Doing Awesome Science and Finding Interesting Results

High Impact Subtitle

by

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requirements for the degree of Doctor of Philosophy
in the Department of Department
in the Graduate School of
Duke University

2021

Abstract

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Acknowledgements

I can only see so far because I stand on the shoulders of giants.

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Contents

List of Figures

List of Tables

Abbreviations

APEX	Ascorbate Peroxidase
AMPA	Alpha-amino-3-hydroxy-5-Methyl-4-isoxazole Propionate
AP-MS	Affinity Purification and Mass Spectrometry
ASD	Autism Spectrum Disorder
BioID	Biotinylation Identification
CNS	Central Nervous System
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
DNA	Deoxyribonucleic Acid
ECM	Extracellular Matrix
EM	Electron Microscopy
PSD	Postsynaptic Density
ER	Endoplasmic Reticulum
GAP	Guanine Nucleotide Activating Protein
GEF	Guanine Nucleotide Exchange Factor
GLM	Generalized Linear Model
HIUGE	Homology-Independent Universal Genome Editing
ID	Intellectual Disability
IRS	Internal Reference Standard
LTD	Long Term Depression
LTP	Long Term Potentiation

LMM	Linear Mixed Model
MS	Mass Spectrometry
NDD	Neurodevelopmental disorder
NB	Negative binomial
PSM	Peptide spectrum match
PPI	Protein-protein interaction
PTM	Post-translational modification
iPSD	inhibitory Postsynaptic Density
RNA	Ribonucleic Acid
SFARI	Simons Foundation Autism Research Initiative
SPQC	Sample Pool Quality Control
SV	Synaptic Vesicle
SVM	Support Vector Machine
TMT	Tandem Mass Tag
OMIM	Online Mendelian Inheritance in Man
NMDA	N-methyl-D-Aspartate
WGCNA	Weighted Gene Co-expression Network Analysis

Chapter 1

Introduction

The human brain functions to regulate our bodies' organs and tissues as well as govern complex behaviors such as cognition and sensation[1]. The brain's key cell type, the neuron, functions to communicate with other neurons via specialized subcellular sites called synapses. Neurons are organized into complex networks or circuits that support the computations that form our thoughts, reflexes, and sensations. At the molecular level, these interactions are supported by the function of proteins–the 'molecular machinery' of the cell (Figure 1.1). Proteins are organized into interacting complexes and larger communities of interacting proteins that co-localize at membrane and non-membrane enclosed subcellular sites, like the synapse, where they function together to perform cellular work[2]. Complex networks of protein and cellular interactions define the human tissues that sustain life.

1.1 Compact Enumeration

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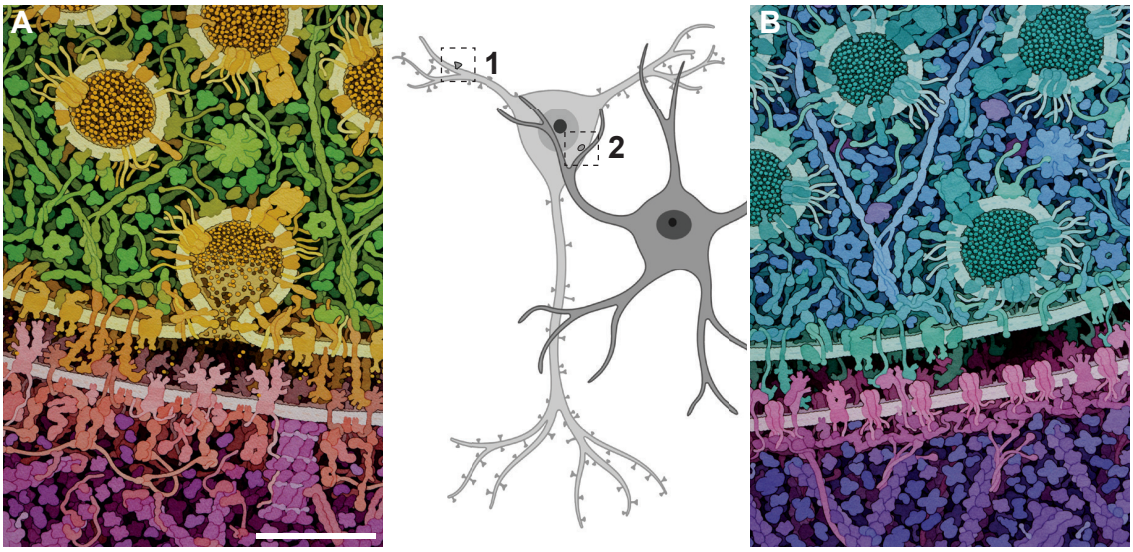

Figure 1.1: Schematic of an excitatory synapse (A) and an inhibitory synapse (B). Excitatory synapses form predominately on dendritic spines (inset 1) and are typified by their asymmetric shape and a dense postsynaptic accumulation of proteins, the excitatory post-synaptic density. Inhibitory synapses form on target a neuron's dendrites, soma (inset 2), and axon. Artwork by in (A) and (B) by David Goodsell[3]. Scale bar in (A) $\sim$ 40 nm.

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1. First item
2. Second item

1.1.1 Referencing labels

You can create labels with the `label` command. Then point to that part of the document with `autoref`. For example, "In chapter 2, I discuss methods for testing for differential abundance in protein proteomics experiments."

