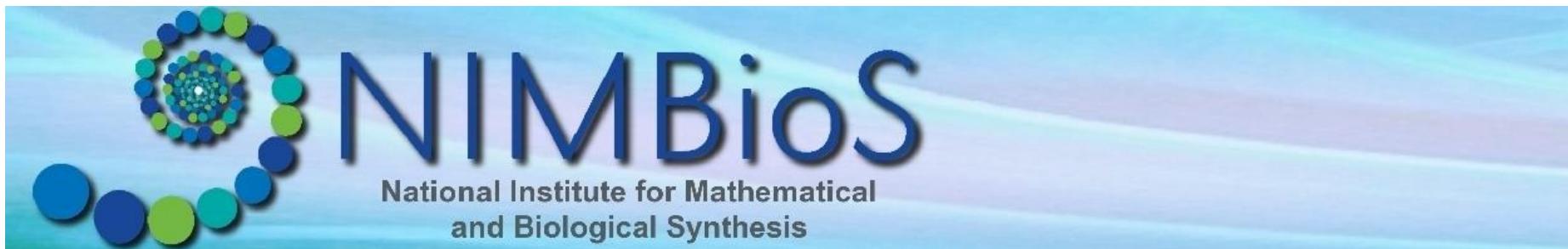


# A Community Mitral Cell Model



**Simon O'Connor,**  
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Olfactory Modeling  
*A NIMBioS Investigative Workshop*  
Organised by  
*Sharon Crook and Brian Smith*  
March 2-4, 2015



# Towards a Community Model

- The idea of a community model of the olfactory system is going to be taken forward by one of the working groups sponsored by NIMBioS that will follow on from the Olfactory Modelling meeting in March 2015.
- The community mitral cell model is a first step with a finite and therefore hopefully achievable goal.

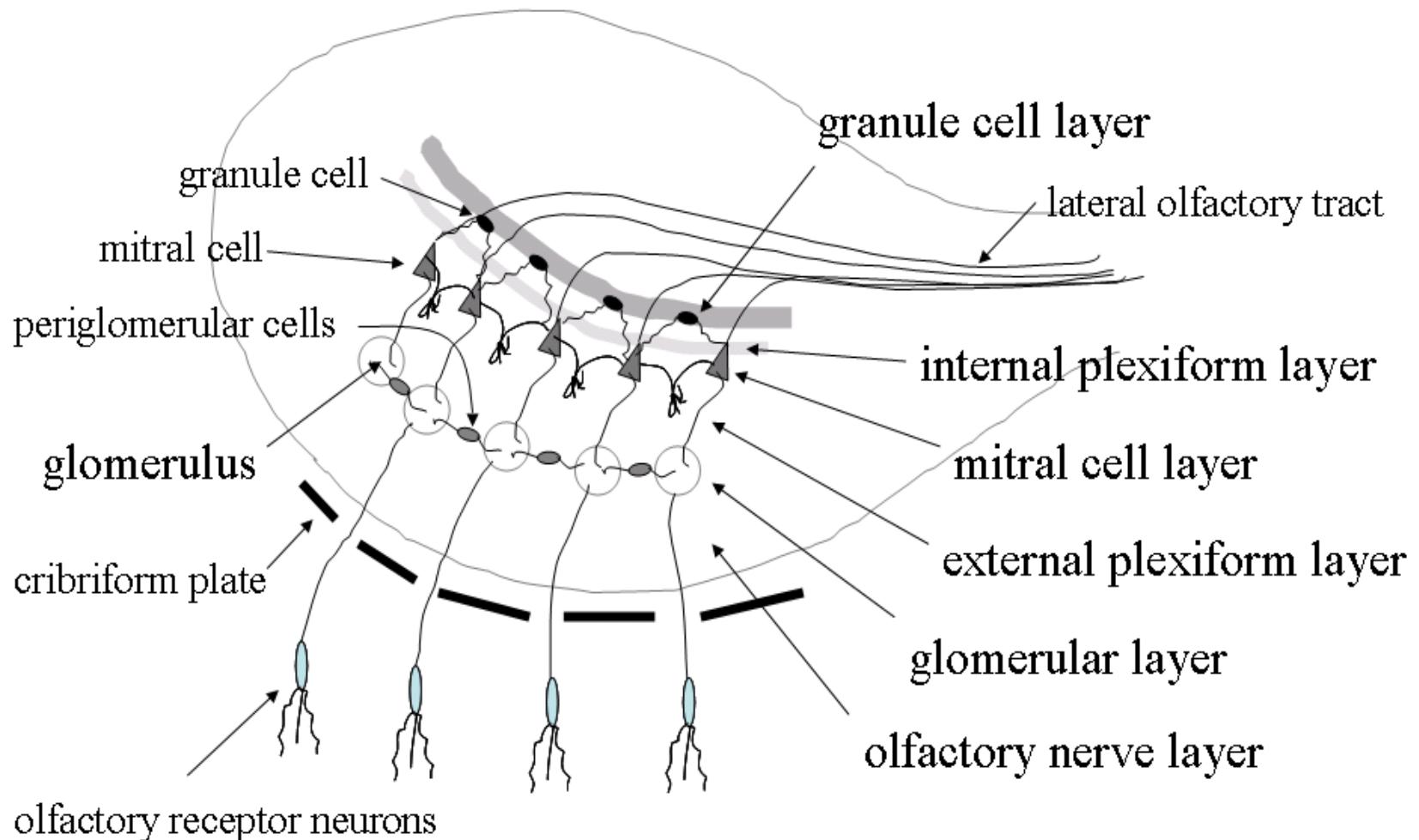
# To be covered in the talk

- 3 slide basic introduction to the olfactory system (for those who don't work in the area)
- Infrastructure needed for running a community project
- The plan
- The Phases

