

# Making sense of biology: Special challenges associated with interpreting *in vivo* data

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## Introduction

Neurochemical data gleaned from *in vivo*, *ex vivo* and *in vitro* experiments can present unique challenges related to interpretation. Often, data analyzed by different accepted methods can lead to alternate conclusions. This workshop will focus on “real world” case studies where alternate analyses produce variable and sometimes opposing interpretations of the experimental systems under investigation. All *In Vivo* Methods Meeting participants are invited to attend and to contribute their expertise and insight.

## Case studies

### 1. Methods for the analysis of quantized release events

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Real-time measurements of neurotransmission often involve the quantification of discrete events, specifically, interpreting electrochemical measurements of exocytosis made at single cells and *in vivo* voltammetric measurements of dopamine release. Individual events can be analyzed for concentration and kinetic parameters, however, linking these seemingly stochastic events to behavior poses some challenges. Discretizing the data and correlation analysis will be contrasted with data averaging to highlight the role discrete events play in regulating behavior.

### 2. Complementary insights from absolute versus normalized levels of evoked axonal dopamine release in mouse brain slices

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The study of axonal dopamine (DA) release in striatal slices using voltammetric methods has provided key information about local DA release regulation, independent of long-pathway influence that is a necessary component of *in vivo* measurements. We used fast scan cyclic voltammetry to examine DA release regulation in a mouse model of early-onset (DYT1) dystonia. We found that absolute evoked extracellular DA concentrations ( $[DA]_o$ ) were lower in DYT1 mice, which are phenotypically hyperactive compared to wildtype control mice, regardless of whether the stimulus was a single pulse (1 p) or a train of 5 pulses at varying frequencies. However, when the data were normalized to 1 p evoked  $[DA]_o$  for each group, a significant difference in “burst sensitivity” was revealed. The physiological interpretation of both sets of data will be discussed.

### 3. Deciphering basal levels of dopamine in the striatum

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The literature contains estimates of basal striatal dopamine levels spanning a considerable range: micromolar to nanomolar. Moreover, there is a range of opinions on the likelihood that reverse transport plays a role in basal DA release. The possibility now presents itself that all of these results and opinions are essentially correct. We will present data to suggest that basal dopamine exhibits at least a spatial distribution (we leave open the possibility that it may also exhibit a temporal distribution). In other words, there is no one, single value for ‘basal dopamine.’ Tentatively, we suggest that DAT plays a substantial role in determining local basal dopamine concentrations.

#### 4. Effects of antidepressants on central monoamines as studied by microdialysis: Fact or artifact?

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In the current study, we compare the effects of monoamine uptake inhibitors on brain monoamine levels as measured using conventional (1.5 µl/min) and quantitative modified ultraslow microdialysis. Effects of uptake inhibitors differ between the methods used, indicating the relevance of changes in *in vivo* recovery when using conventional microdialysis to study brain pharmacology.

#### 5. Interpreting neurotransmitter release in light of altered baseline levels

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In microdialysis studies, pharmacologic or physiologic stimulation of neurotransmitter release is often quantified relative to baseline neurotransmitter levels. However, a number of factors can influence basal dialysate neurotransmitter concentrations such that these are not the same across experimental groups. In these cases, analyzing release data as percent of baseline versus area under the curve can lead to different conclusions. Data will be presented to illustrate contrasting results and interpretations.

### Discussion

An open discussion including all workshop participants will follow the case studies. The goals of this workshop are to stimulate discussion about how to approach situations where different methods of analysis generate alternate interpretation of neurochemical data and to generate ideas for reaching consensus among alternate methods of analysis.