# A Community Mitral Cell Model

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

Olfactory Modeling
*A NIMBioS Investigative Workshop*
Organised by
*Sharon Crook and Brian Smith*
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NIMBioS
National Institute for Mathematical and Biological Synthesis

# 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.

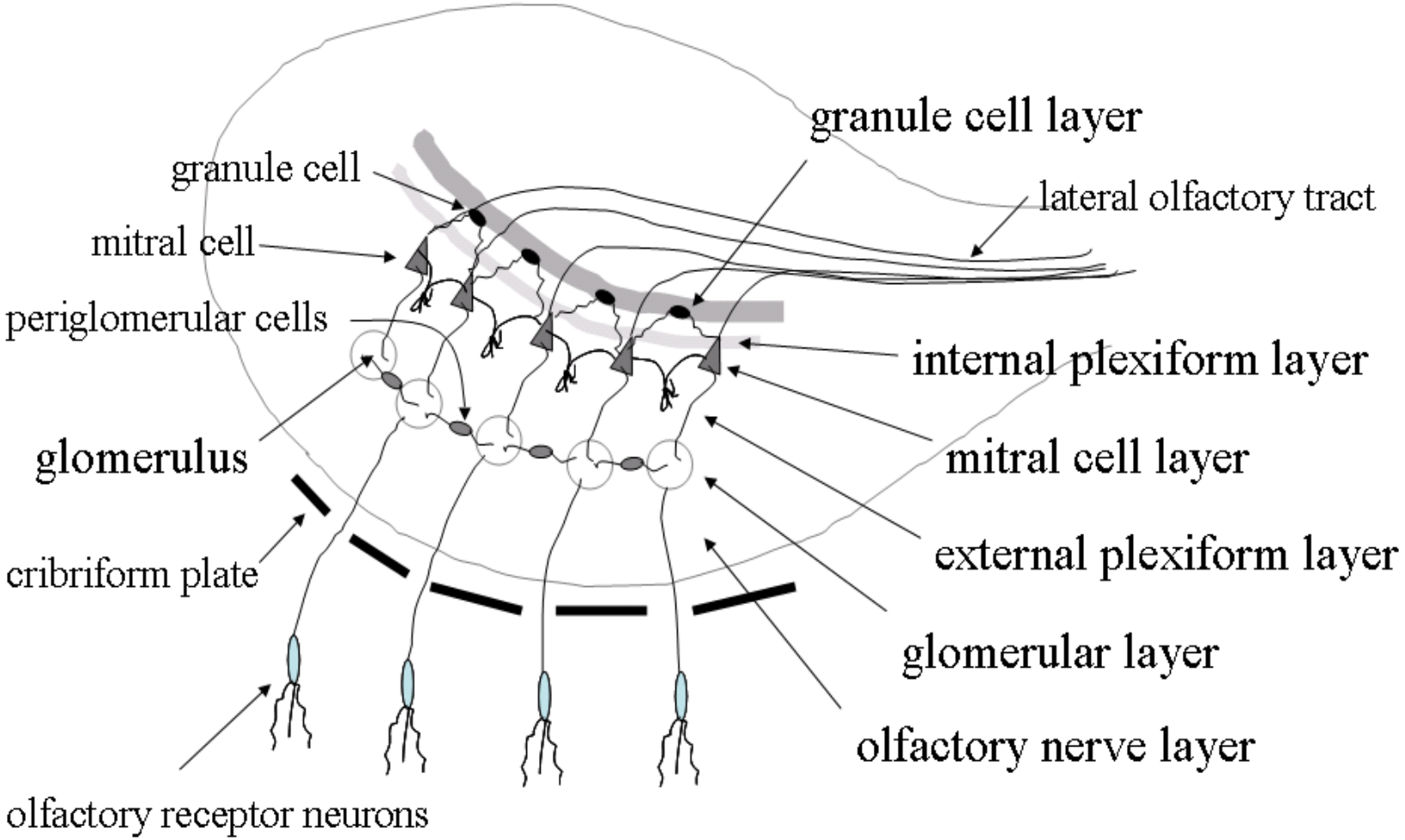
# To be covered in the talk

- 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

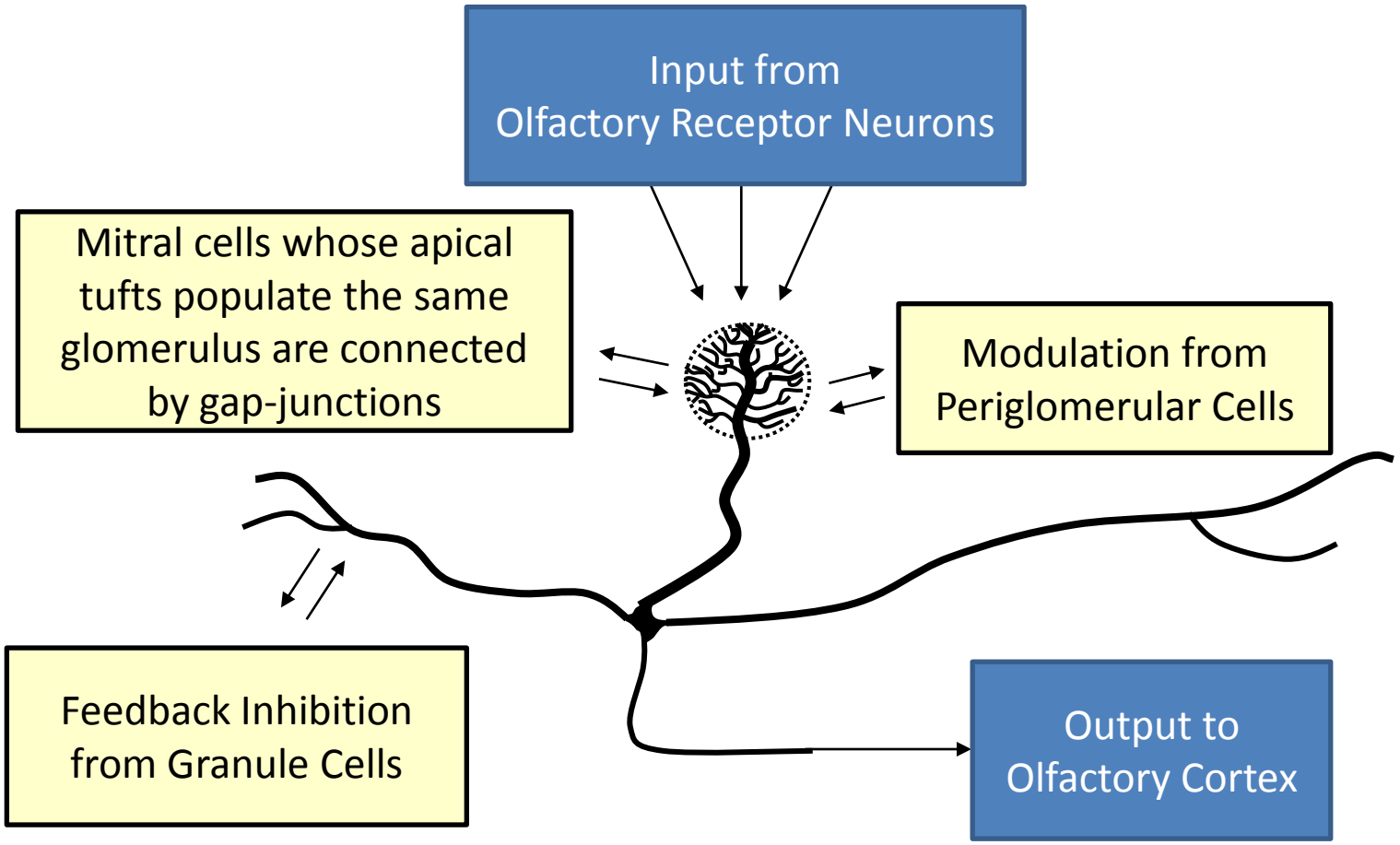
# Olfactory System Multichannel Input

- 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

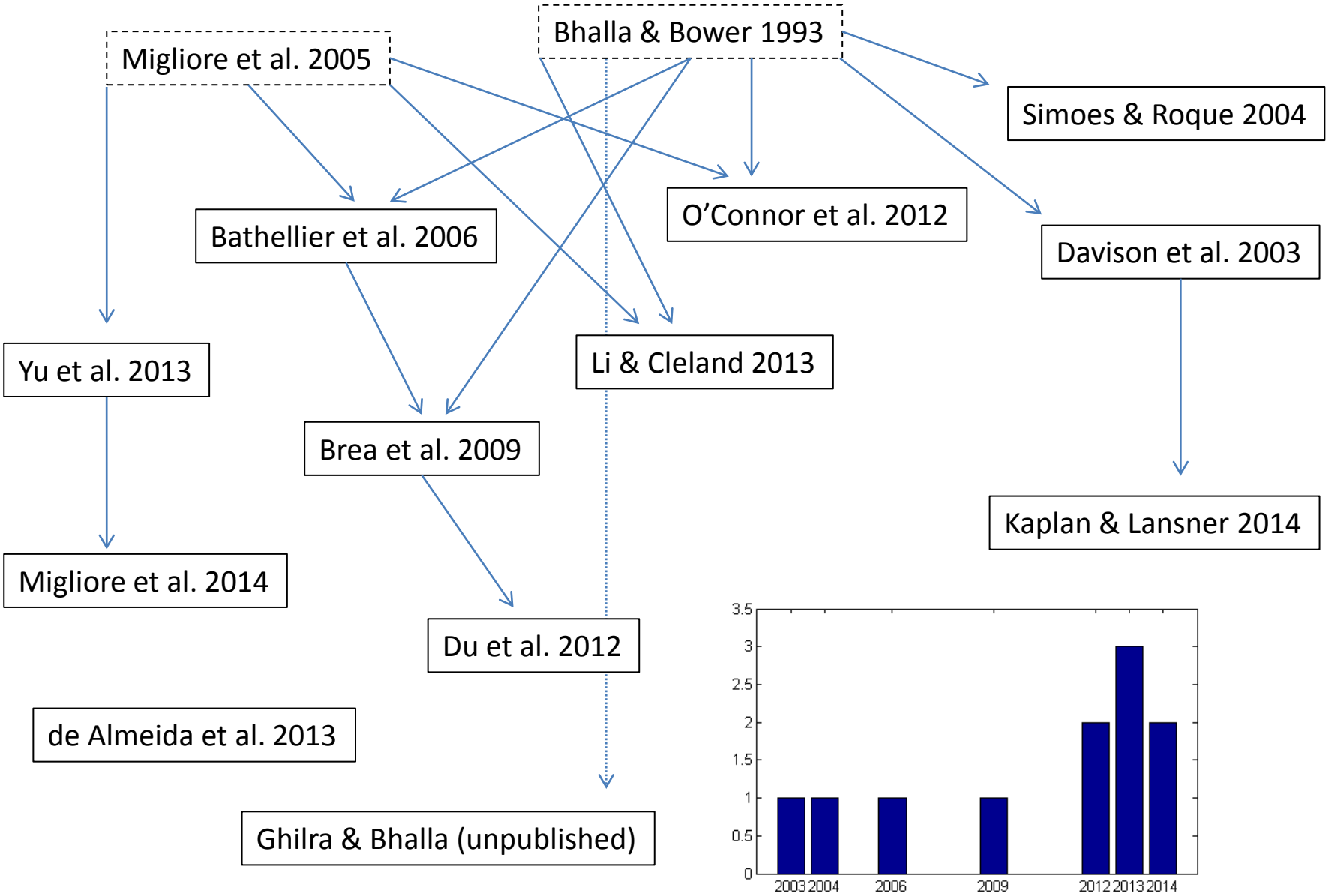