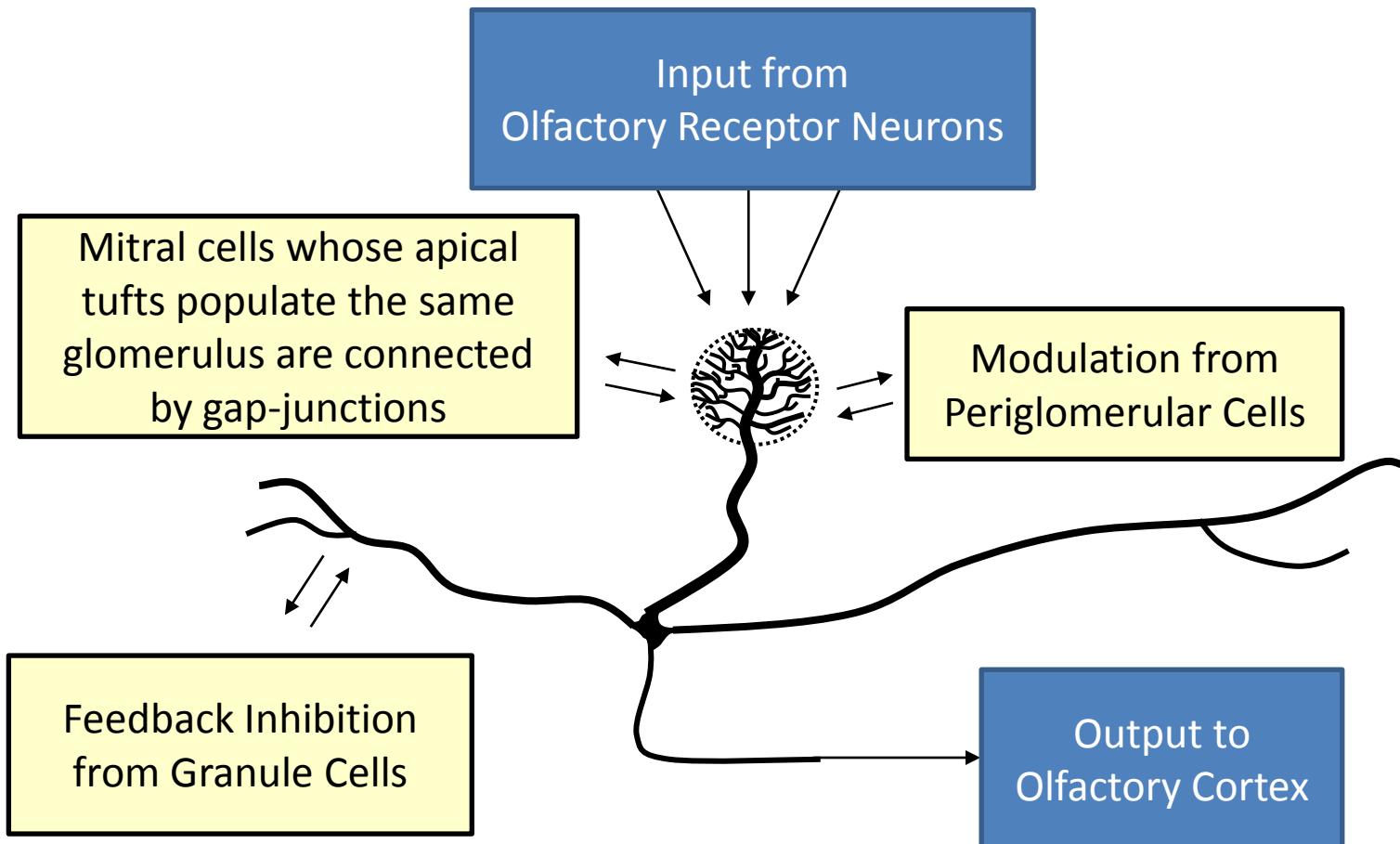
# Olfactory System Multichannel Input

- Rodents have ~ 1000 -1200 olfactory Receptors types (Humans have lost the use of about 70% so around 300 expressed)
- Only one receptor type expressed in each olfactory receptor neuron and all olfactory receptor neurons expressing a particular neuron type converge on a single glomerulus (convergence ratio ~ 10,000:1)
- A glomerulus is a neuropil that consists of the apical tufts of ~ 25 mitral cells along with interconnections with around 2000 periglomerular cells and the apical tufts of tufted cells
- Modulation of mitral cell output is complex and multilevel

# Olfactory System



# Mitral Cells



# Network models of the olfactory bulb:

## An outsider's perspective

University of  
Hertfordshire

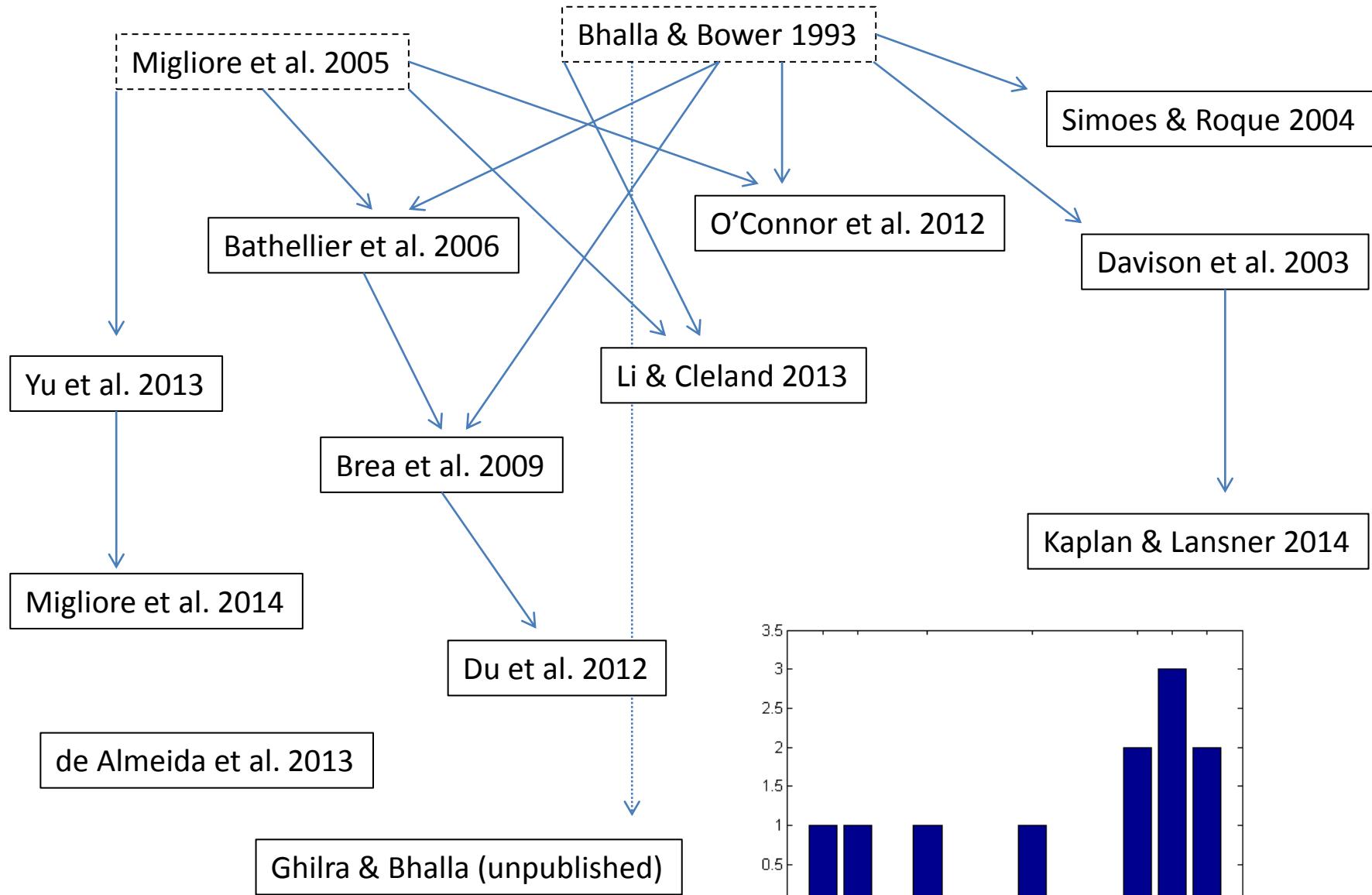


Volker Steuber, Science and Technology Research Institute, University of Hertfordshire, UK

Model	Mitral cells	Granule cells	Other cells / features	Ion channels and sources	Simulator	Access
Davison 2003	25-100 (4 cpts)	144-14400 (3 cpts)		MC: <b>NaF fKdr sKdr KA KCa CaL</b> GC: <b>NaF sKdr KA KM</b>	NEURON	ModelDB
Simoes-de-Souza 2004	64 (7 cpts)	100 (12 cpts)		MC: <b>NaF fKdr sKdr KA KCa CaL</b> GC: <b>NaF sKdr KA KM</b>	GENESIS	ModelDB (single cells)
Bathellier 2006	100 (1 cpt)	implicit		MC: <b>NaF* NaP Kdr* KA Ks</b>	C++	ModelDB
Brea 2009	100 (1 cpt)	1000 (2 cpts)		MC: <b>NaF* NaP Kdr* KA Ks</b> GC: <b>NaF sKdr KA KM</b>	C++?	
Du 2012	800 (1 cpt)	implicit		MC: <b>NaF* NaP Kdr* KA Ks</b>	?	
O'Connor 2012	6 (118 cpts)			MC: <b>NaF Kdr KA KCa CaL</b>	GENESIS, NEURON, nC	ModelDB OSB
de Almeida 2013	50 (2 cpts)	50 (1 cpt)	50 PGCs (1 cpt)	MC and GC: LIF PGC: leaky integrators	MATLAB	ModelDB
Li 2013	25 (14 cpts)	100 (2 cpts)	25 PGCs (4 cpts)	MC: <b>NaF* NaP fKdr KA Ks KCa CaL</b> GC: <b>NaF Kdr KA CaT CaP CaN KM KCa</b> PGC: <b>NaF Kdr KA CaT CaP H KM KCa</b>	NEURON	ModelDB
Yu 2013	500 (312 cpts)	10000 (21 cpts)		MC: <b>NaF Kdr KA</b> GC: <b>NaF Kdr KA</b>	NEURON	ModelDB
Kaplan 2014	320 (4 cpts)	32000 (3 cpts)	6400 PGCs (3 cpts)	MC: <b>NaF fKdr sKdr KA KCa CaL</b> GC, PGC: <b>NaF sKdr KA KM</b>	NEURON	ModelDB (Github)
Migliore 2014	635 (189-1433 cpts)	13260-69013 (33-257 cpts)	3D synth morph	MC: <b>NaF Kdr KA</b> GC: <b>NaF Kdr KA</b>	NEURON	ModelDB OSB in progr.

