Guiding the modeller: Organizing and selecting experimental data for single cell models using the CoCoDat database.

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Abstract

Collating, organizing and selecting quantitative experimental data are timeconsuming tasks necessary for building and constraining biophysically realistic neuronal models. The CoCoDat (*Co*llation of *Co*rtical *Dat*a) database has been designed as an advanced environment for storing, organizing and retrieving detailed, uninterpreted quantitative data on morphology, electrophysiology and connectivity from the published literature according to neurophysiological concepts. All experimental data are linked to exact bibliographical references and detailed records of procedures used in the experiments that produced the data. We demonstrate the usefulness of CoCoDat for implementation of an example model of a layer 5 pyramidal neuron from the rat barrel cortex.

Key words: Databasing, microcircuitry, quantitative experimental data, realistic modelling.

Data collation and selection for realistical modelling

When modelling biophysically realistic cortical microcircuits a large amount of experimental data describing cellular components and their interconnections are necessary to construct and constrain the models. Single neuron morphologies determining the passive membrane properties are populated with subdomain-specific distributions of ionic and synaptic conductances to constitute a model of the firing properties and functional response of the neuron. The CoCoDat database has been designed to facilitate the time-consuming tasks of collating, organizing and selecting the optimal experimental data for such modelling projects

[3]. CoCoDat is implemented using the relational database approach with four major data groups under the headings *Literature, Experimental Methodology, Mapping of Recording Site* and *Experimental Findings*. All data are initially anchored in detailed bibliographical data for the publication in question. Further information is divided into records of methods and mapping respectively, before it reunites at the level of the quantitative data records in the categories needed for modelling: *Morphology, FiringProperties, IonicCurrents, IonicConductances, SynapticCurrents* and *Connectivity*. All data in CoCoDat are entered as given in the original publication. The basic database structure is derived from the CoCoMac database of cortical connectivity in the macaque monkey [11]. CoCoDat currently contains a total of 208 quantitative experimental records in the six above mentioned categories. These are linked to 65 recording sites from 37 publications.

Using CoCoDat for data selection

To illustrate the usefulness of CoCoDat in selecting data for detailed neuronal modelling, we consider an example model based on a detailed morphological reconstruction of a layer 5 regular spiking pyramidal cell from the rat barrel cortex [9]. All experimental data in CoCoDat are linked to a *RecordingSite* consisting of hierarchically organized *BrainSites* describing the location of the recording on the four levels of description: *BrainRegion*, *Layer*, *NeuronType* and *NeuronCompartment*. To extract information on the example cell these criteria are selected on the CoCoDat *SearchBoard*. An initial query of the current database contents on ionic currents from all compartments (*GM-Comp_gen)* of layer 5 (*GM-IsoCtx_L5*) pyramidal neurons (*GM-C_Pyr*) in the barrel cortex (*GM-Ctx_B*) of the rat produces no results, but when allowing for an automatic relaxation of the search-criteria by the search-routine we receive results from the closest possible match (Fig. 1).