Volker Steuber, Science and Technology Research Institute, University of Hertfordshire, UK

University of Hertfordshire

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

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

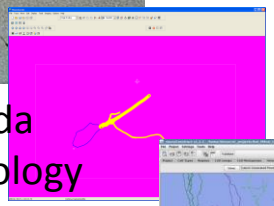
# Network models of the olfactory bulb: lineage



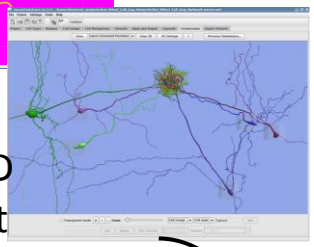
# Frankenstein's Mitral Cell, experiments in collaboration from ModelDB to OSB

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

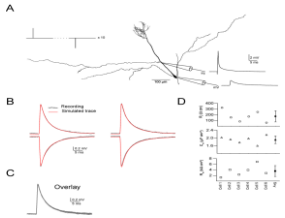
Biocytin filled cell



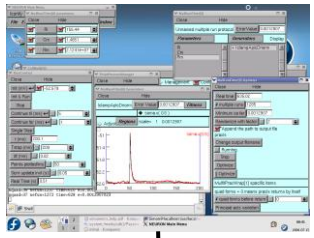
NeuroLucida 3D morphology reconstruction