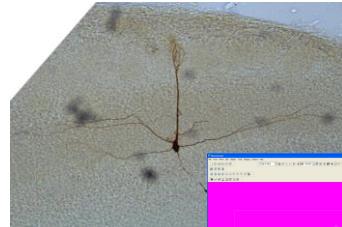
Channels from: **Bhalla & Bower (1993)** **Wang et al. (1996)** **Wang (1993)** **Migliore et al. (1999)** other

# Network models of the olfactory bulb: lineage



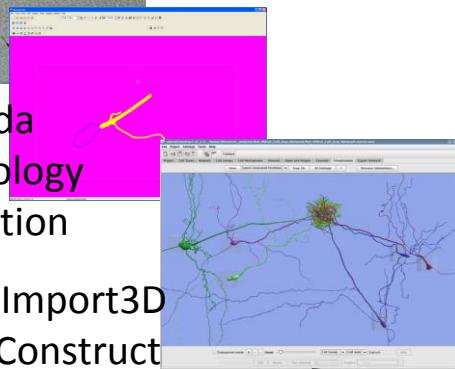
# Frankenstein's Mitral Cell, experiments in collaboration from ModelDB to OSB

Simon O'Connor, Biocomputation Group, University of Hertfordshire, UK

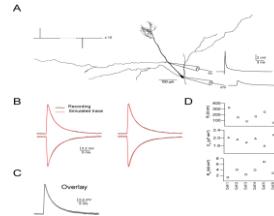


Biocytin filled cell

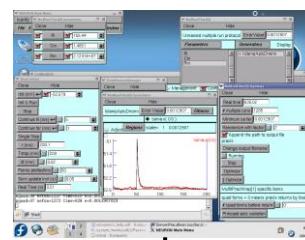
NeuroLucida  
3D morphology  
reconstruction



Neuron Import3D  
+ neuroConstruct



Dual Patch  
Clamp  
Recordings



Neuron  
Multi Run Fitter

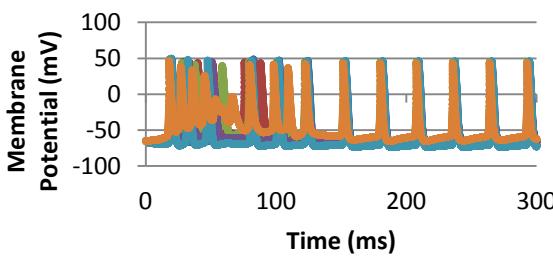
ModelDB

Lca, Kca and Ca pool  
from Bhalla and  
Bower 1993  
(Genesis Tab + vdep)

Na, Kdr and KA ion  
channels from  
Migliore et al 2005  
(Neuron mod files).

NeuroML

- Cell 1
- Cell 2
- Cell 3
- Cell 4
- Cell 5



O'Connor et al 2012

Open  
Source  
Brain



# Hosted on Github...

The screenshot shows a web browser window displaying a GitHub repository page. The URL in the address bar is <https://github.com/Simon-at-Ely/OlfactoryBulbMitralCell>. The page title is "Simon-at-Ely / OlfactoryBulbMitralCell".

The repository summary section includes:

- 26 commits
- 1 branch (branch: master)
- 0 releases
- 2 contributors

The "Code" tab is selected, showing the repository's structure and recent activity:

- Update README.md by Simon-at-Ely on Mar 22 (latest commit: 6bcd784732)
- SingleMitarCellsNoCalcium modified: Mitral\_cell\_test.py (2 years ago)
- neuroConstruct Adding generated cells & example network in nml2 (11 months ago)
- old\_model modified: neuroConstruct/Mitral\_Cell\_Simple\_Gap\_Network.nxc (a year ago)
- .gitignore Updated a number of the channels to ensure erev k = -80 (a year ago)
- README.md Update README.md (a month ago)

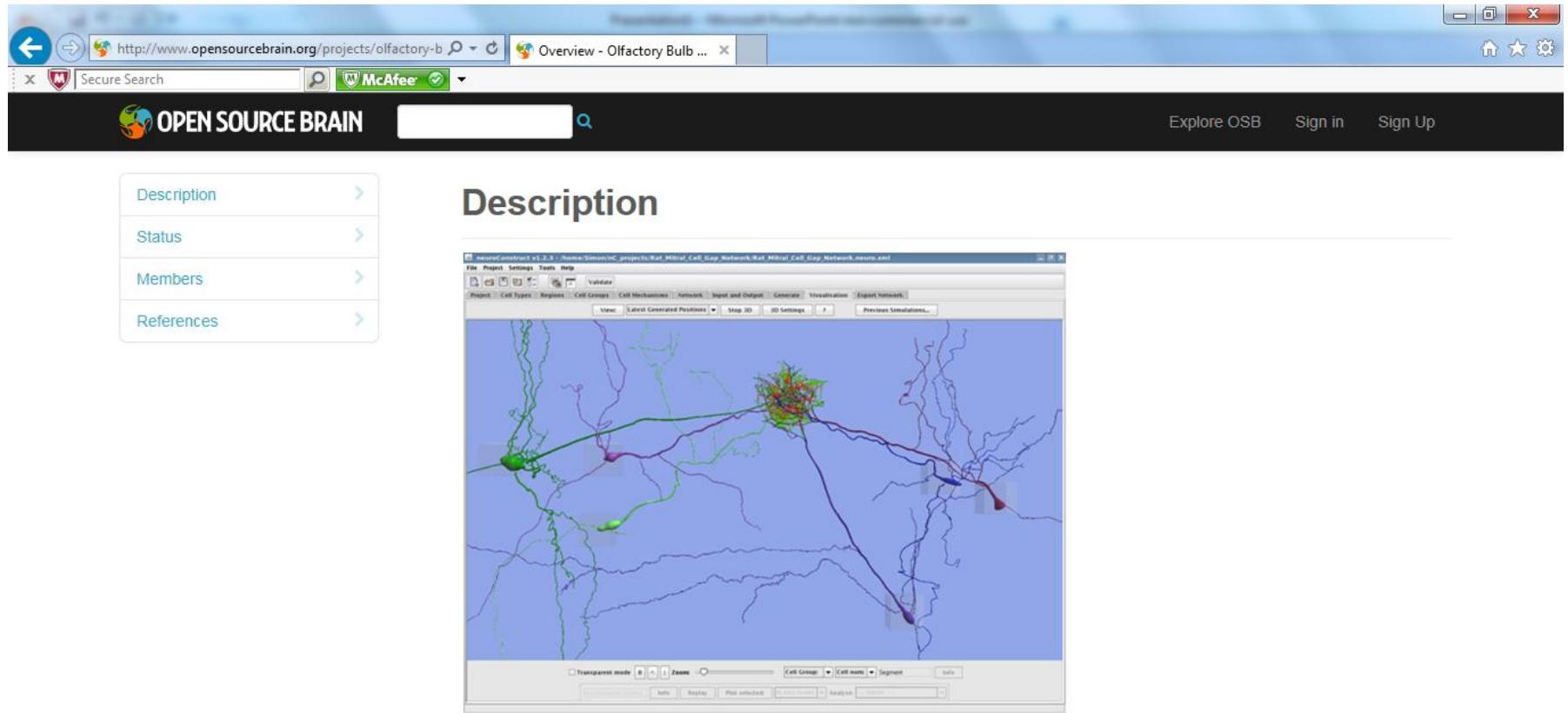
The repository name "OlfactoryBulbMitralCell" is displayed prominently at the bottom of the page.