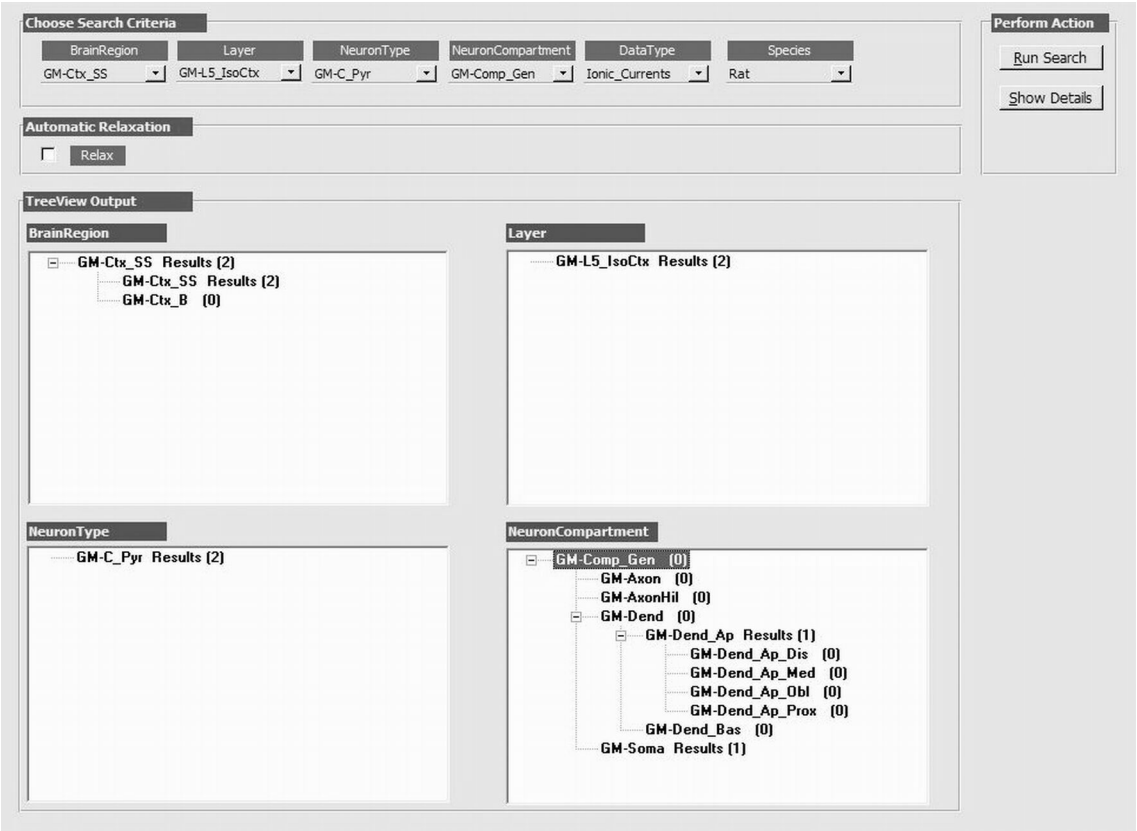


Figure 1: The CoCoDat *SearchBoard*. The upper frame contains the search criteria (after relaxation). The four panels show the hierarchical relationships between the *BrainSites* constituting the returned *RecordingSites*. Numbers in parenthesis indicate the number of returned *RecordingSites* a *BrainSite* is part of.

To produce results, the original criterion for *BrainRegion* (barrel cortex) has been relaxed to its *parent* in the anatomical hierarchy, - the somatosensory cortex. The four panes on the *SearchBoard* illustrate the distribution of results on the four levels of description by visualizing the hierarchies (expanded using the "+" signs on each branch-point) of *BrainSites* constituting the *RecordingSites* to which returned results are linked. Using this kind of visualization gives the user an immediate idea of the types of available results as well as the possibility to appraise the logical distance between the originally desired *RecordingSite* and the ones obtained after relaxation, thus helping the user to select the best match.

Both the automatic relaxation and general search routine utilize the hierarchical organization of *BrainSites* on the four levels of description. These hierarchies detail the anatomical parent and child(ren) of each *BrainSite* in the database, ensuring that data linked to substructures of

the initially user-specified *RecordingSite* will also be returned by the query: Specifying e.g. dendrite as *NeuronCompartment* will also return results from basal dendrite as well as apical dendrite and subdomains thereof. When selecting automatic relaxation of one of the four levels of the description, the search routine will use the hierarchical relations to select the parental *BrainSite* in case no results are returned for the initial criteria (in the example above relaxing from barrel to somatosensory cortex). This relaxation will continue until the query produces results, or the top of the hierarchy is reached.

The detailed data can be inspected in several ways beginning with a summary detailing the full *RecordingSite* and the qualitative characteristics of the data (Fig. 2). For each *RecordingSite* the user can expand these into a detailed view containing all quantitative data, references and quotes from the published literature.