Neuron Import3D + neuroConstruct



Dual Patch Clamp Recordings



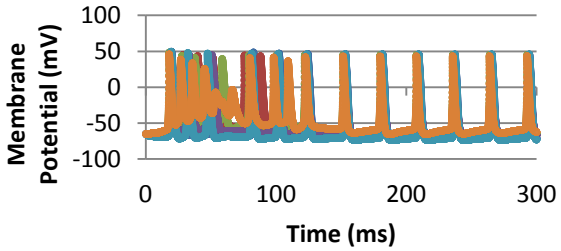
Neuron Multi Run Fitter

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

O'Connor et al 2012

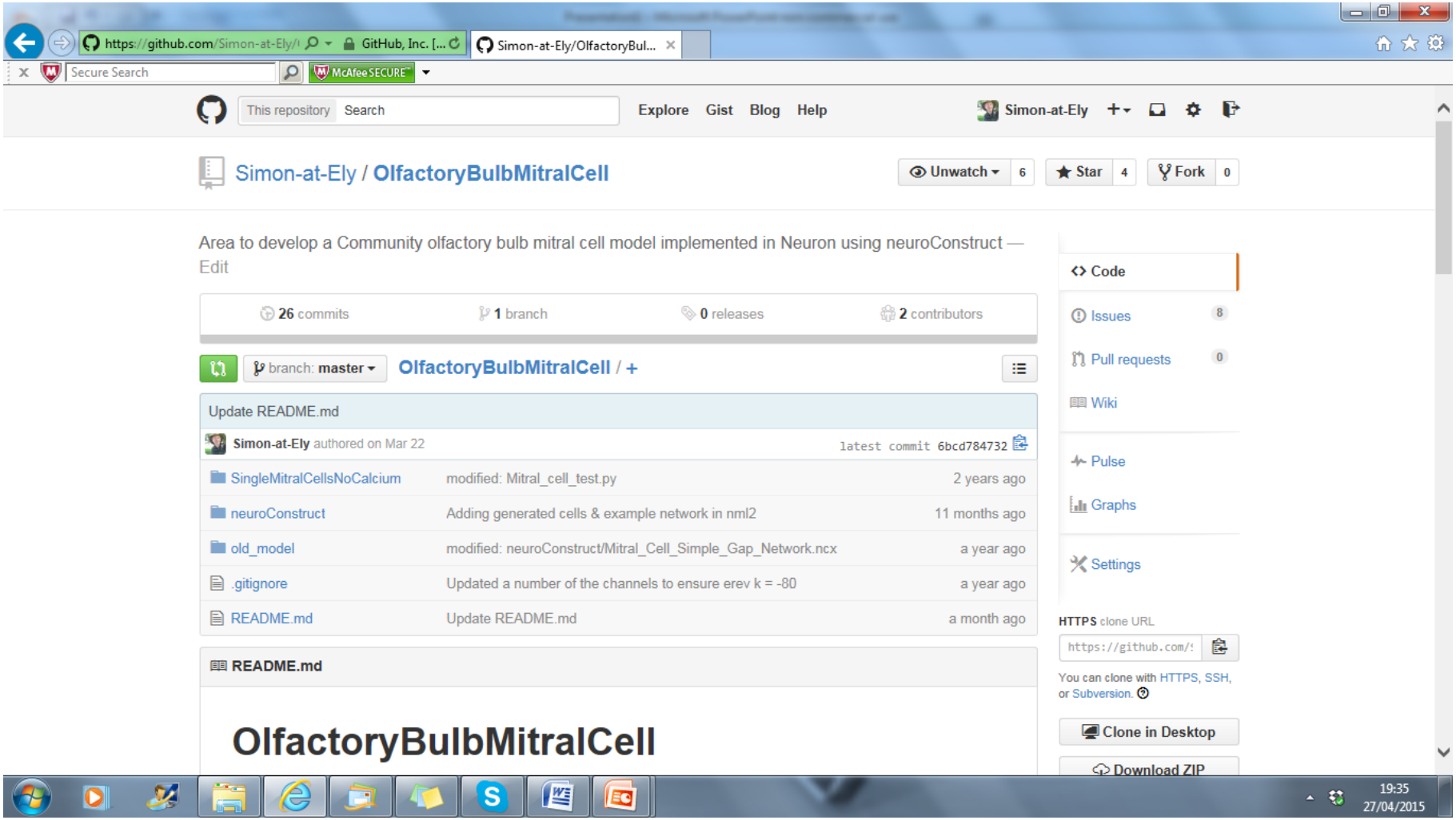



- Cell 1
- Cell 2
- Cell 3
- Cell 4
- Cell 5

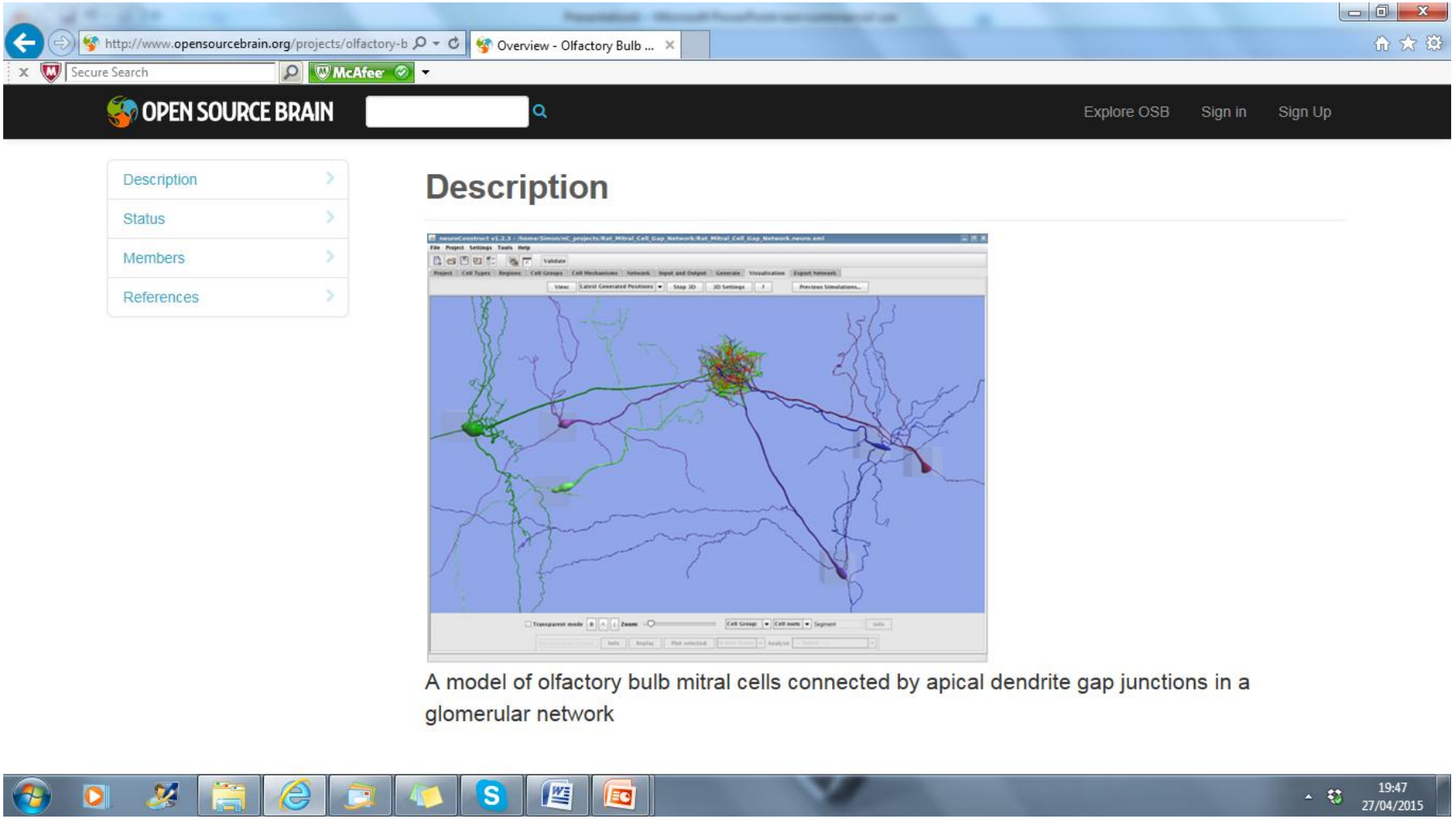
Open Source Brain

http://www.opensourcebrain.org/projects/olfactory-bulb-network-model-o-connor-angelo-and-jacob-2012/wiki

# Hosted on Github…



# … and OSB


http://www.opensourcebrain.org/projects/olfactory-b
Overview - Olfactory Bulb ...
Secure Search
McAfee
OPEN SOURCE BRAIN
Explore OSB
