Computational models and plausible (?) assumptions

It is best to base models on hypotheses
that require as little guessing as possible.

But some guessing is inevitably required because

- we know a lot about some things
- we know a bit about many
- we know very little about most--
  especially in biology

Parameter values: imprecise, and variable

Imprecison: most measured biological parameters are known to 2 significant figures at most.

Natural variability: even among cells of the same class, parameters vary from cell to cell within an individual, and across individuals.

How to deal with this?

Dealing with parameter variance *continued*

Eliminate variability within a cell class and across animals by basing parameters on experimental measurements taken from a single cell in a single animal?

Nope.

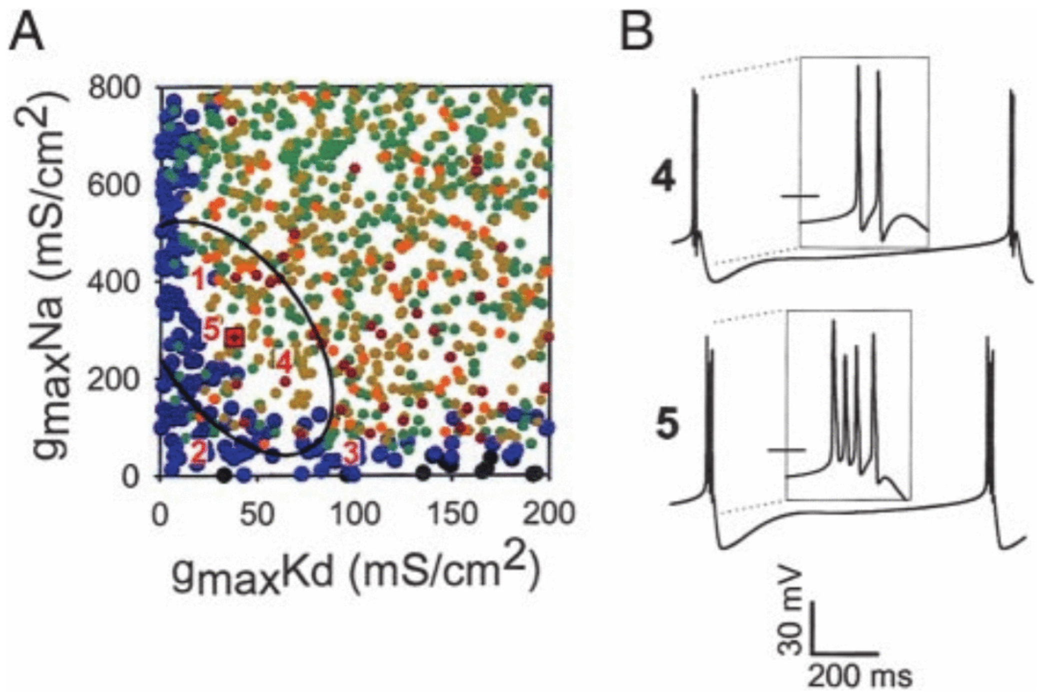
Cells deteriorate quickly (tens of minutes) so it is hard to measure even one parameter from a cell, let alone many.

Many experimental methods are so specialized and invasive that it is impractical to study more than one cell class in a single experiment using tissue from one animal.

Dealing with parameter variance *continued*

Reduce variance by averaging?

Fails if parameters covary (Golowasch et al. 2009).



Ref: Golowasch et al.. Failure of averaging in the construction of a conductance-based neuron model. Journal of Neurophysiology 87:1129-1131, 2002. PMID 11826077.

Parameters from other cells or species?

What if the hypothesis involves cells that we don't know much about?

Try to make plausible assumptions constrained by what is known about

. . . similar cell classes in the same species

. . . or in different species

. . . or not so similar cells in not so similar species.

Modeling may aid the interpretation of experimental results.

But predictions based on modeling studies are something else,
especially if they involve "plausible assumptions,"
because plausibility is not reality.

Predictions need to be confirmed by experimentation.

Reading the scientific literature

Common types of articles:

- Research report
- Review of a topic (often includes speculative hypotheses)

Today's papers: two research reports and a review.

Mainen, Z.F. and Sejnowski, T.J.. Influence of dendritic structure on firing pattern in model neocortical neurons. Nature 382:363-366, 1996.

Morse et al.. Abnormal excitability of oblique dendrites implicated in early Alzheimer's: a computational study. Frontiers in Neural Circuits, vol. 4, 2010, DOI 10.3389/fncir.2010.00016.

Shepherd, Gordon M and Rowe, Timothy B.. Neocortical lamination: insights from neuron types and evolutionary precursors.Frontiers in Neuroanatomy, vol. 11, 2017. DOI 10.3389/fnana.2017.00100.

Anatomy of a research report

Title

Authors and their affiliations

Abstract (brief synopsis)

Introduction (why did we do this? why should you care?)