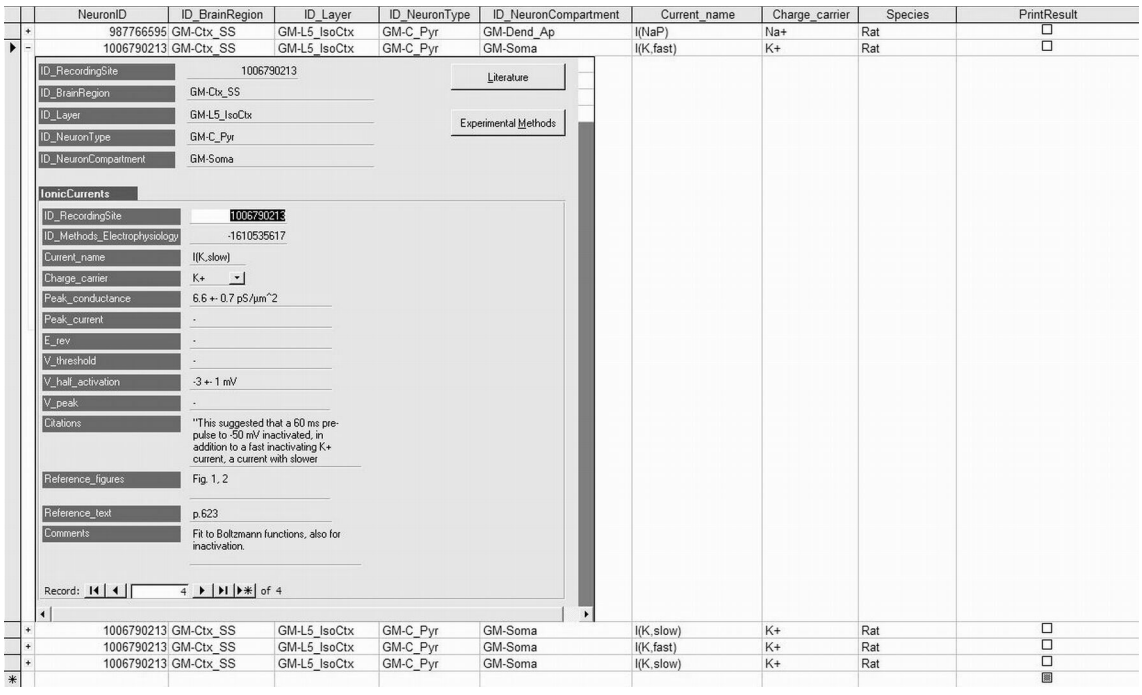
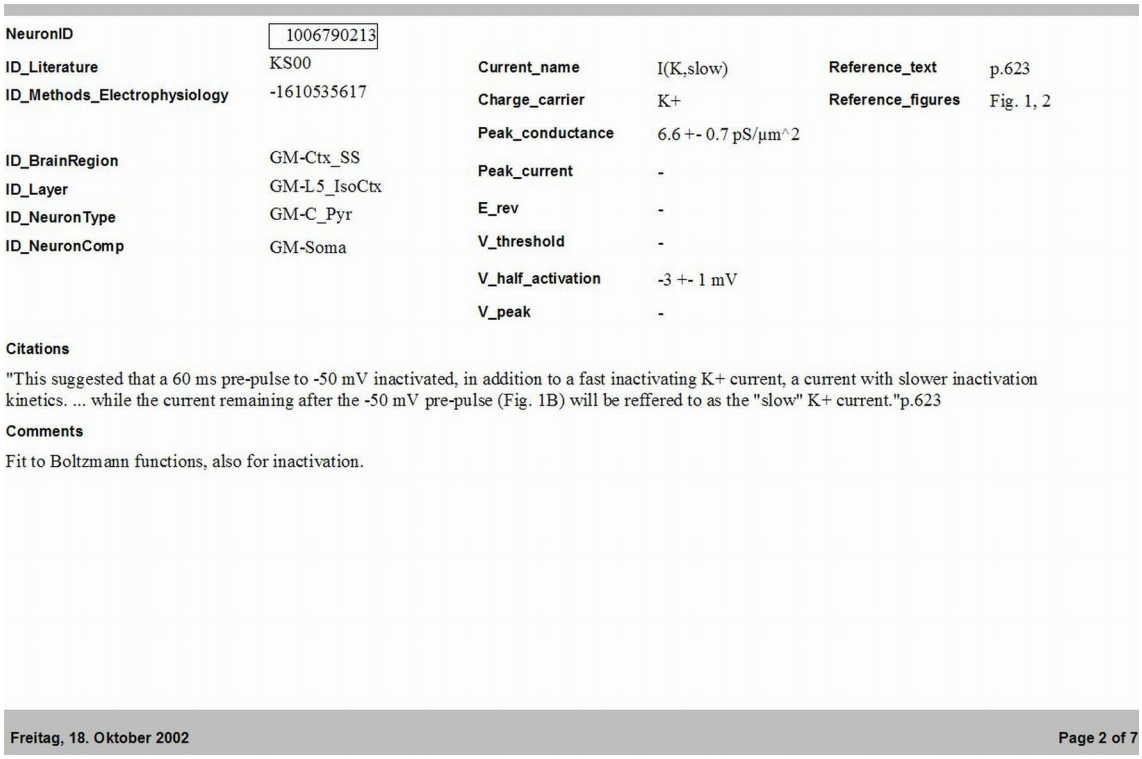