Chapter 2

My Second Chapter

2.1 Equations

Statistical testing in proteomics is usually done for each protein-level subset of the data. The simplest model includes a single fixed-effect term, Condition which represents experimental treatment groups such as Genotype (e.g. WT versus Mutant) or Treatment (e.g. BioID versus Control). Consider the following linear model, given in matrix form, which is fit to the data from a single protein:

$$Y_p = X\beta_p + \epsilon_p \tag{2.1}$$

Y_p is a vector of log_2 intensity for protein p. The matrix X stores information about the experiment's fixed-effect covariate, Condition. β_p is a vector of regression coefficients, obtained from the fit model. We also estimate ϵ_p which quantifies any residual error and by definition is normally and independently distributed:

$$\epsilon_p \overset{iid}{\sim} N(0, \sigma^2) \tag{2.2}$$

Linear, fixed-effect models can be extended to include additional mixed-effects to provide a description of more complex sources of variation in an experimental design[4]:

$$\begin{aligned} Y_p &= Z\alpha_p + X\beta_p + \epsilon_p \\ \alpha_p &\overset{iid}{\sim} N(0, \sigma_Z^2) \end{aligned} \tag{2.3}$$

The mixed-effect term, $Z\alpha_p$, includes Z, a matrix of mixed-effects. The parameter α_p quantifies error among these mixed-effects (also called random effects). By definition, the random-effect error is independently and normally distributed (Equation 2.3). Using linear mixed-models we can untangle variance attributed to a biological effect of interest from other sources of variation which mask this response.

2.2 Example Table

Put the table (Table 2.1) caption above its contents.

Table 2.1: Here is a description of my table.

Column 1	Column 2	Column 3
A	74	122
B	90	66
C	85	153
D	88	88

2.3 Using the Minted Package

You can use the `minted` package to lint source code. The code is not run, but it might be nice to showcase how smart you are by showing some source code. Note that if a minted environment is used, then you must pass the `-shell-escape` option to your LaTeX compiler.

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#!/bin/bash

echo "hello world!"
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Chapter 3

Putting Figure Captions on the Second Page

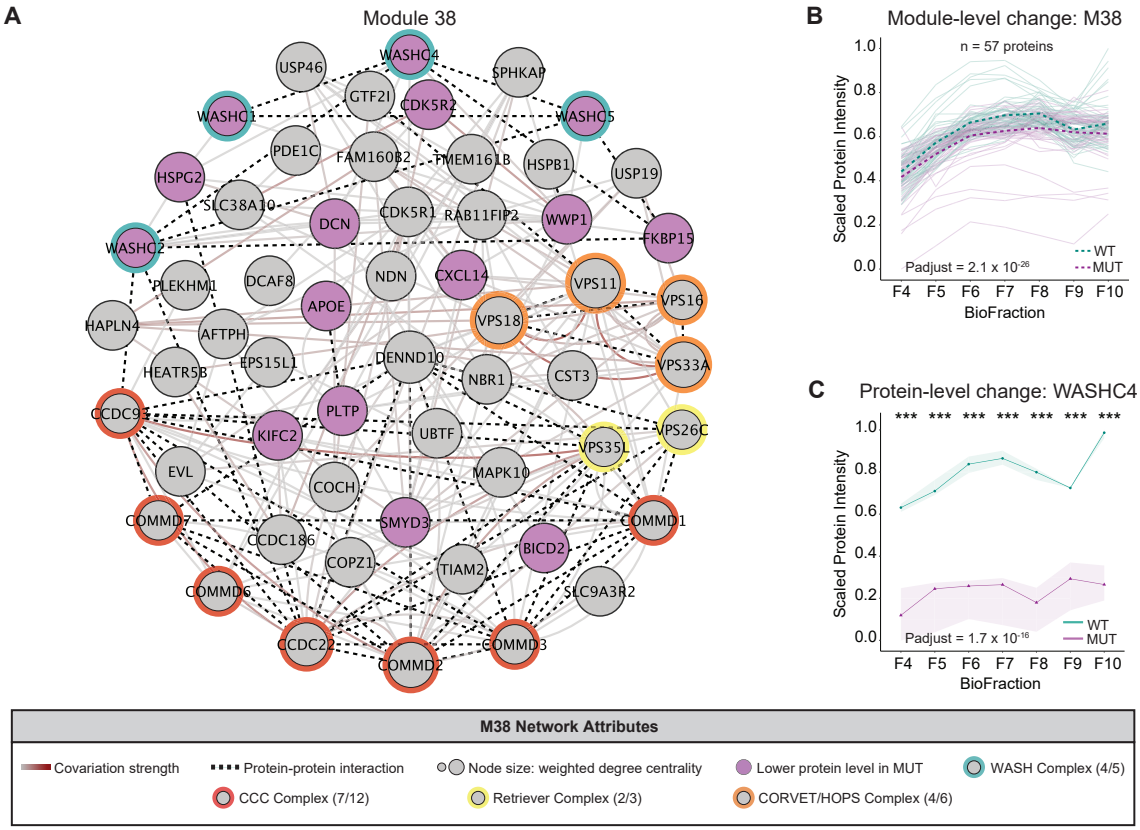

Figure 3.1: Figure adapted from[5]. Figure caption continued on next page.

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Chapter 4

Conclusions

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