On the right side of the page, there is a sidebar with various links and options:

- Code
- Issues (8)
- Pull requests (0)
- Wiki
- Pulse
- Graphs
- Settings
- HTTPS clone URL: <https://github.com/> (with a clipboard icon)
- You can clone with HTTPS, SSH, or Subversion. (with a help icon)
- Clone in Desktop
- Download ZIP

The browser taskbar at the bottom shows several pinned icons, and the system tray indicates the date and time as 19:35 on 27/04/2015.

# ... and OSB



A model of olfactory bulb mitral cells connected by apical dendrite gap junctions in a glomerular network



19:47  
27/04/2015

# Forum on Github Issues

Screenshot of a GitHub issue page for the repository "Simon-at-Ely / OlfactoryBulbMitralCell".

The issue is titled "Further development of a gap-junction connected mitral cell model representing a single glomerulus #7". It was opened by Simon-at-Ely on Sep 18 2013, with 4 comments.

Comment by Simon-at-Ely (Sep 18 2013):

In 2005, Migliore et al published a model in which they showed that asynchronous oscillations in two mitral cells connected by gap-junctions between their apical tufts would rapidly synchronise. In the following years we further developed the Migliore et al (2005) model (O'Connor et al. 2012, Figure 1 and 2) to:

- incorporate 6 NeuroLucida mitral cell morphology reconstructions.
- include fitted passive parameters from dual patch clamp recordings for each of the mitral cell reconstructions.
- incorporate calcium mechanisms ( $LCa$ ,  $KCa$ , Ca pool) from Bhalla and Bower 1993.

[http://www.opensourcebrain.org/attachments/download/92/Mitral\\_Cell\\_Model.png](http://www.opensourcebrain.org/attachments/download/92/Mitral_Cell_Model.png)

Figure 1 – Olfactory bulb gap-junction connected network model created using neuroConstruct (O'Connor et al. 2012).

[http://www.opensourcebrain.org/attachments/download/94/MC\\_Net\\_Model\\_Output.jpg](http://www.opensourcebrain.org/attachments/download/94/MC_Net_Model_Output.jpg)

Labels: question

Milestone: No milestone

Assignee: No one—assign yourself

Notifications: Unsubscribe

You're receiving notifications because you authored the thread.

Bottom navigation bar icons: Windows, Media Player, Internet Explorer, File Explorer, Start, Task View, File, Word, Excel.

Bottom right corner: 19:55, 27/04/2015

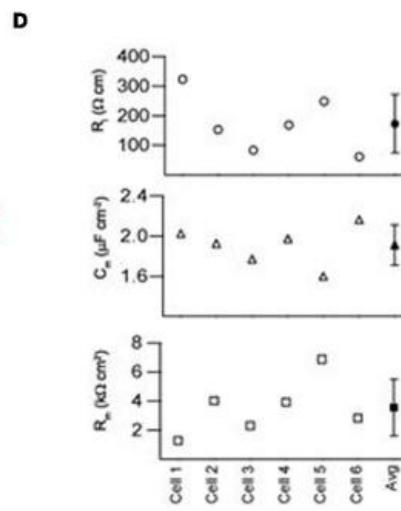
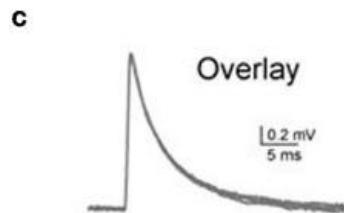
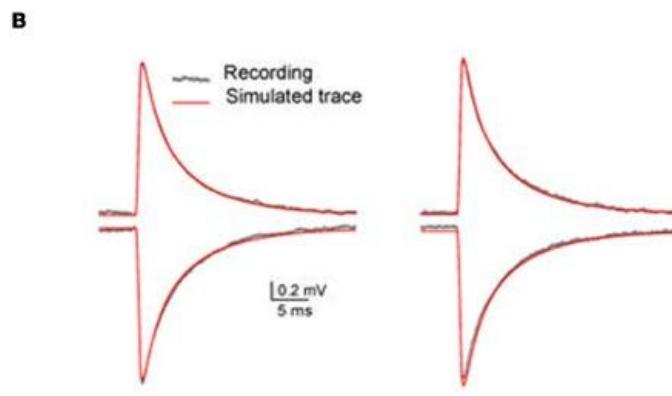
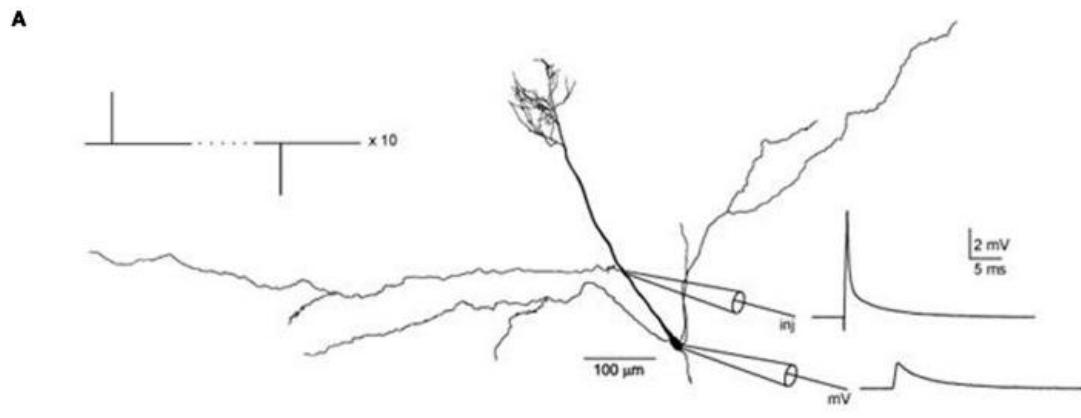
# The Plan

- Recruit collaborators from both the experimentalist and modelling communities
- Discuss how to develop the model using the Github issue forum
- Use constraining data from the experimentalist community
- Try the suggestions of the forum as branches of the model on Github

# Back to Basics

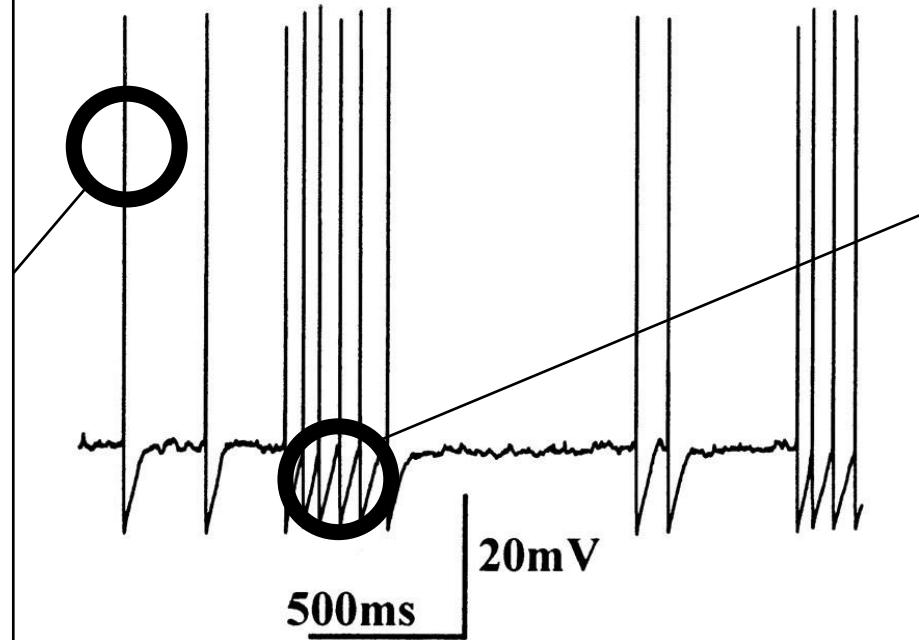
- The current model consists of a Gap-Junction connected network of 6 mitral cells representing a single glomerulus
- To explore ion channel dynamics we will need to revert back to single cells
- The single cell models have a good passive model foundation from fitting to dual patch clamp recordings
- Phased development of the ion channel dynamics