Figure 2: The CoCoDat *SummaryForm* is opened from the *SearchBoard.* An expandable table summarizes search results and *RecordingSites*. By clicking the "+" signs a detailed view of the experimental records can be inspected. Results are selected for printable *Reports* by ticking the boxes in the rightmost column.

In addition to the detailed data the user can call up the detailed bibliographic and methodological information registered in the database by clicking the designated buttons on

the graphical form. After inspecting the quantitative information the user can select which datasets to export to printable format by returning to the *SummaryForm* and marking these in the designated tickboxes. Similar reports can be generated for the associated literature and experimental methodology (Fig. 3).



NeuronID	1006790213				
ID_Literature	KS00	Current_name	I(K,slow)	Reference_text	p.623
ID_Methods_Electrophysiology	-1610535617	Charge_carrier	K+	Reference_figures	Fig. 1, 2
		Peak_conductance	6.6 +- 0.7 pS/µm^2		
ID_BrainRegion	GM-Ctx_SS	Peak_current	-		
ID_Layer	GM-L5_IsoCtx	E_rev	-		
ID_NeuronType	GM-C_Pyr	V_threshold	-		
ID_NeuronComp	GM-Soma	V_half_activation	-3 +- 1 mV		
		V_peak	-		

Citations

"This suggested that a 60 ms pre-pulse to -50 mV inactivated, in addition to a fast inactivating K+ current, a current with slower inactivation kinetics. ... while the current remaining after the -50 mV pre-pulse (Fig. 1B) will be reffered to as the "slow" K+ current."p.623

Comments

Fit to Boltzmann functions, also for inactivation.

Figure 3: Reports of selected data can be automatically generated and are marked with the date of the search.

Implementing a first approximation model

The reconstructed morphology of a layer 5 regular spiking pyramidal neuron from the rat barrel cortex [9] was converted from NeuroLucida to GENESIS format using the software tool CVAPP [2]. To enable comparison between simulation results and experimental I-V characteristics, a general set of voltage-gated currents were sought in the CoCoDat database using records of *Experimental Methodology* describing modelling studies as an entry point. The extracted current equations were used for layer 5 pyramidal cells from visual cortex but also suited a diversity of other brain regions and cell types indicating general usefulness as a first approximation [6]. Inspection of the experimental I-V curves revealed a "sag" following

hyperpolarizing current injections characteristic of the activation of an H-current. Accordingly the GENESIS implementation of a hippocampal H-current available as prototype [12] was added to the model.

The I-V characteristics of a first-step model implemented in GENESIS using the reconstructed morphology and described current equations shows a relatively good likeness to the experimental results after adjusting only somatic conductance densities in the model (Fig. 4).

