masks the presence of the DAP. Only when we tried to match oxytocin cells injected with apamin we noticed the necessity of the DAP. If we translate this fact into the energy balance functionality, the combination of the DAP and the AHP makes oxytocin cells reliably follow slow changes in the concentration of different peptides produced in the gut, like CCK.

Conclusions

We now have a very accurate model for oxytocin cells.
We have identified how their membrane properties enable them to be very sensitive to small changes in inputs while still having a stable firing rate.
The model is predictive in matching experimental observations when the AHP is blocked

* MacGregor D J, Leng G (2012). Phasic Firing in Vasopressin Cells: Understanding Functional Significance through Computational Models. *PLoS Comput Biol*, 8(10):e1002740.

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