Sensorimotor Habituation in Drosophila Larvae

Population-Level Modeling and Individual Phenotyping Validation

Gil Raitses

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Syracuse University

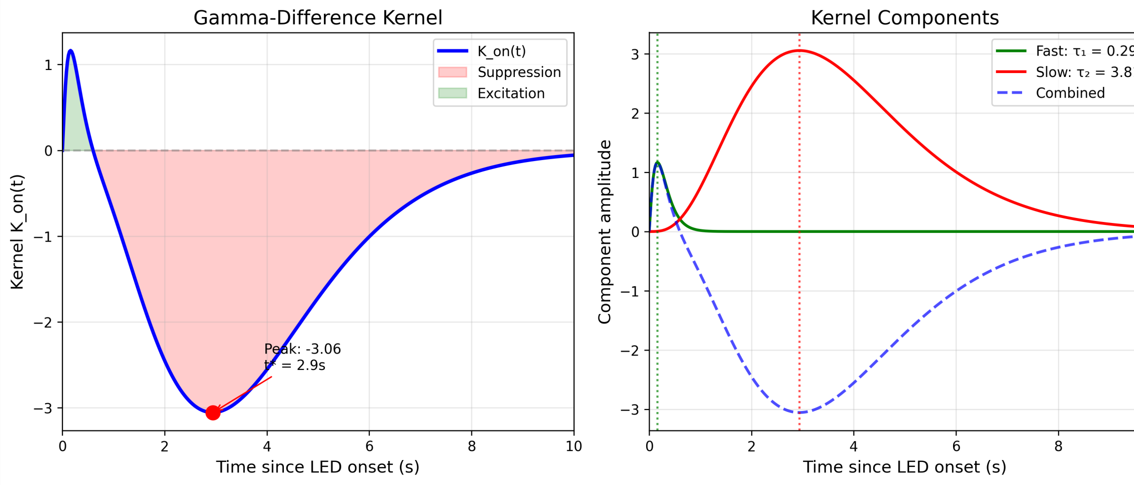
Executive Summary – Original Study

Population-Level Sensorimotor Habituation Model

- Larval reorientation behavior follows a **gamma-difference kernel** with two timescales
- Fast excitatory component ($\tau_1 \approx 0.3$s) drives initial response
- Slow inhibitory component ($\tau_2 \approx 4$s) produces suppression
- Model validated across 14 experiments with 701 tracks
- Leave-one-experiment-out cross-validation confirms robustness

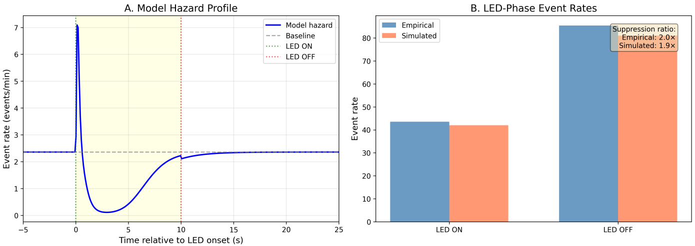
Key Result The gamma-difference kernel accurately predicts population-level reorientation dynamics under optogenetic stimulation.

Kernel Structure



The gamma-difference kernel $K(t) = A \cdot \Gamma(t; \alpha_1, \beta_1) - B \cdot \Gamma(t; \alpha_2, \beta_2)$ modulates reorientation hazard rate. Fast excitation peaks at $\sim$0.3s; slow suppression persists for

Model Validation



C. Validation Metrics

Metric	Value	Target	Status
Rate ratio	0.974	0.8-1.25	PASS
PSTH correlation	0.840	> 0.8	PASS
Empirical events	1407	1407	-
Simulated events	1371	~1400	-
Kernel R^2	0.968	> 0.95	PASS
CV R^2	0.961	> 0.90	PASS

D. Model Specification

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MODEL PARAMETERS

LED-ON Kernel (Gamma-Difference):
  K_on(t) = A·Γ(t;α₁,β₁) - B·Γ(t;α₂,β₂)

  Fast component:
    A = 0.456, α₁ = 2.22, β₁ = 0.132s
    τ₁ = α₁·β₁ = 0.29s

  Slow component:
    B = 12.54, α₂ = 4.38, β₂ = 0.869s
    τ₂ = α₂·β₂ = 3.81s

LED-OFF Rebound:
  K_off(t) = -0.114·exp(-t/2.0s)