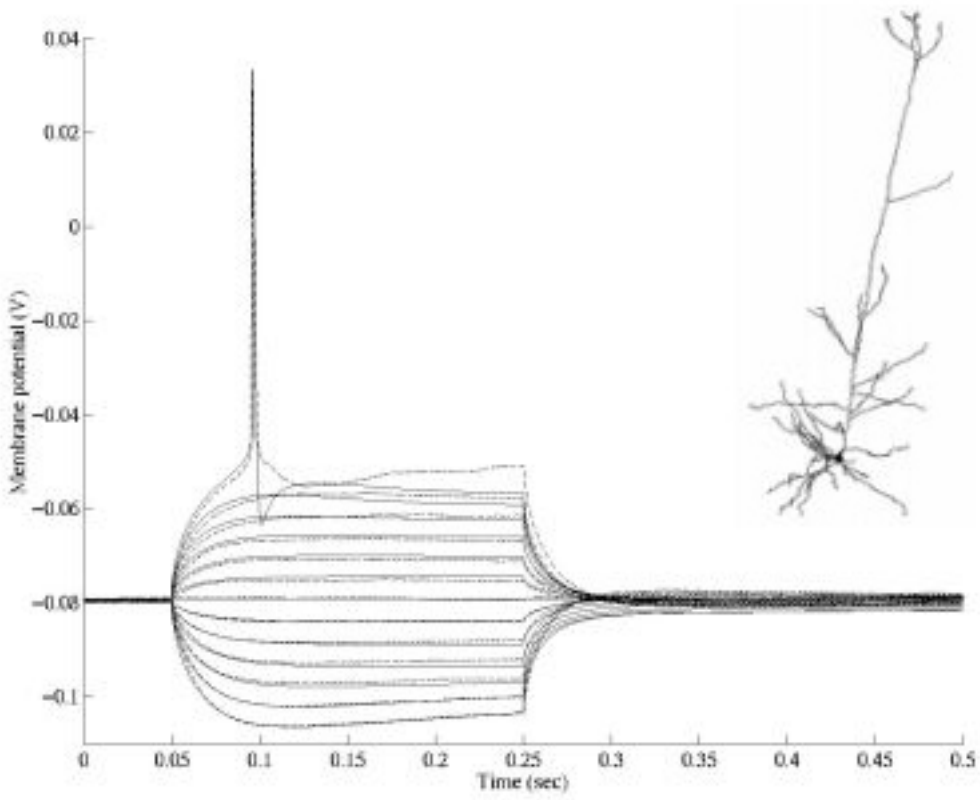


Figure 4: Comparing the response of the model (solid line) and recorded cell (dashed line) to a series of 200 msec current injections (from –360 pA to 360 pA). The inset shows the reconstructed neuronal morphology.

Further improvement of the model necessitates the implementation of data more specific to the particular neuron modelled. Table 1 contains a summary of the results returned by the earlier described query to the CoCoDat database as well as results of a similar query in the *IonicConductances* data category.

RecordingSite	*IonicCurrents*	*IonicConductances*
Somatosensory Cortex *Layer 5* *Pyramidal cell* *Soma*	$I_{K,\ slow}$ and $I_{K,\ fast}$ [5].	$K_{very\ slow,\ inact.}$, $K_{slow,\ inact.}$, $K_{fast,\ inact.}$ and BK [5].
Somatosensory Cortex *Layer 5* *Pyramidal cell* *Apical dendrite*	I_{NaP} [8]	K and BK [5].

Table 1: The experimental information extracted from CoCoDat by searching for ionic currents and conductances from layer 5 pyramidal neurons in the somatosensory cortex of rats.

As can be seen from the tabulated results information is available on potassium currents and conductances in the neuron soma and apical dendrite [5] as well as the presence of a persistent sodium current in the apical dendrite [8]. It is likely that the implementation of the detailed information from the CoCoDat search in the neuronal model would rectify the discrepancies between experimentally obtained and simulated I-V curves shown above, as these are most evident following the action potential elicited at the strongest depolarizing current injection. This indicates that the repolarization, which is typically governed by potassium conductances, is insufficiently described in this first approximation modelling step.

Discussion

Several databases and data-collections with single neuron and microcircuitry data already exist, but these are either limited to a e.g. reconstructed morphologies [1,2,4], tailored to a particular species [10] or provide only qualitative information and literature references [7]. CoCoDat provides a general database of microcircuitry and single cell information with direct access to quantitative data with detailed records of experimental methodology and specific references to relevant pages and figures in the original publication. The flexible tools for dynamically retrieving and visualizing datasets for neuronal structures specified on four anatomical levels of description facilitates the selection of optimal data for a given modelling project. The possibility for exporting selected datasets in printable format after inspection of

the quantitative details allows for easy tracking of data available at the time of model construction.