# O'Connor, Angelo and Jacob 2012



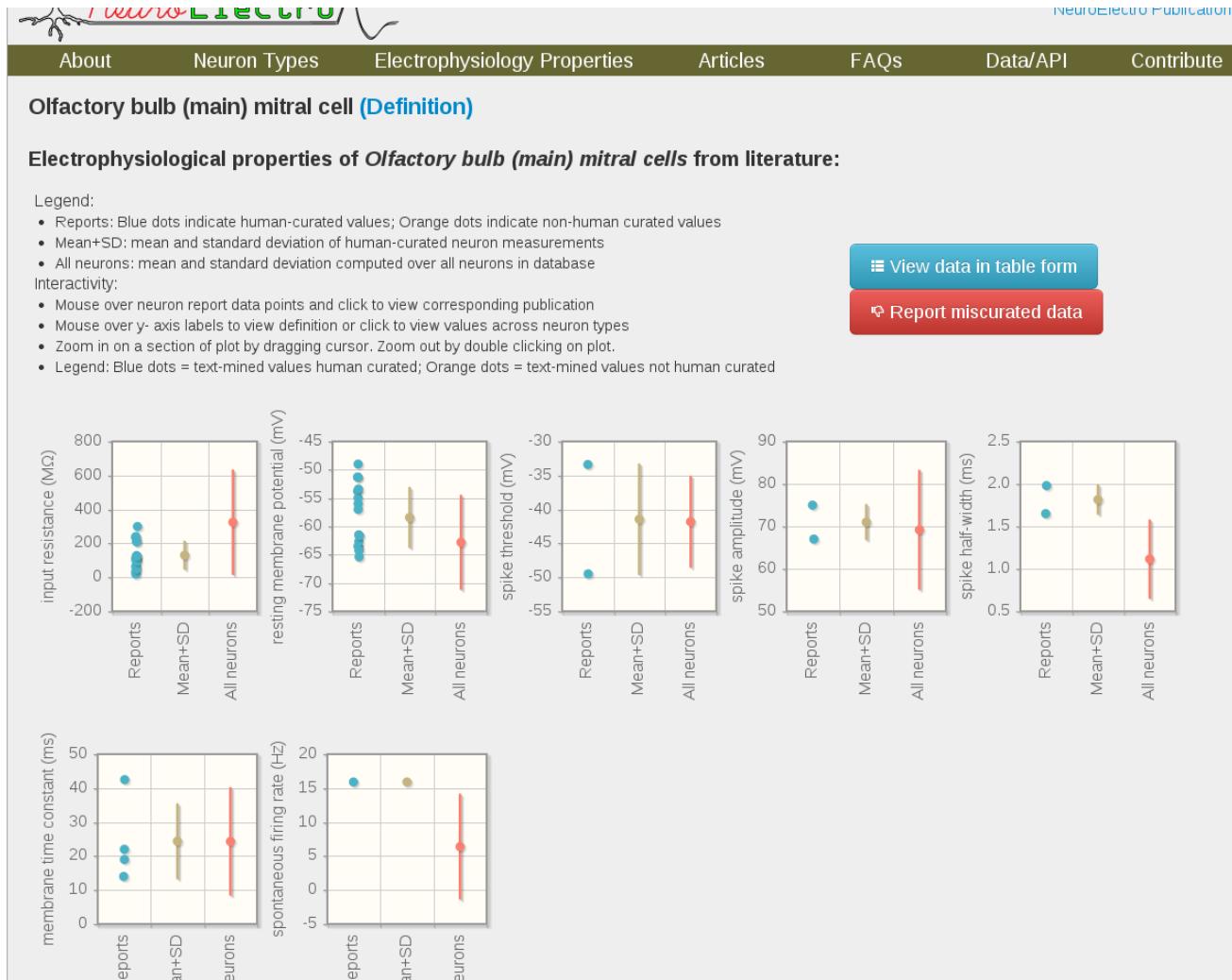
**Phase 1** strip back the model to the **basic sodium and potassium currents** responsible for the action potential and see if they can be improved by **fitting to average spike shapes** or more recent data on these ion channels. Originals are NeuroML conversions of the channels in Migliore et al. 2005 . The model needs to be able **replicate the back propagation of the action potential** Chen and Shepherd 1997).

# Phases 1 and 2



**Phase 2** work on calcium and KCa ion channels to reproduce the bursting behaviour of the mitral cells. The model currently contains NeuroML conversions of the calcium and KCa ion channels from Bhalla and Bower (1993). Constrain channels with any available date and burst properties to Balu et al (2004).

# Phase 1 Constraining Data



# Wang, McKenzie and Kemm 1996

Table 1. Time constants for activation and decay of  $I_A$

	-20 mV	-10 mV	0 mV	10 mV	20 mV	30 mV	40 mV	50 mV
$\tau_{\text{activation}}$	$12.18 \pm 1.79$ (7)	$9.11 \pm 2.26$ (5)	$6.68 \pm 1.54$ (6)	$6.51 \pm 1.56$ (5)	$4.94 \pm 1.24$ (7)	$3.56 \pm 1.05$ (6)	$3.45 \pm 1.01$ (7)	$3.05 \pm 0.73$ (6)
$\tau_{\text{decay}}$	—	$51.17 \pm 2.45$ (10)	$47.84 \pm 3.02$ (8)	$48.32 \pm 3.25$ (8)	$45.21 \pm 3.76$ (10)	$44.11 \pm 2.74$ (9)	$46.19 \pm 2.01$ (9)	$43.44 \pm 2.05$ (9)

The activation time constants ( $\tau_{\text{activation}}$ ) were obtained by fitting the rising segments of the current traces (up to the maximal peaks) and the decay constants ( $\tau_{\text{decay}}$ ) were obtained by fitting the current traces starting from the maximal peaks. Values are means  $\pm$  s.e.m. (ms) with the number of experiments indicated below in parentheses.