Sign in
Sign Up
Description
Status
Members
References
Description
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

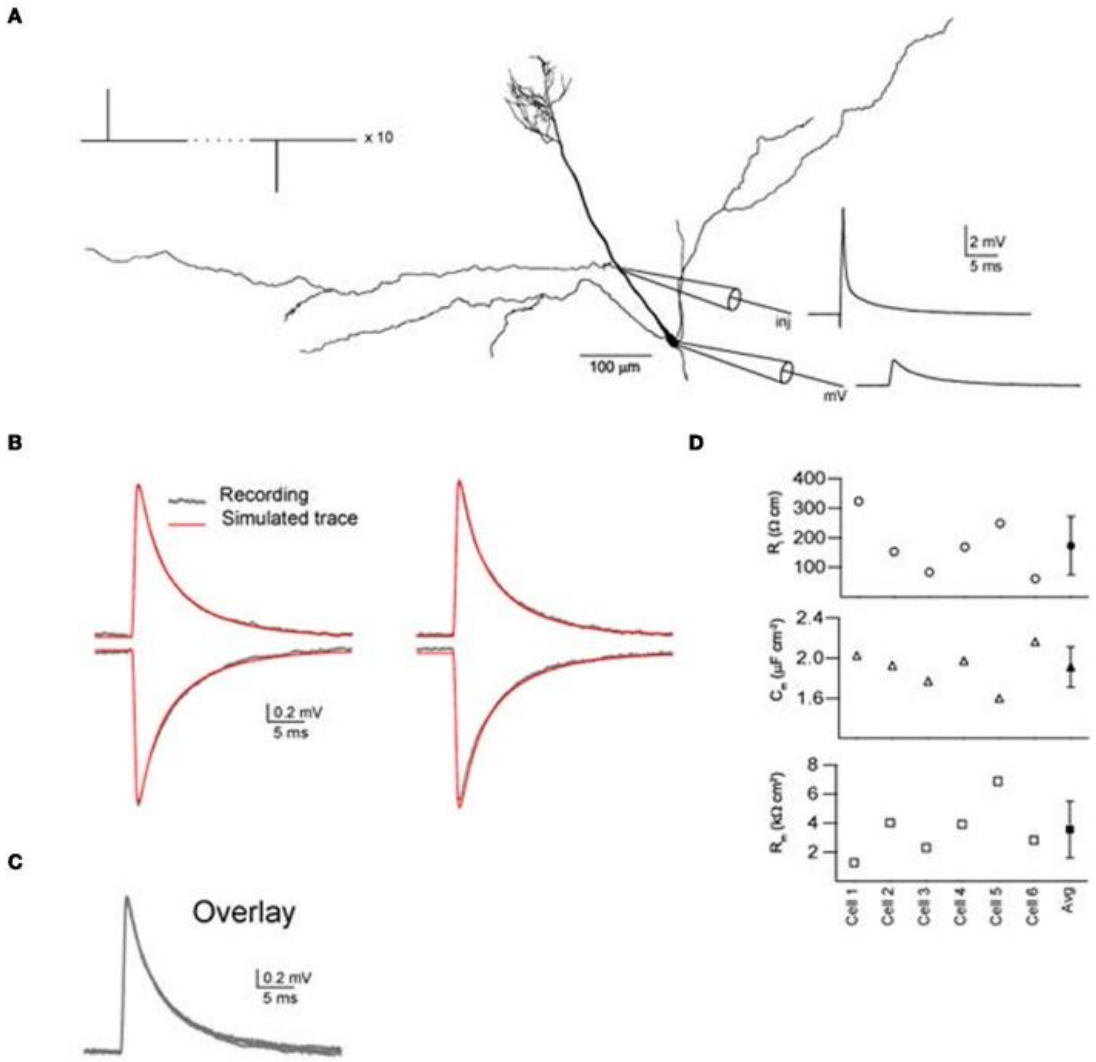
# The Plan

- 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

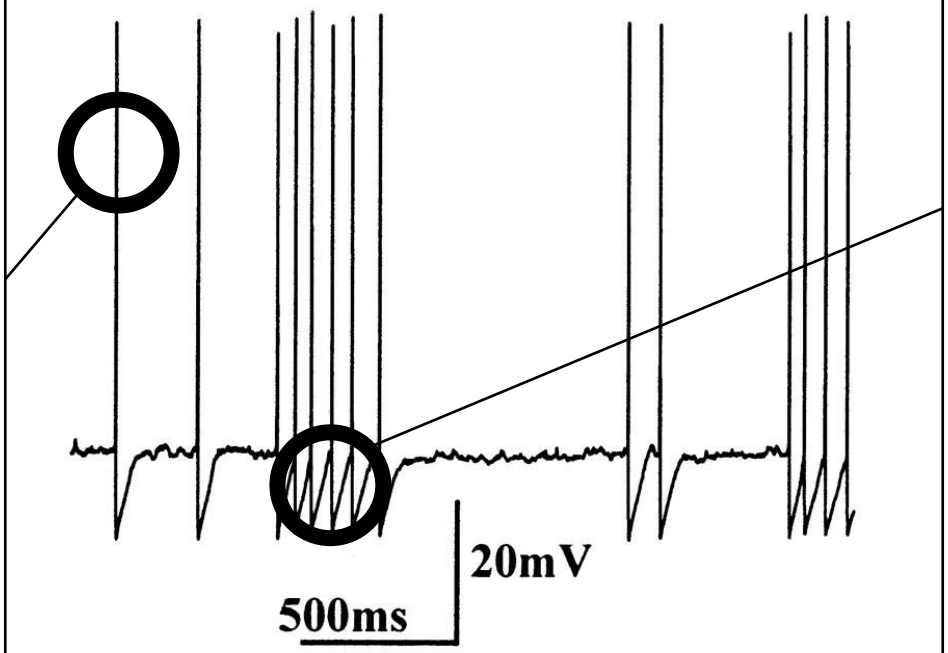
- The current model consists of a Gap-Junction connected network of 6 mitral cells representing a single glomerulus
- To explore ion channel dynamics we will need to revert back to single cells
- The single cell models have a good passive model foundation from fitting to dual patch clamp recordings
-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

