Systematic automated validation of detailed models of hippocampal neurons against electrophysiological data

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Introduction

Motivation: Anatomically and biophysically detailed data-driven neuronal models can be useful tools in understanding and predicting the behavior and function of neurons. There are now a large number of different models of many cell types available in the literature, that were developed using different methods and for different purposes These published models were usually built to capture some important or interesting properties of the given neuron type, i.e., to reproduce the results of a few selected experiments. It is often unknown, how these models would behave outside their original context, or whether they are able to generalize beyond their original scope. It is a hard and complex task to systematically compare model behaviours.

Solution: Systematic, automatized validation is needed.

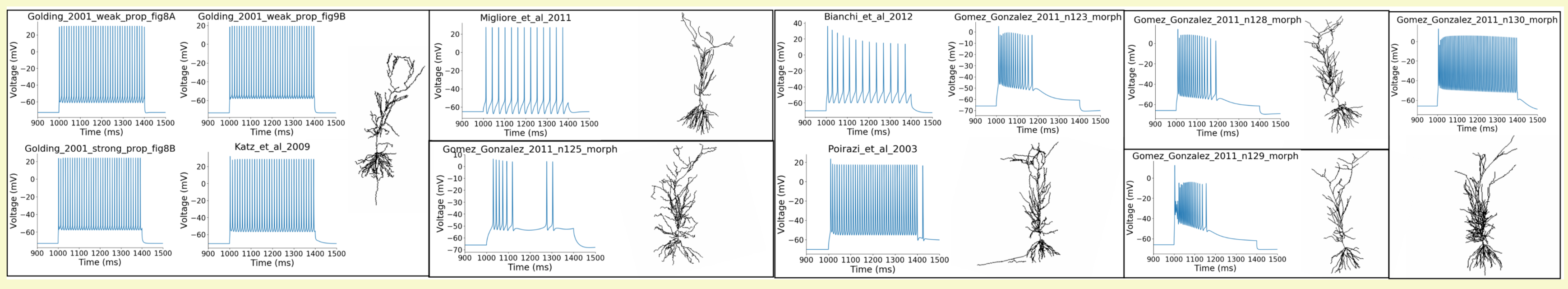
We have developed an automated test suite called HippoUnit for the systematic validation and comparison of models of rat hippocampal CA1 pyramidal cells. Here we present how we applied HippoUnit to test and compare the behavior of several different CA1 pyramidal cell models available on ModelDB (McDougal et al. 2017), against electrophysiological data from the literature.

HippoUnit

A Python test suite based on the SciUnit framework (Omar & Gerkin, 2014) which was developed for the validation of scientific models against experimental data. The tests of HippoUnit automatically run simulations on CA1 pyramidal cell models built in the NEURON simulator that mimic the electrophysiological protocol from which the target experimental data were derived. Then the behavior of the model is evaluated and quantitatively compared to the experimental data using various feature-based error functions. https://github.com/KaliLab/hippounit

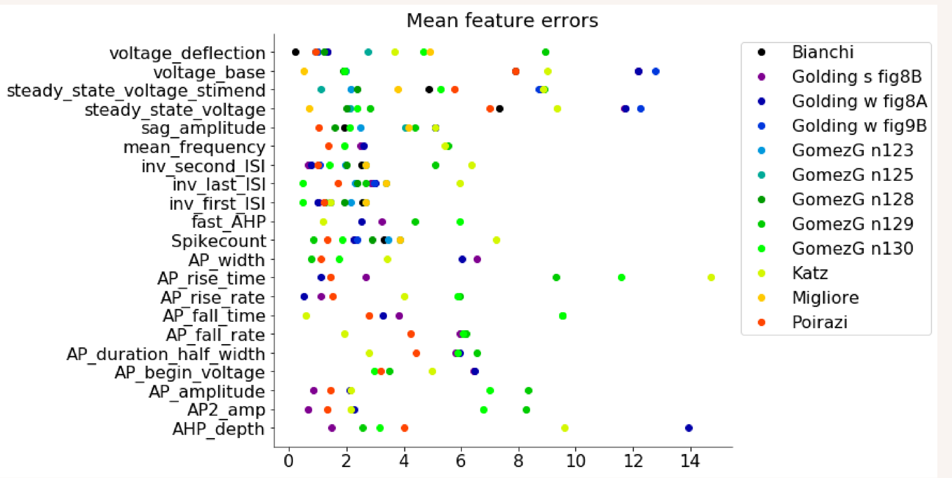
CA1 pyramidal cell models from literature that have been tested