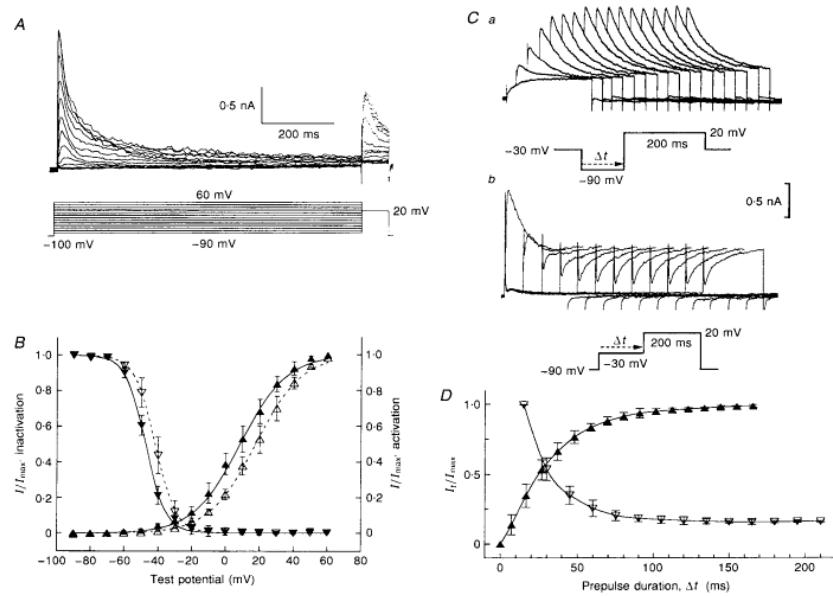
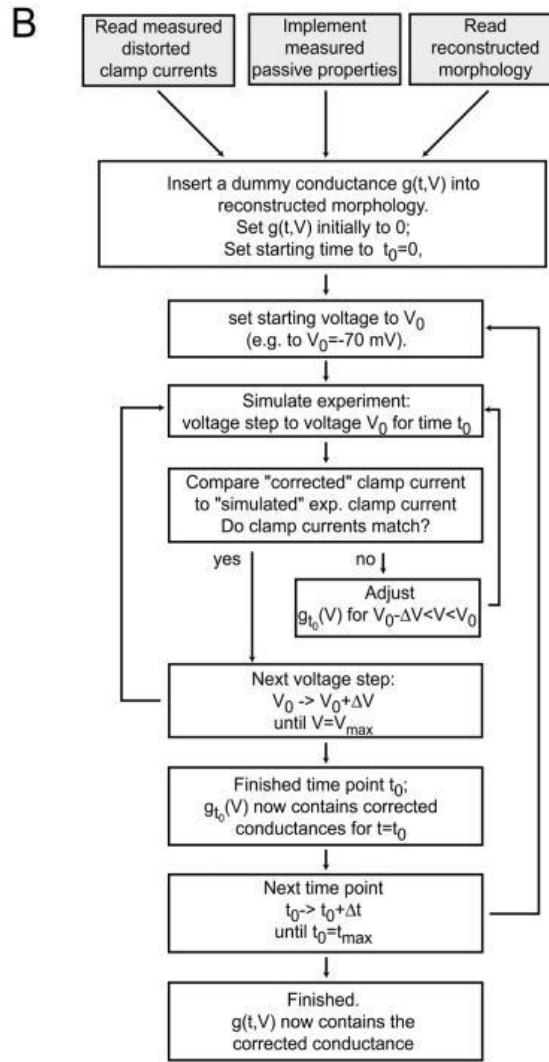
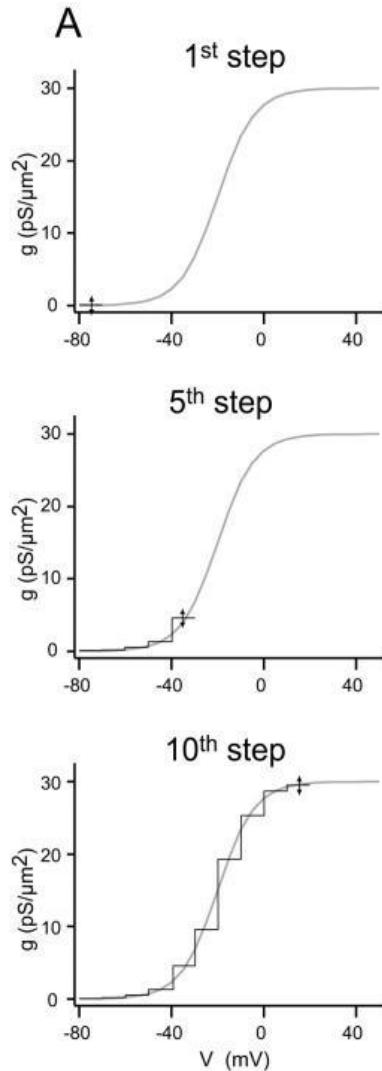
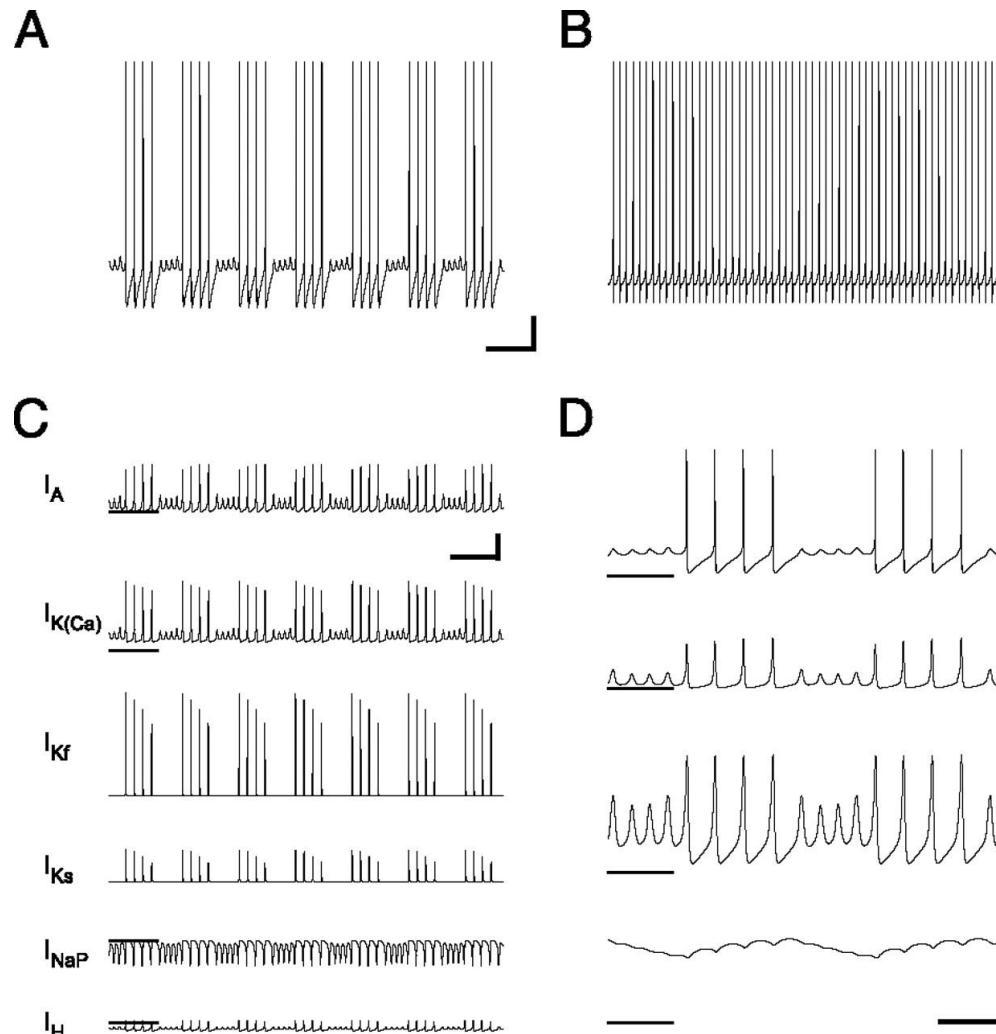


Figure 4. Kinetics of  $I_A$

# Schaefer et al. 2003



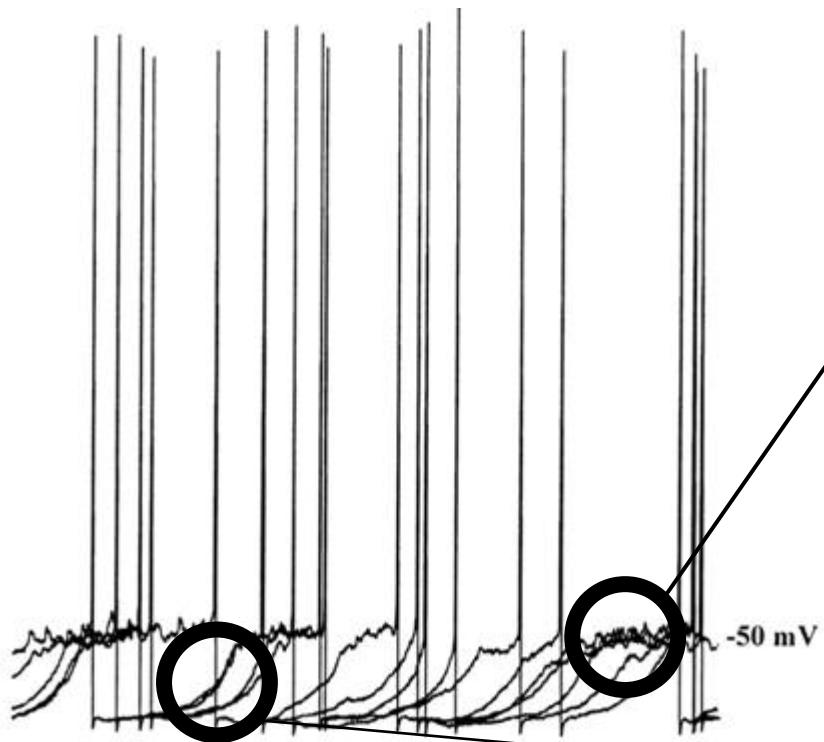
## Mechanisms and currents underlying mitral cell bursting.