# O’Connor, Angelo and Jacob 2012



# Phases 1 and 2

**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).**




**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 |
|---|---|---|---|---|---|---|---|---|
| $\tau_{activation}$ | 12·18 ± 1·79 (7) | 9·11 ± 2·26 (5) | 6·68 ± 1·54 (6) | 6·51 ± 1·56 (5) | 4·94 ± 1·24 (7) | 3·56 ± 1·05 (6) | 3·45 ± 1·01 (7) | 3·05 ± 0·73 (6) |
| $\tau_{decay}$ | — | 51·17 ± 2·45 (10) | 47·84 ± 3·02 (8) | 48·32 ± 3·25 (8) | 45·21 ± 3·76 (10) | 44·11 ± 2·74 (9) | 46·19 ± 2·01 (9) | 43·44 ± 2·05 (9) |

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

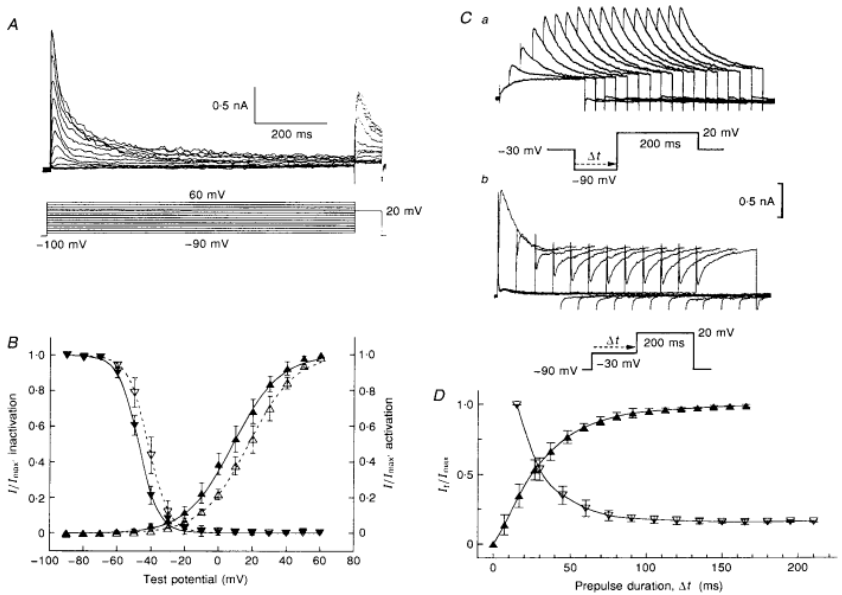
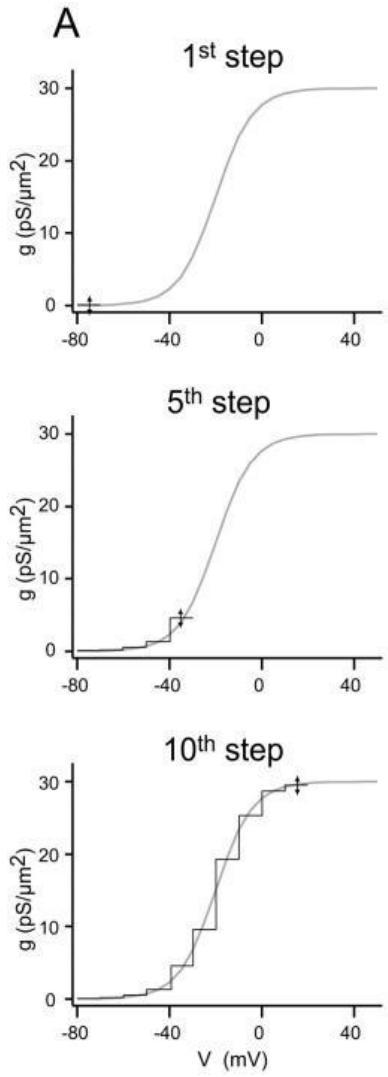
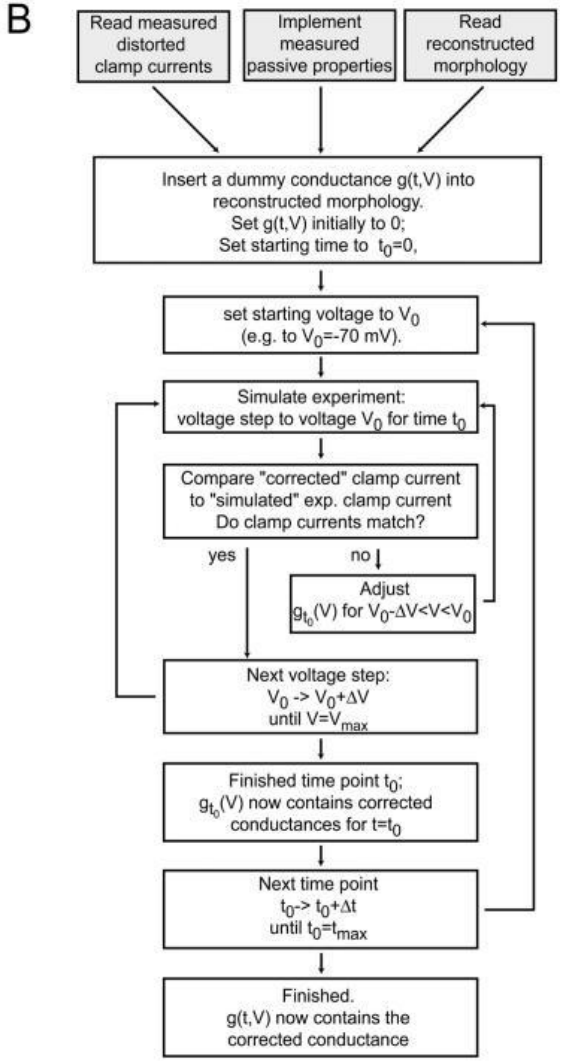