- **Golding et al. (2001)** (ModelDB: 64167): Shows the dichotomy of the back-propagation efficacy at distal trunk regions. Three versions are tested (Fig. 8A, Fig. 8B and Fig. 9B of the paper)
- **Katz et al. (2009)** (ModelDB: 127351): Based on Golding et al. (2001) model. Investigates the effect of the distribution of synapses on the apical dendrites on the dendritic integration.
- **Migliore et al. (2011)** (ModelDB: 138205): Studies schizophrenic behaviour. Based on models developed to investigate the initiation and propagation of action potentials in oblique dendrites.
- **Bianchi et al. (2012)** (ModelDB: 143719): Shows the mechanisms behind depolarization block observed experimentally. Based on Shah et al. (2008) and Poirazi et al. (2003) models .
- **Poirazi et al. (2003)** (ModelDB: 20212): Was designed to clarify the issues about the integrative properties of thin apical dendrites.
- **Gómez González et al. (2011)** (ModelDB: 144450): Based on the Poirazi et al. (2003) model. Replicates the experimental data of Losonczy and Magee (2006) on the nonlinear signal integration of radial oblique dendrites. The model was adjusted to five different detailed morphologies.

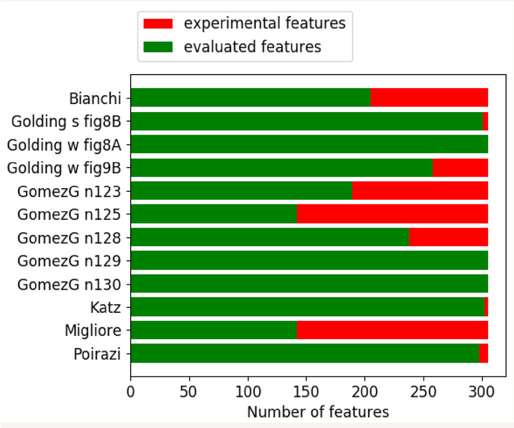


The morphologies of the different models and their voltage responses to a 0.6 nA 400 ms current injection.

The **Somatic Features Test** evaluates (using eFEL) and compares to experimental data the features of the somatic membrane potential response to somatic current injections of varying amplitudes.



Mean feature errors (# sd) of the different models. Feature error values are averaged over the different input step amplitudes.