Using the option of automatic search criteria relaxation facilitates the fast retrieval of data from neuronal structures matching the modelled object as closely as possibly, letting the user determine the least important initially selected criteria. A thorough investigation of the data space is possible by submitting on or more queries while manually selecting the parental *BrainSite* on one or more of the four levels of description after results are returned, thus giving the user an overview of closely related experimental results. By submitting a query with all four *BrainSites* set at the top-most *general* level the entire content of the database in a given *DataCategory* can be extracted for inspection.

The CoCoDat database is available for download at the URL http://www.cocomac.org as a zip-archive of an mdb file for Microsoft Access 2000. A planned future version implemented in mySQL would allow for a direct online interface as well as data submission to a central database.

Acknowledgements

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References:

[1] G.A. Ascoli, J.L. Krichmar, S.J. Nasuto, S.L. Senft, Generation, description and storage of dendritic morphology data, Phil. Trans. R. Soc. Lond. B 356 (2001) 1131-1145.
[2] R.C. Cannon, D.A. Turner, G. Papyali, H.V. Wheal, An on-line archive of reconstructed hippocampal neurons, J. Neurosci. Methods. 84 (1998)49-54.
[3] J.D.-Johnsen, J. Maier, K.E. Stephan, R. Kötter, CoCoDat: Collation of Cortical Data on Neurons and Microcircuitry. Systematic Storage and Retrieval of Experimental Data for Biophysically Realistic Modeling, in: R. Kötter, ed., NEUROSCIENCE DATABASES - A Practical Guide, (Kluwer Academic Publishers, 2003) 109-120.
[4] R.B. Gonzales, C.J. DeLeon Galvan, Y.M. Rangel, B.J. Claiborne, Distribution of thorny excrescences on CA3 pyramidal neurons in the rat hippocampus, J. Comp. Neurol. 430(3) (2001) 357-368.

[5] A. Korngreen and B. Sakmann,Voltage-gated K+ channels in layer 5 neocortical pyramidal neurones from young rats: subtypes and gradients, J Physiol 525 (2000) 621-639.
[6] Z.F. Mainen and T.J. Sejnowski, Influence of dendritic structure on firing pattern in model neocortical neurons, Nature 382 (1996) 363-366.
[7] J.S. Mirsky, P.M. Nadkarni, M.D. Healy, P.L. Miller, G.M. Shepherd, Database tools for integrating and searching membrane property data correlated with neuronal morphology, J. Neurosci. Methods 82(1) (1998) 105-121.
[8] T. Mittmann, S. M. Linton, P. Schwindt, W. Crill, Evidence for persistent Na+ current in apical dendrites of rat neocortical neurons from imaging of Na+-sensitive dye, J. Neurophysiol. 78(2) (1997) 1188-1192.
[9] D. Schubert, J.F. Staiger, N. Cho, R. Kötter, K. Zilles, H.J. Luhmann , Layer-specific intracolumnar and transcolumnar functional connectivity of layer V pyramidal cells in rat barrel cortex, J. Neurosci. 21(10) (2001) 3580-3592.
[10] L. Stein, P. Sternberg, R. Durbin, J. Thierry-Mieg, J. Spieth, WormBase: network access to the genome and biology of Caenorhabditis elegans, Nucleic Acids Res. 29 (2001) 82-86.
[11] K.E. Stephan, L. Kamper, A. Bozkurt, G.A.P.C. Burns, M.P. Young, R. Kötter, Advanced database methodology for the collation of connectivity data on the macaque brain (CoCoMac), Phil. Trans. R. Soc. Lond. B 356 (2001) 1159-1186.
[12] R.D. Traub, R. K. S. Wong, R. Miles, H. Michelson, A model of a CA3 hippocampal pyramidal neuron incorporating voltage-clamp data on intrinsic conductances, J. Neurophysiol. 66 (1991) 635-650.