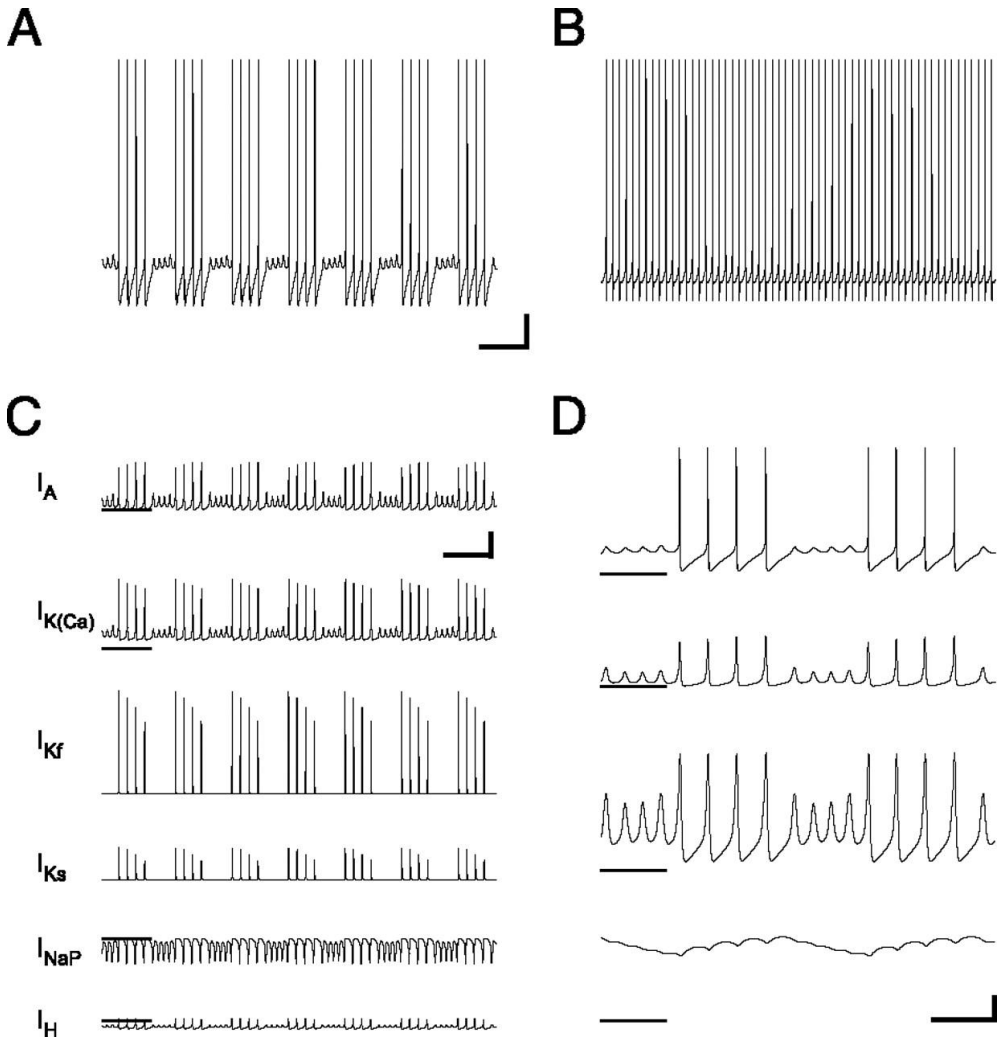

**Figure 4. Kinetics of $I_A$**

# Schaefer et al. 2003



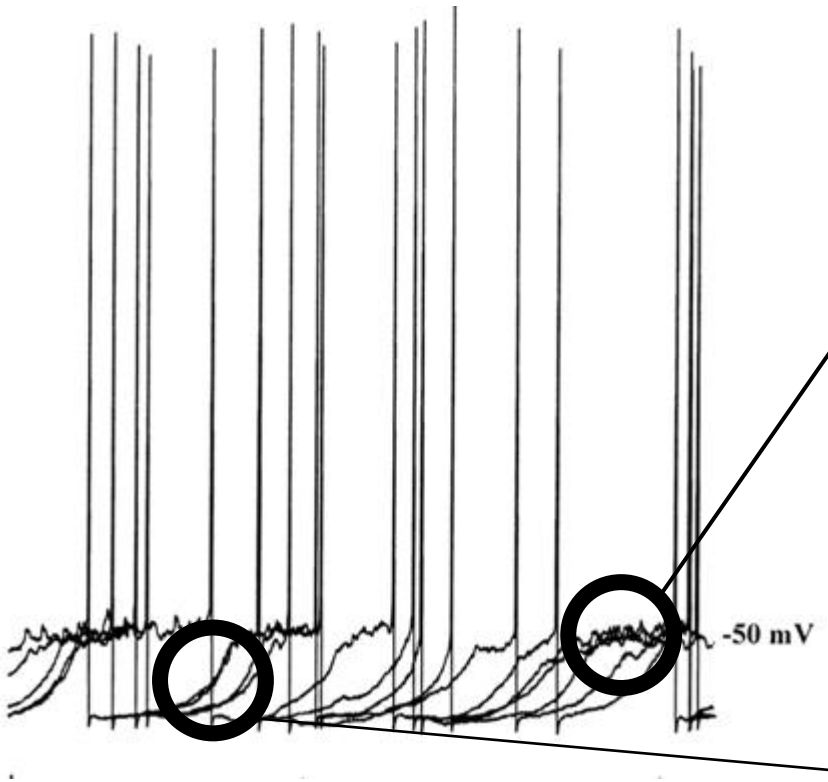
# Mechanisms and currents underlying mitral cell bursting.