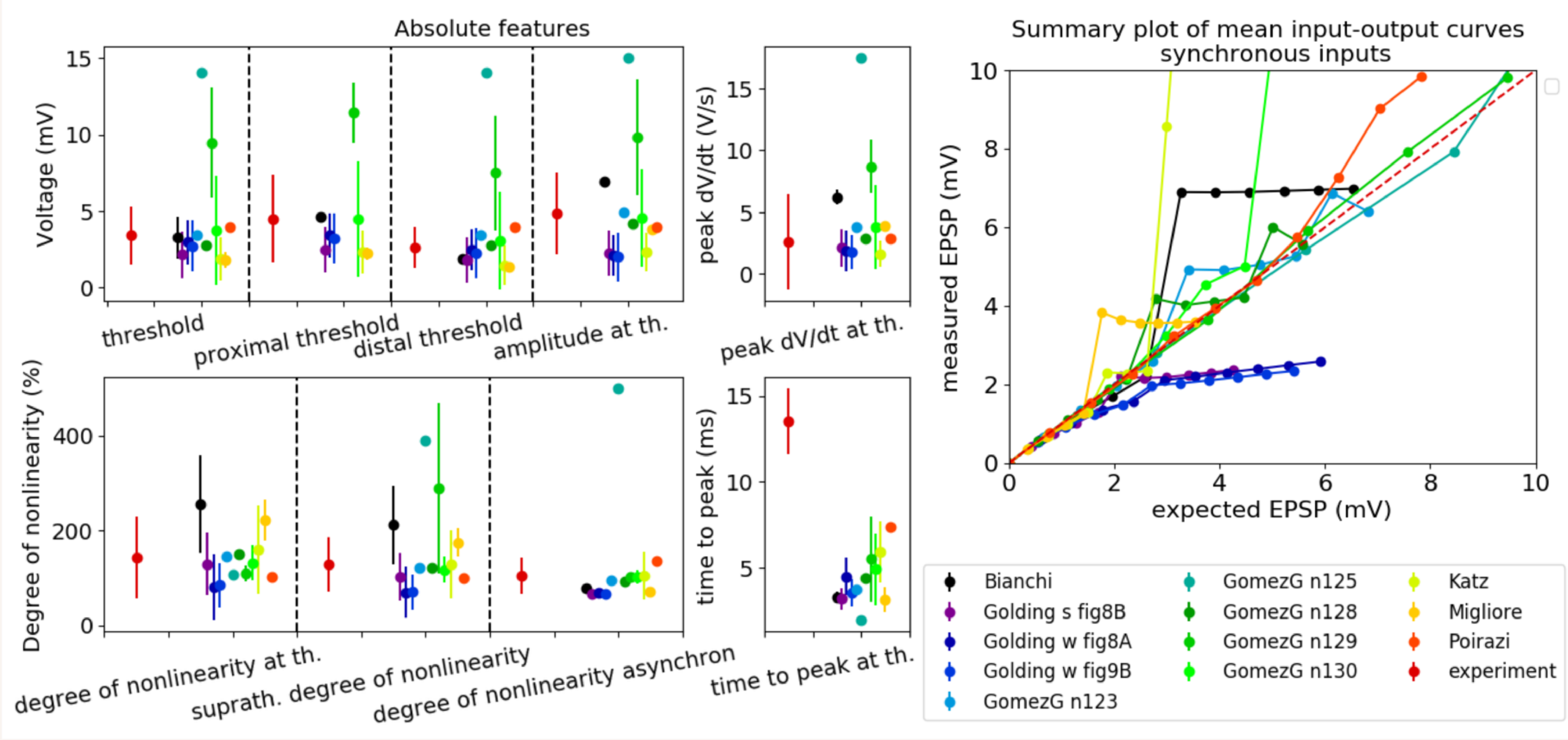


Experimental data obtained from patch clamp recordings in rats by Judit Makara were used.

Number of experimental features attempted to be evaluated for the models (red), and number of successfully evaluated features (green).

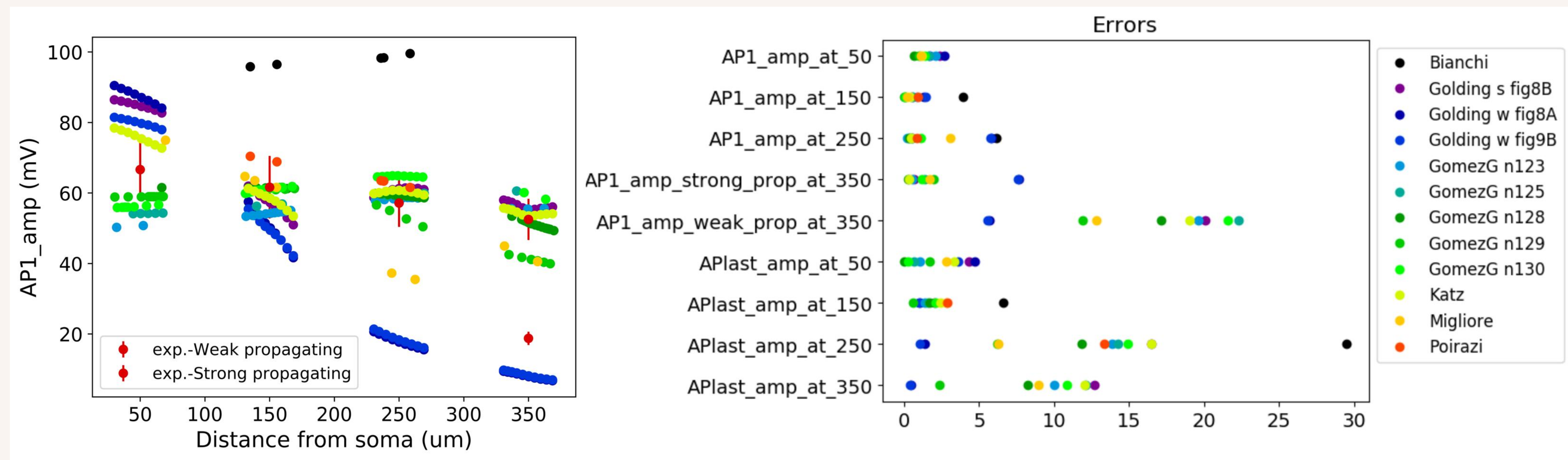
Absolute feature values extracted from the models' voltage response to somatic current injection of varying amplitude compared to experimental values (darkest red) that were extracted from the data set. (Not all the evaluated features are shown here)