Daniel B. Rubin, and Thomas A. Cleland J Neurophysiol  
2006;96:555-568

Journal of Neurophysiology

# Phase 3 Modelling Sub-Threshold Oscillations and Bistability

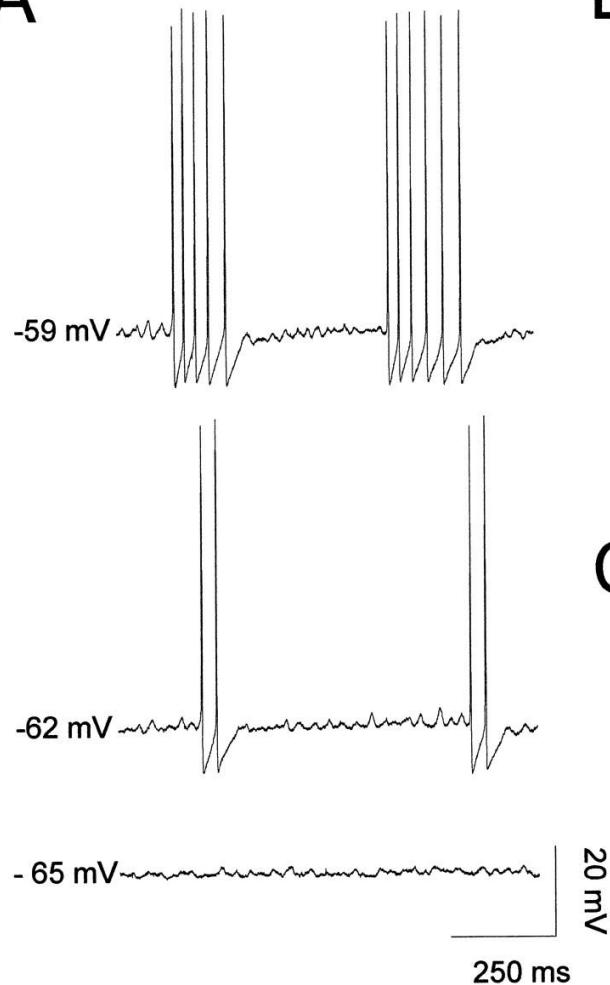


**Phase 3a:** model the sub-threshold oscillations that **Desmaisons et al (1999)** reported were produced by the persistent sodium current  $I_{NaP}$  interacting with  $I_H$  **Rubin and Cleland 2006** (Fransén et al. 2004) and incorporate the newer data on  $I_H$  heterogeneity **Angelo and Margrie 2011**.

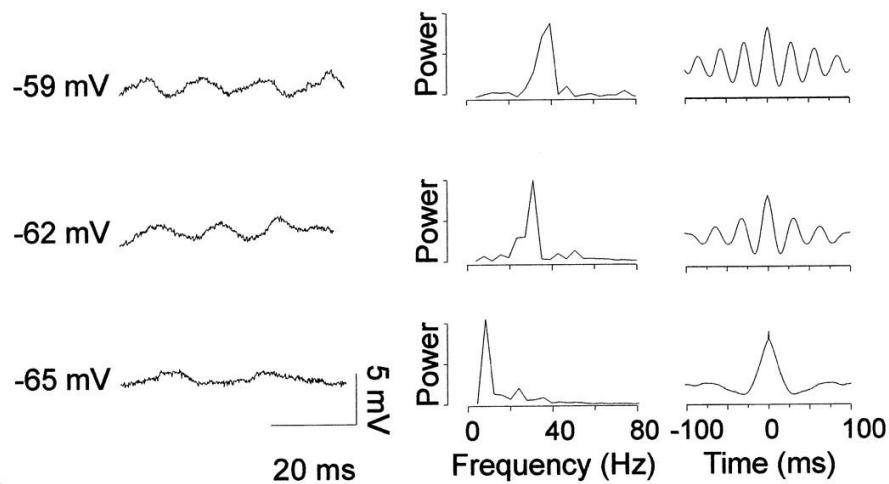
**Phase 3b:** model bistable properties in the mitral cells as reported in **Heyward et al. (2001)** with a down state produced by activation of an ohmic potassium current  $I_{K(ATP)}$  **Rubin and Cleland 2006**.

## Subthreshold membrane potential oscillations are voltage-dependent.

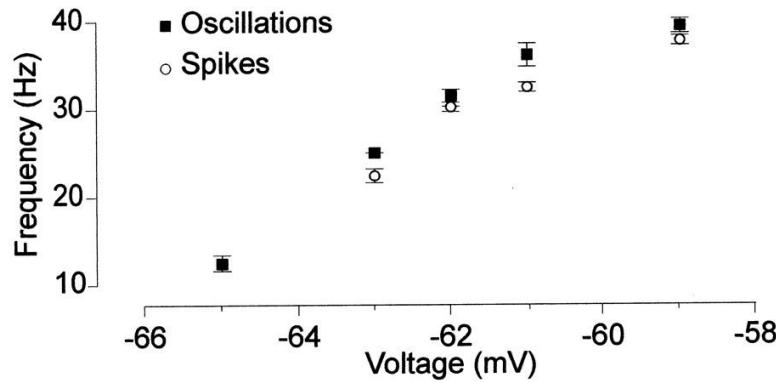
A



B



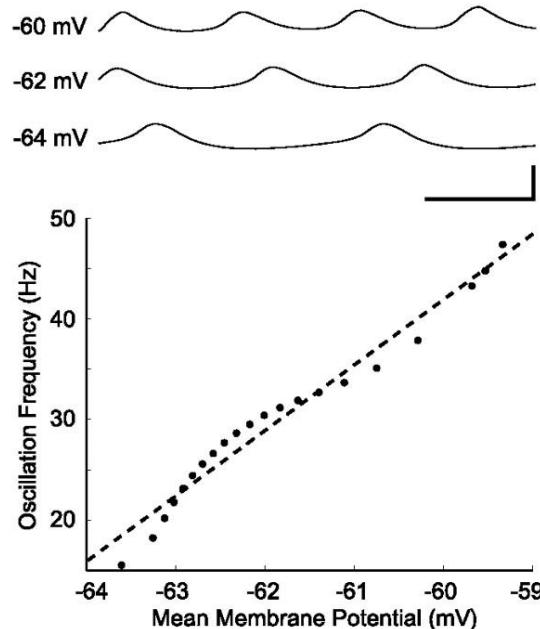
C



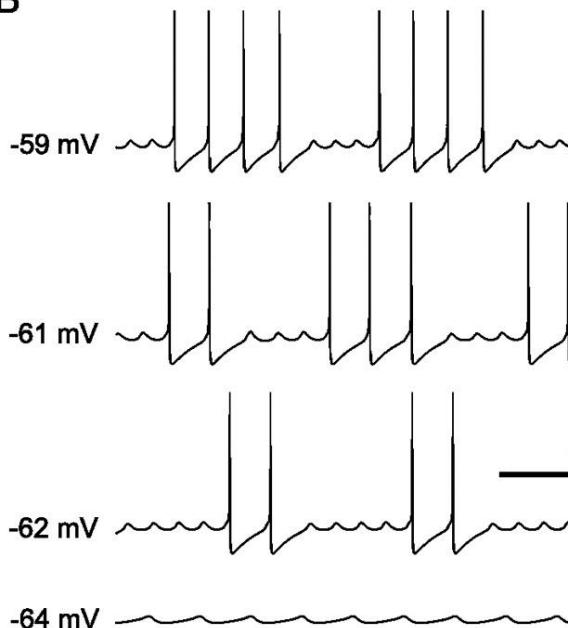
David Desmaisons et al. J. Neurosci. 1999;19:10727-10737