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

Journal of Neurophysiology

# Phase 3 Modelling Sub-Threshold Oscillations and Bistability

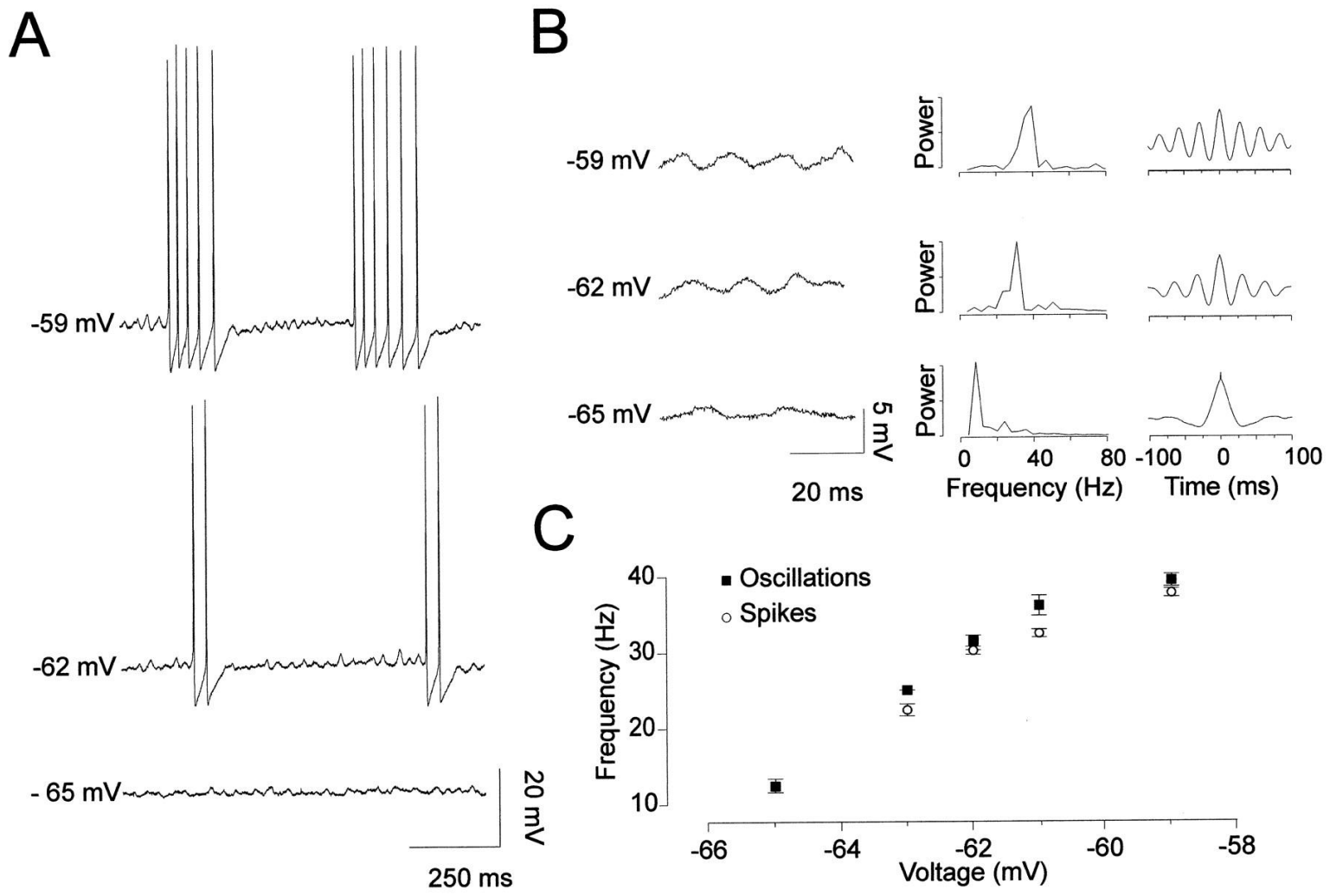



Philip Heyward et al. J. Neurosci. 2001;21:5311-5320

**Phase 3a**: model the sub-threshold oscillations that **Desmaisons et al (1999)** reported were produce 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**.

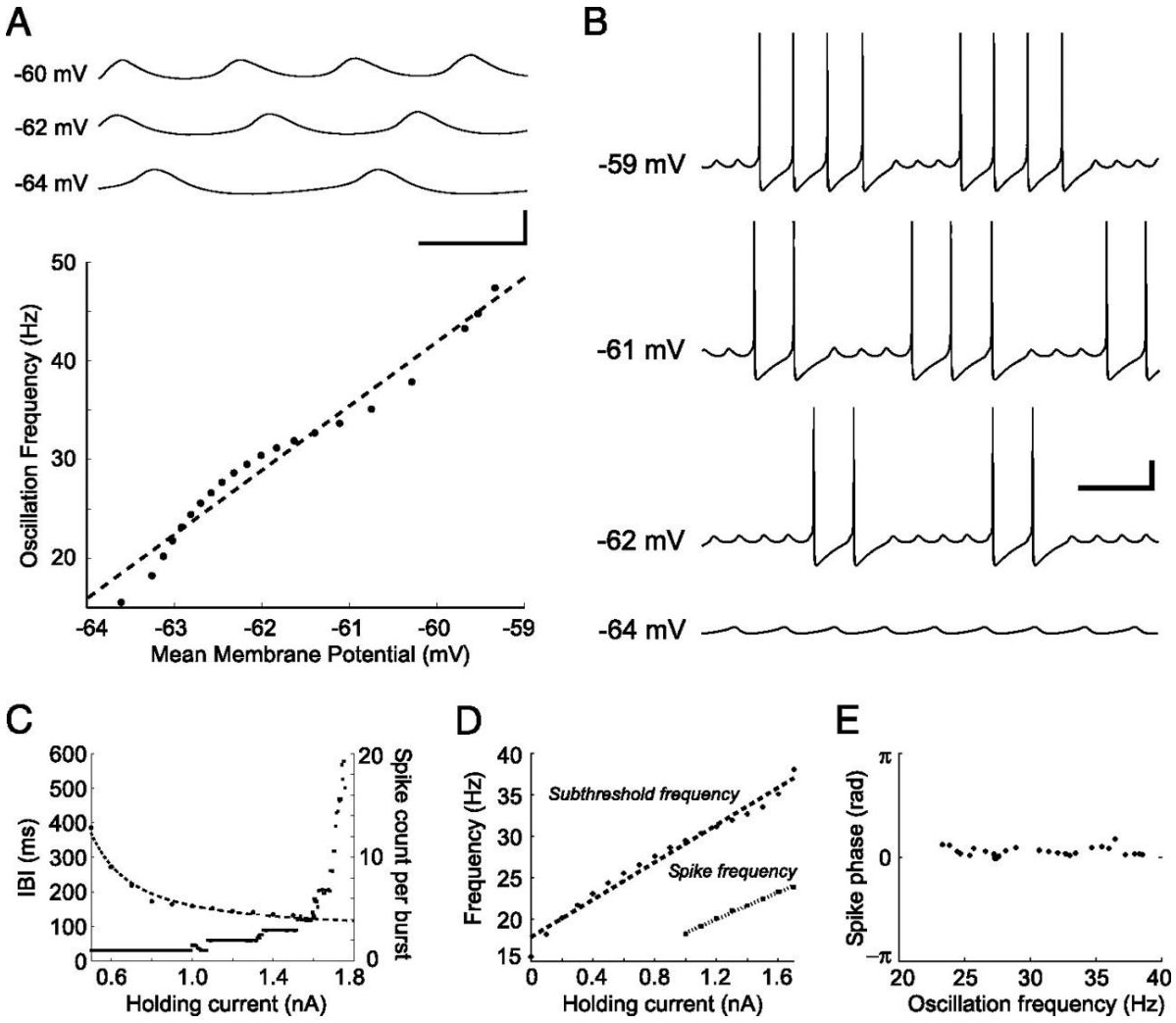
**Phase 3b**: **model bistable properties in the mitral cells** as reported in **Heyward et al. (2001)** with a down state produced by activation of an ohmic potassium current $I_{K(ATP)}$ **Rubin and Cleland 2006.**