The **Oblique Integration Test** probes the integration properties of the radial oblique dendrites for increasing number of synchronous and asynchronous inputs. (Losonczy, Magee 2006)



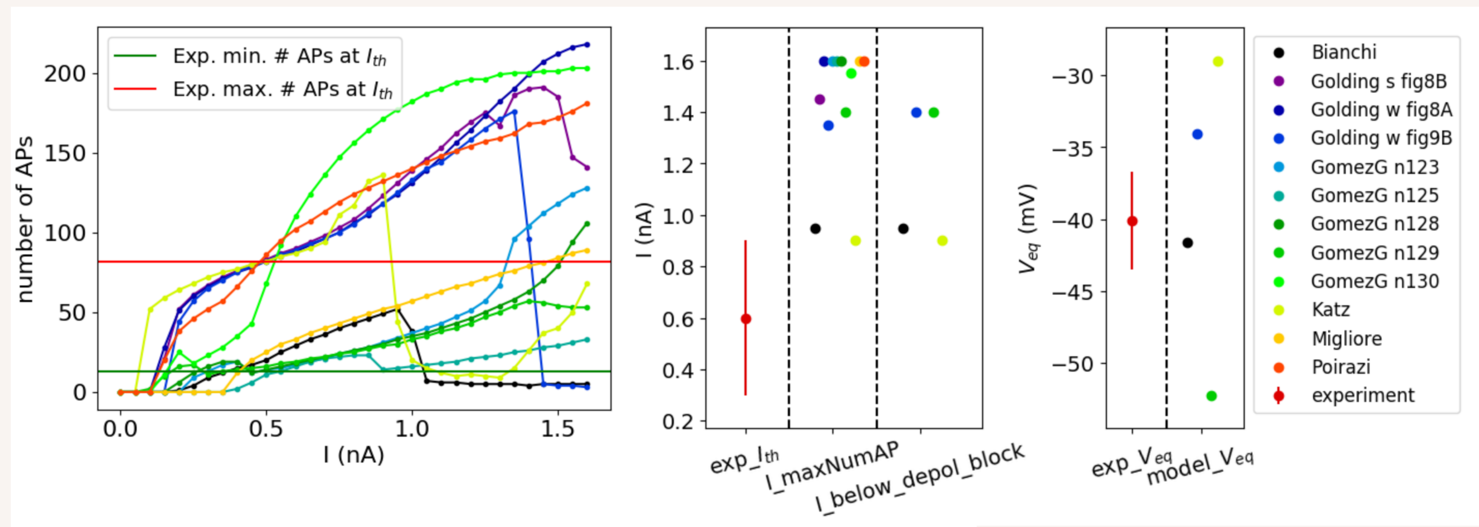
Comparison of the models' responses to experimental results (dark red) according to features of dendritic integration. (left), and the averaged input – output curves of all the dendritic locations examined .

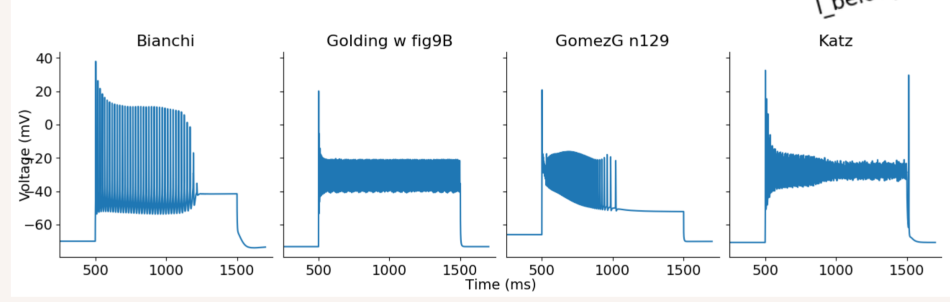
The **Back-propagating AP Test** Evaluates the mode and efficacy of back-propagating action potentials at different locations on the apical trunk. The amplitude of the first and last AP of a train (frequency around 15 Hz) is compared to experimental data from Golding et al. (2001).