Methods (one of the most important parts of the paper)

Results (descriptions of what happened)

Discussion (what new thoughts should we now have, comparison with previous reports, questions that remain to be answered, plans for future work)

Acknowledgments (who helped, funding sources)

Conflict of interest statements (especially if profits are to be made)

References (articles that report related prior work or competing hypotheses, URLs of open source tools--usually software--that were used)

Mainen and Sejnowski 1996

Mainen, Z.F. and Sejnowski, T.J.. Influence of dendritic structure on firing pattern in model neocortical neurons. Nature 382:363-366, 1996.

If this was an observational study, why did the authors do it?

If it was a hypothesis-driven study, what was the hypothesis?

Are assumptions stated clearly and justified? (usually happens in the Methods section)

What new thoughts should you have after reading it? (the paper's main findings and conclusions or inferences)

Morse et al. 2010

Morse et al.. Abnormal excitability of oblique dendrites implicated in early Alzheimer's: a computational study. Frontiers in Neural Circuits, vol. 4, 2010, DOI 10.3389/fncir.2010.00016.

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Shepherd and Rowe 2017

Some of the key concepts (as of 2017)

Telencephalon: cerebral hemispheres plus hippocampus, basal ganglia, and olfactory bulb

Four major classes of (excitatory) cortical neurons, named after their projections: IntraTelencephalic (IT), Pyramidal Tract (PT), CorticoThalamic (CT) (Fig. 1).

Three main classes of inhibitory interneurons, outside the scope of this paper.

Cortical circuits involve feedforward and feedback excitation and inhibition.

"Basic 3 layer cortical circuit" evolved into more complex circuits (Fig . 2)