## Basic electrophysiological properties of the model mitral cell.

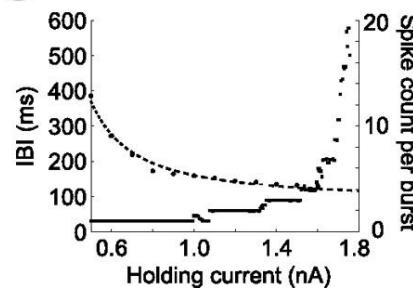
A



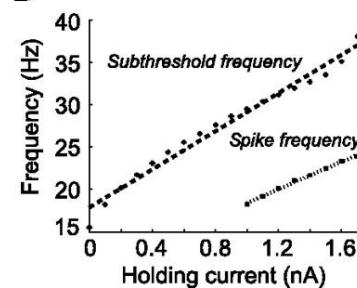
B



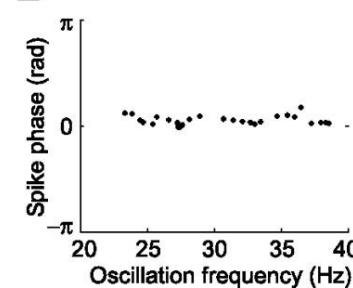
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D



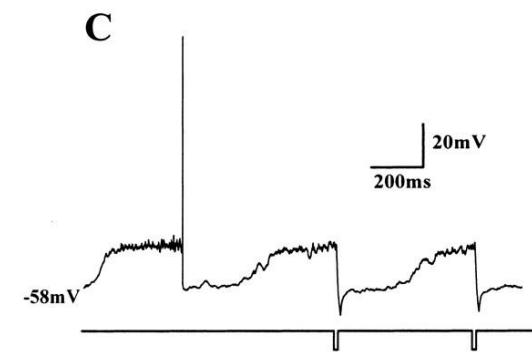
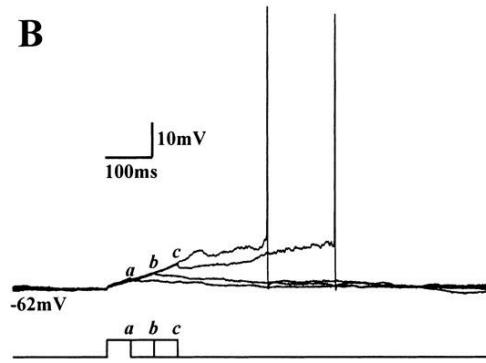
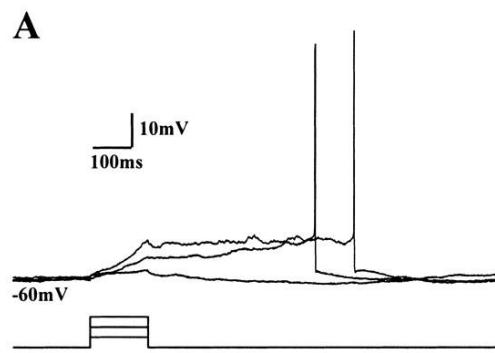
E



Daniel B. Rubin, and Thomas A. Cleland J Neurophysiol  
2006;96:555-568

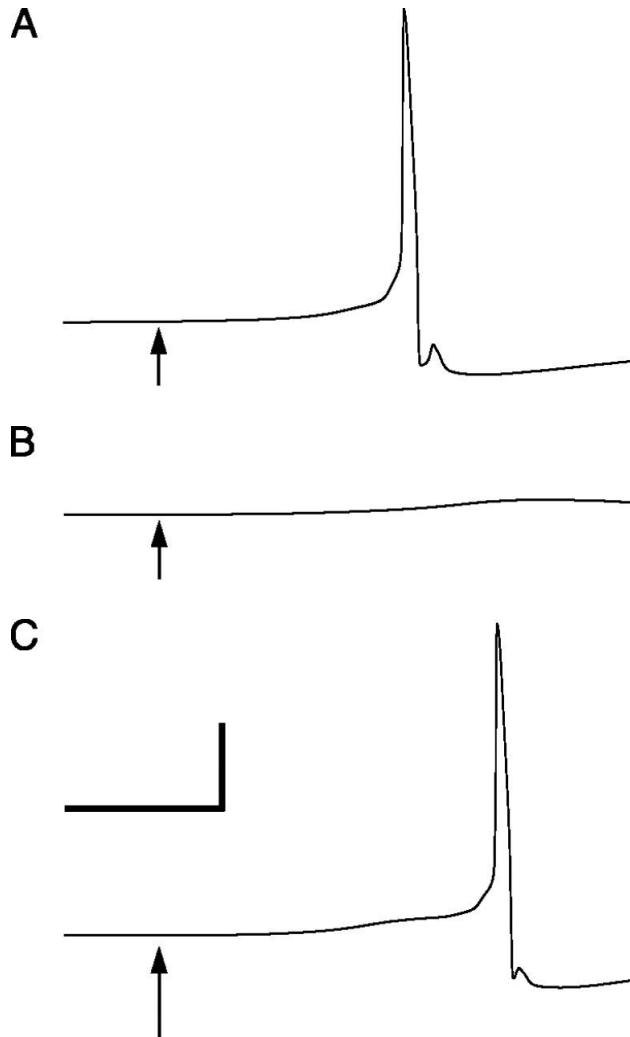
Journal of Neurophysiology

**Voltage-dependent membrane properties are involved in the generation and maintenance of the upstate.**



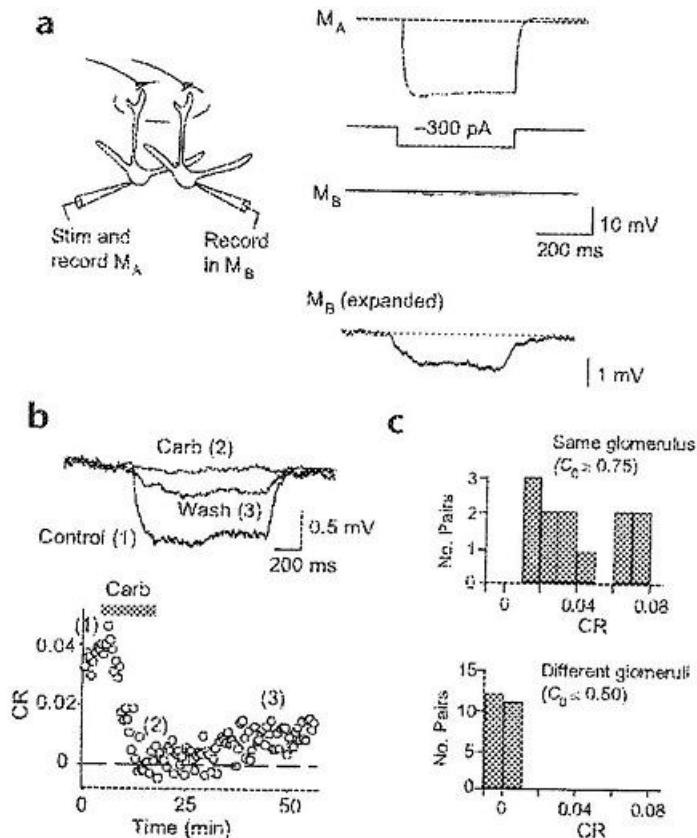
Philip Heyward et al. J. Neurosci. 2001;21:5311-5320

**Activation of an ohmic potassium current  $IK(ATP)$  generates a down-state.**



Daniel B. Rubin, and Thomas A. Cleland J Neurophysiol  
2006;96:555-568  
*Journal of Neurophysiology*

# Phase 4 Reassemble the gap-junction connected mitral cell network



**Phase 4:** put the network model back together and improve the constraints on the gap junction to current state of knowledge

# What Next?

- Other mitral Cell properties: biophysical heterogeneity of mitral cells (Padmanabhan and Urban, 2010, 2013), action potential attenuation in the lateral dendrites (Christie and Westbrook 2003) versus no attenuation of calcium transients in the lateral dendrites (Xiong and Chen 2002); glutamate auto excitation (Schoppa and Westbrook 2002) in mitral cells...
- Add middle and deep tufted cells to the model: how does the biophysics of tufted cells differ from mitral cells? Do the apical tufts of mitral cells and tufted cells interconnect in the glomerulus via gap junctions?

All welcome to join in the development of this community model

- Contact Simon O'Connor to volunteer:

[Simon.oconnor@btinternet.com](mailto:Simon.oconnor@btinternet.com)

- And follow the discussion forum at:

<https://github.com/Simon-at-Ely/OlfactoryBulbMitralCell/issues/7>

Thank you for Listening