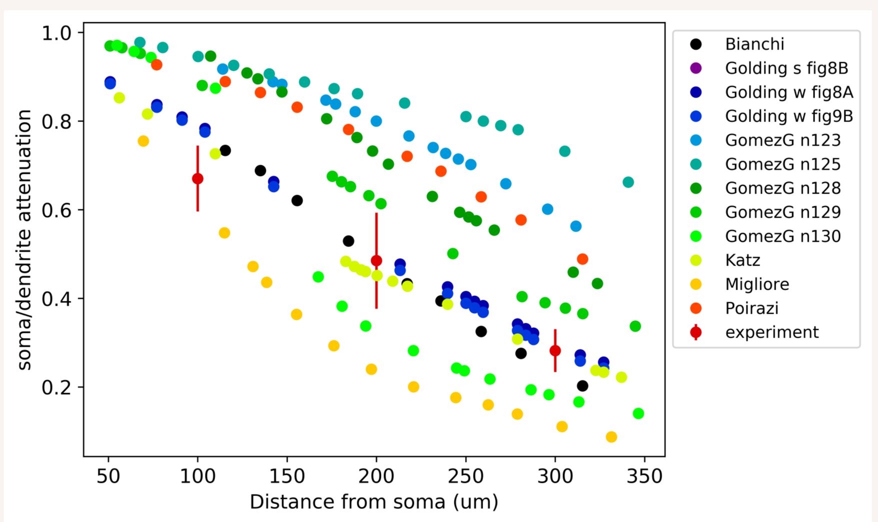
The amplitudes of the first back-propagating action potentials (in an around 15 Hz train) as a function of recording location distance from the soma (left), and Feature error scores achieved by the different models on the Back-Propagating AP Test (right)

The **Depolarization Block Test** aims to determine whether the model enters depolarization block in response to prolonged, high intensity somatic current stimuli. (Bianchi et al. 2012)





Number of APs fired by the models in response to current injections of increasing intensity (top left). Depolarization block feature values extracted from the models' behavior. (top right). Voltage traces of models, that the test declared as depolarization block. (bottom)



The **PSP Attenuation Test** evaluates how much the post synaptic potential (using EPSC stimulus) attenuates from the main apical dendrite (different distances) to the soma. (Magee & Cook 2000)

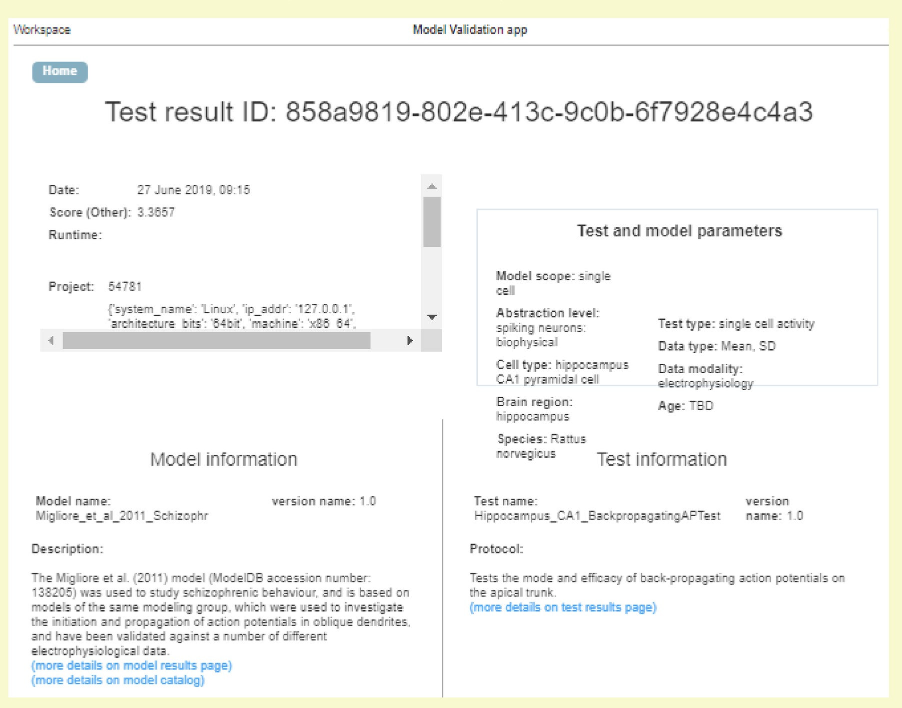
Soma/dendrite EPSP attenuation as a function of the input distance from the soma in the different models.