Shepherd and Rowe 2017

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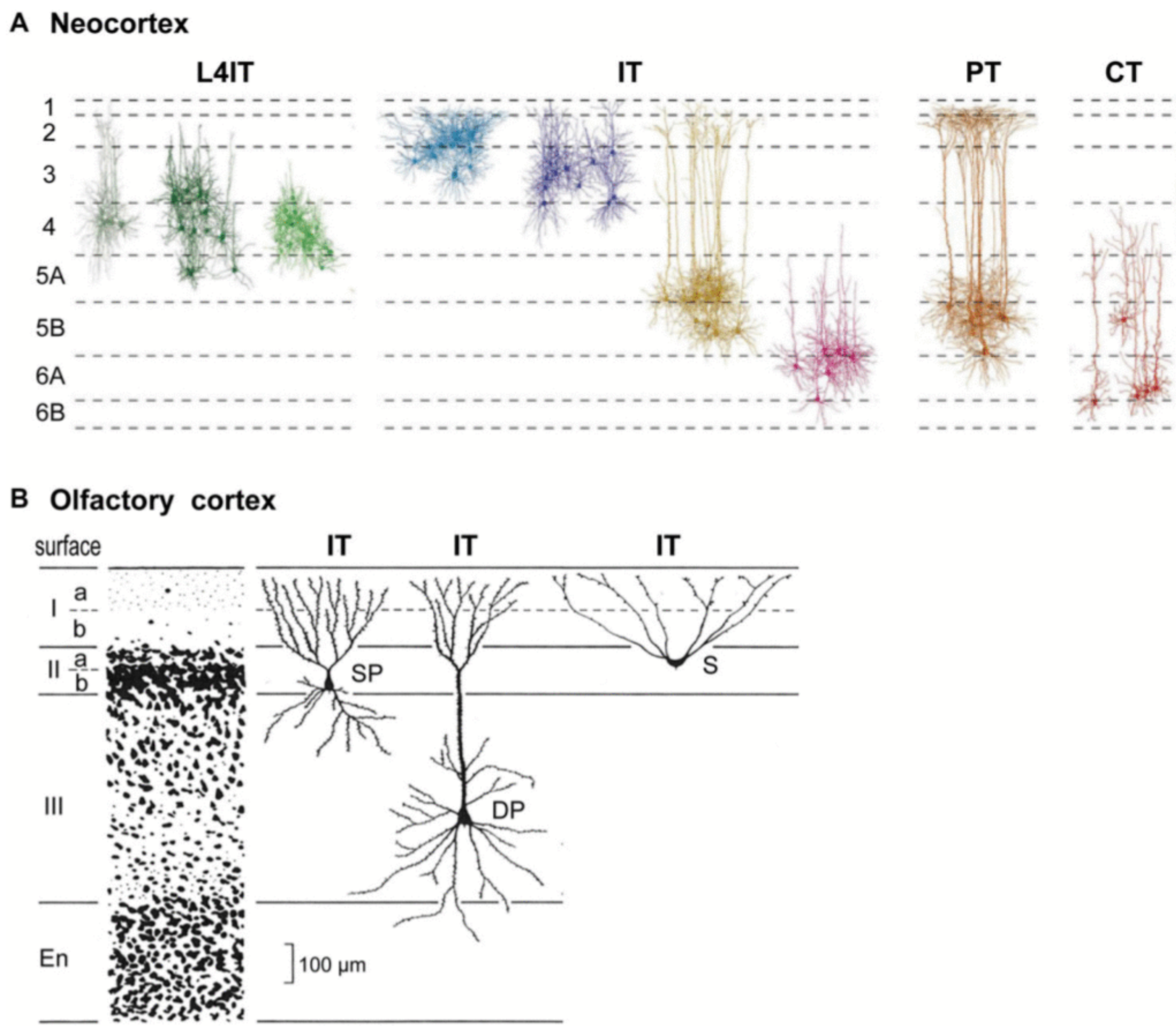
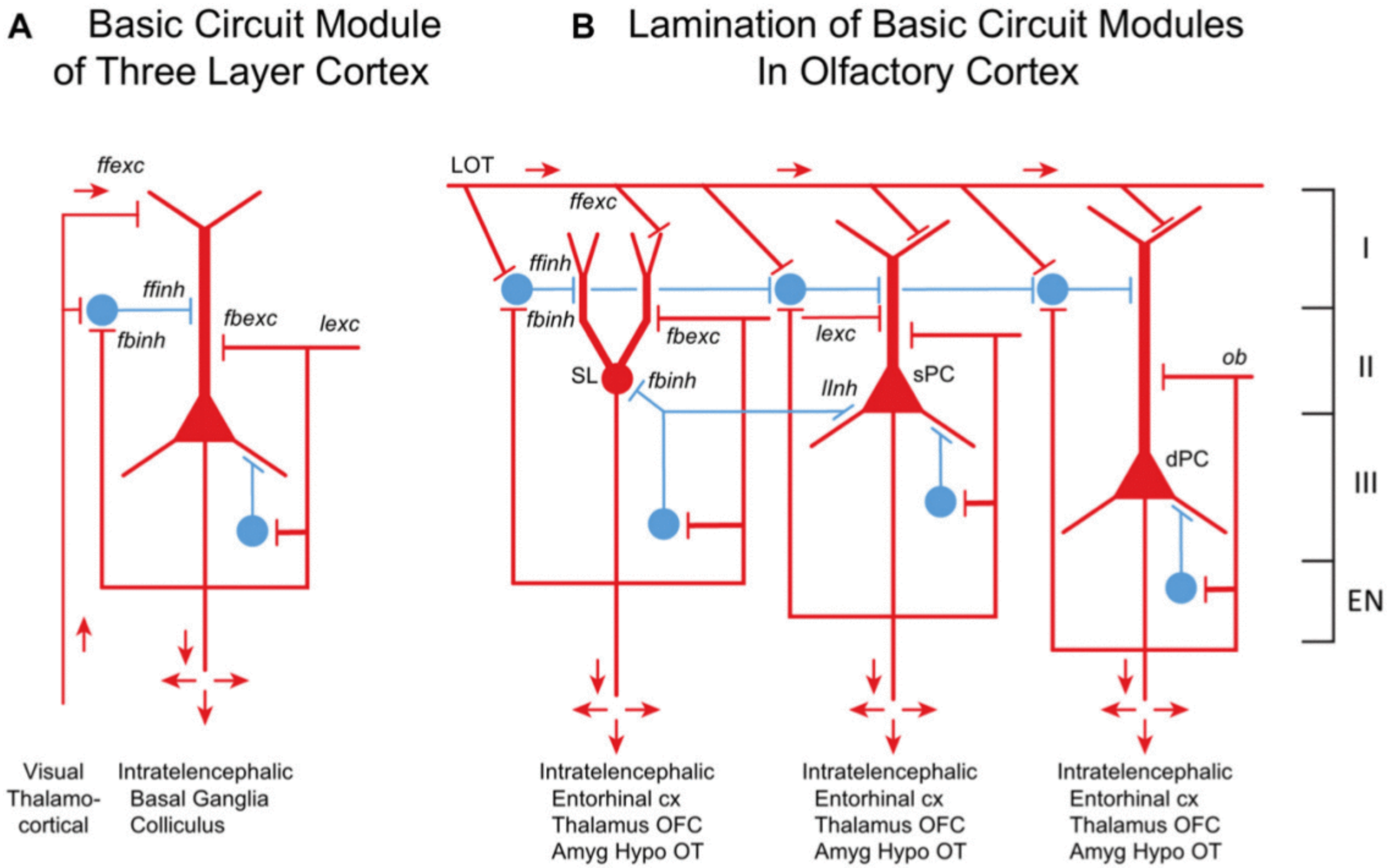


Shepherd and Rowe 2017

"Basic 3 layer cortical circuit" evolved into more complex circuits (Fig . 2A and B)



Shepherd and Rowe 2017

"Basic 3 layer cortical circuit" evolved into more complex circuits (Fig . 2C)