# Subthreshold membrane potential oscillations are voltage-dependent.




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

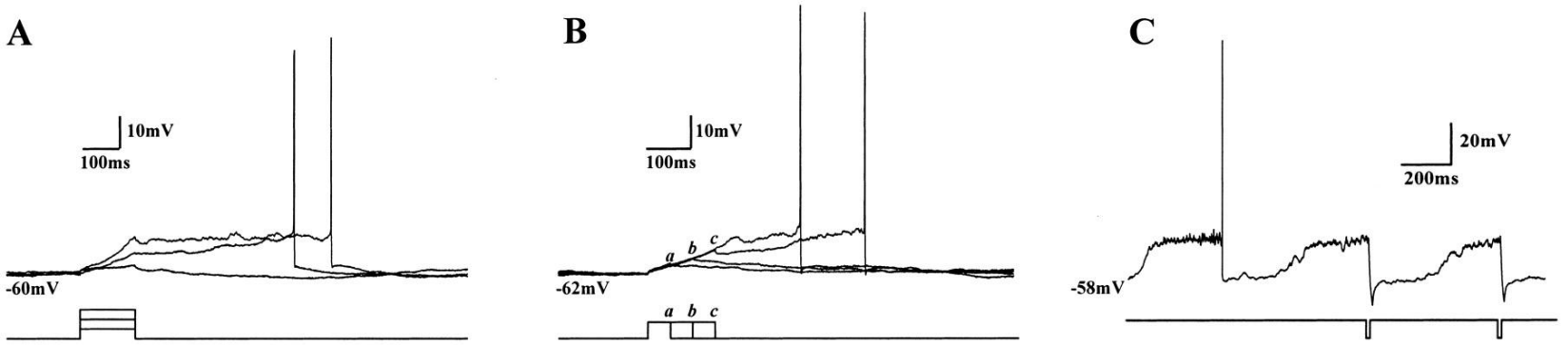
# Basic electrophysiological properties of the model mitral cell.




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

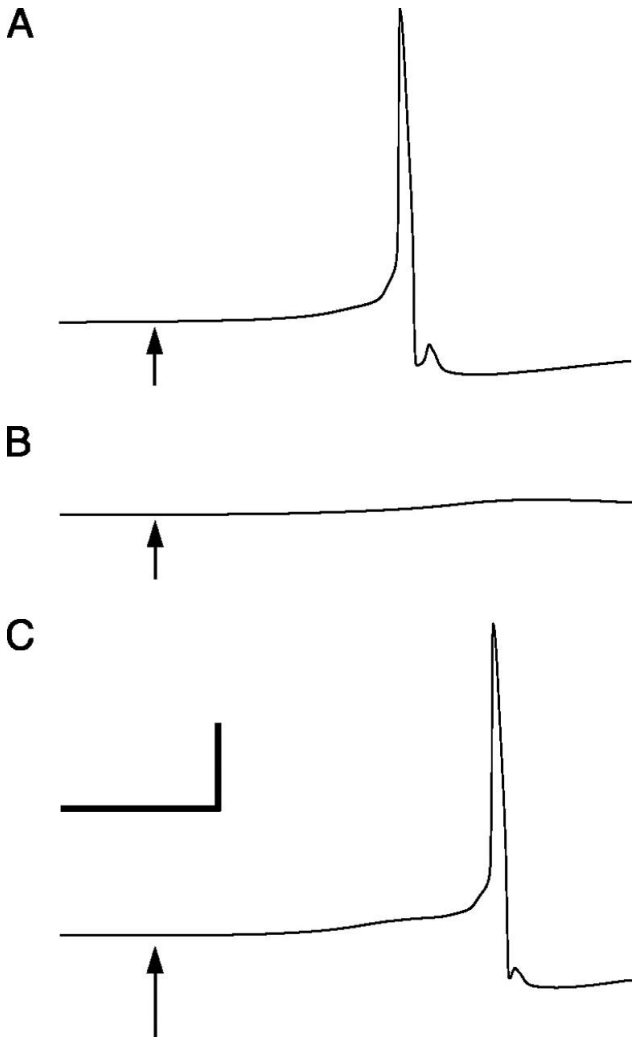
Journal of Neurophysiology

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




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

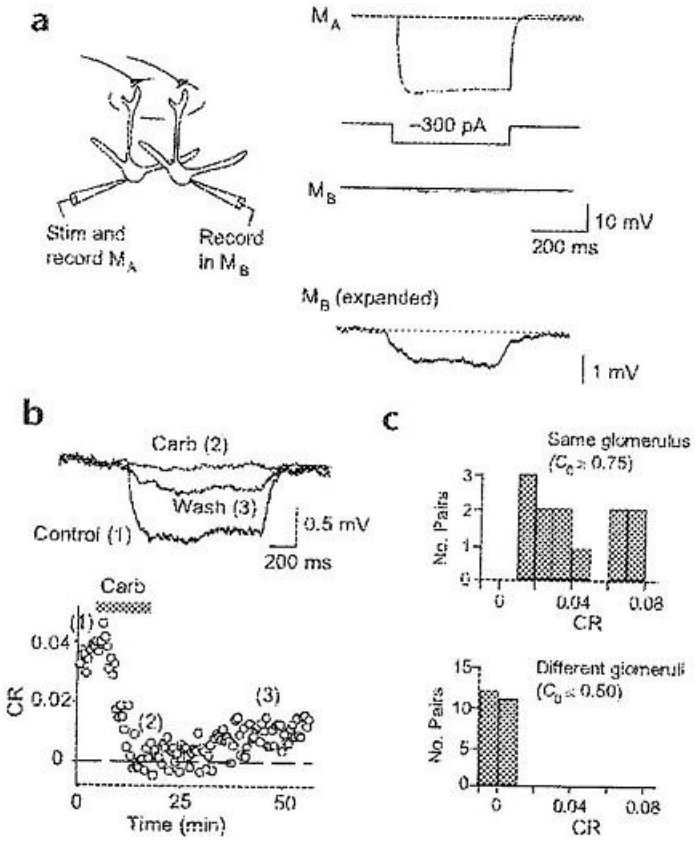
**Activation of an ohmic potassium current IK(ATP) generates a down-state.**




**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




Schoppa and Westbrook 2002

**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

- And follow the discussion forum at:

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

# Thank you for Listening