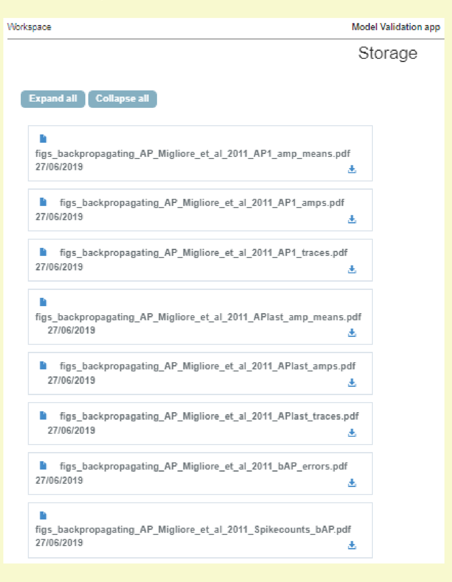
Integration into the validation framework of the Human Brain Project

As part of the Human Brain Project, we have developed a software framework for quantitative validation testing that explicitly supports applying a given validation test to different models. The framework consists of a set of Python modules, building on the SciUnit package, and a web service. The framework allows validations to be permanently recorded, examined and reproduced.

	hippo_ca1_bap (1.0)	hippo_ca1_depolblock (1.0)
bianchi_2012(1.0)	11.5350090578	0.925589478031
golding_2001(fig8B)	4.94284832613	100.0
golding_2001(fig8A)	2.89672815491	100.0
golding_2001(fig9B)	2.55697788364	12.3164891362
gomez_2011(n123_morph)	3.74715631897	100.0
gomez_2011(n125_morph)	4.06770801183	100.0
gomez_2011(n128_morph)	2.88601506953	100.0
gomez_2011(n129_morph)	1.79328685347	2.96512704747
gomez_2011(n130_morph)	3.97204692535	100.0
katz_2009(1.0)	4.57749910901	1.75580928614
migliore_2011(1.0)	3.36571679386	100.0
poirazi_2003(1.0)	4.48336505013	100.0

Running the validation tests through the Validation Framework a score matrix can be created where the scores are hyperlinks to the validation framework's result page for that score. Here detailed information on the test, the model and the result can be found.

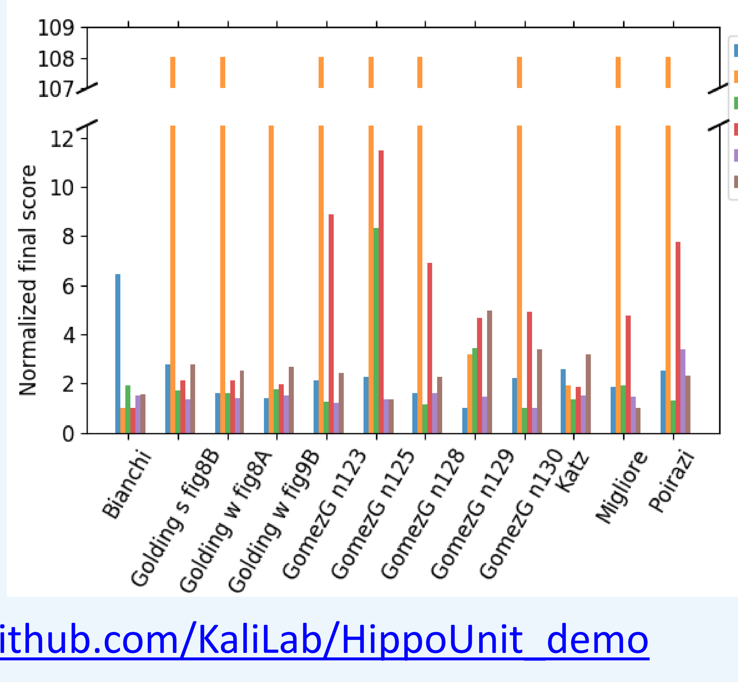




The Results page also has links to all the output files of the test.

Conclusion

- We have developed a validation tool called HippoUnit to make it possible to systematically test the generalization properties of models of hippocampal CA1 pyramidal cells and make quantitative comparisons between the models and experimental data.
- Using Hippounit, we compared the behavior of several hippocampal CA1 pyramidal cell models in several distinct domains, and found that all of these models perform well in some domains (typically on features they were built to capture) but badly in others.



Normalized final scores achieved by the different models on the different tests of HippoUnit.

- Detailed validation results and Jupyter notebooks on how to use HippoUnit are available at: https://github.com/KaliLab/HippoUnit_demo
- By providing the software tools and examples on how to validate these models, we hope to encourage the modeling community to use more systematic testing during model development, in order to create neural models that generalize better, and make the process of model building more reproducible and transparent.

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