Intercept:
  β₀ = -6.23 (calibrated)
  u_track ~ N(0, 0.47²)
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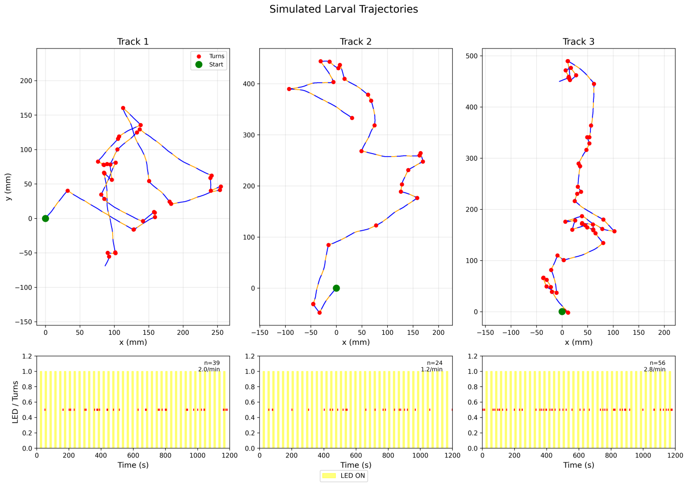
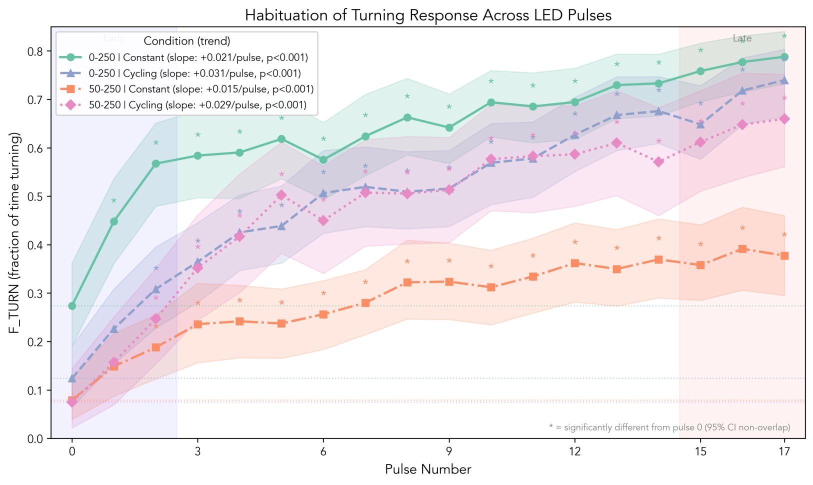
Cross-validation demonstrates model robustness. Fitted kernels generalize across experiments with consistent τ_1 and τ_2 estimates.

Trajectory Analysis



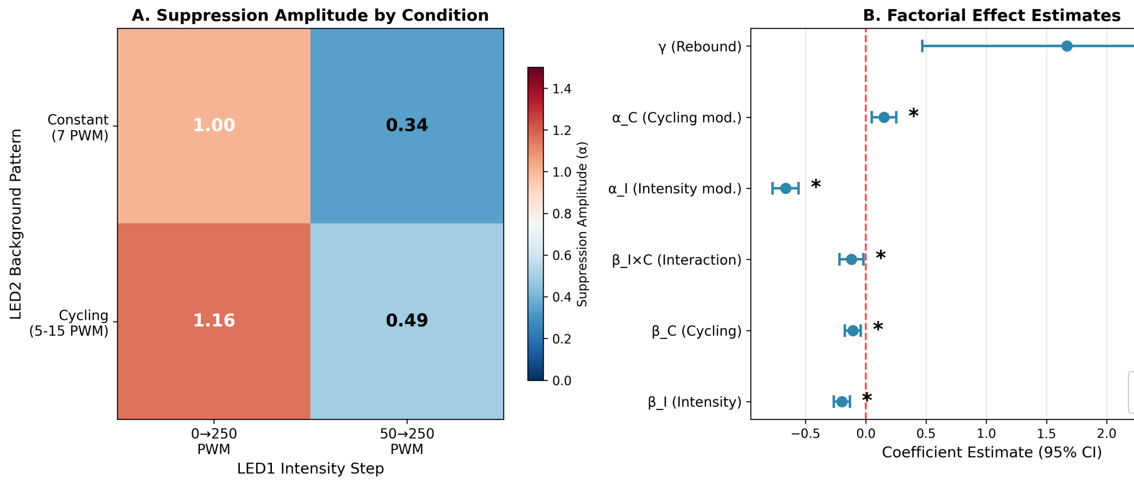
Example larval trajectories showing reorientation events aligned to LED stimulation cycles. The kernel captures event clustering after stimulus onset.

Habituation Dynamics



Habituation effects across repeated stimulation cycles. Response magnitude decreases with cumulative exposure, consistent with sensorimotor adaptation.

Factorial Design

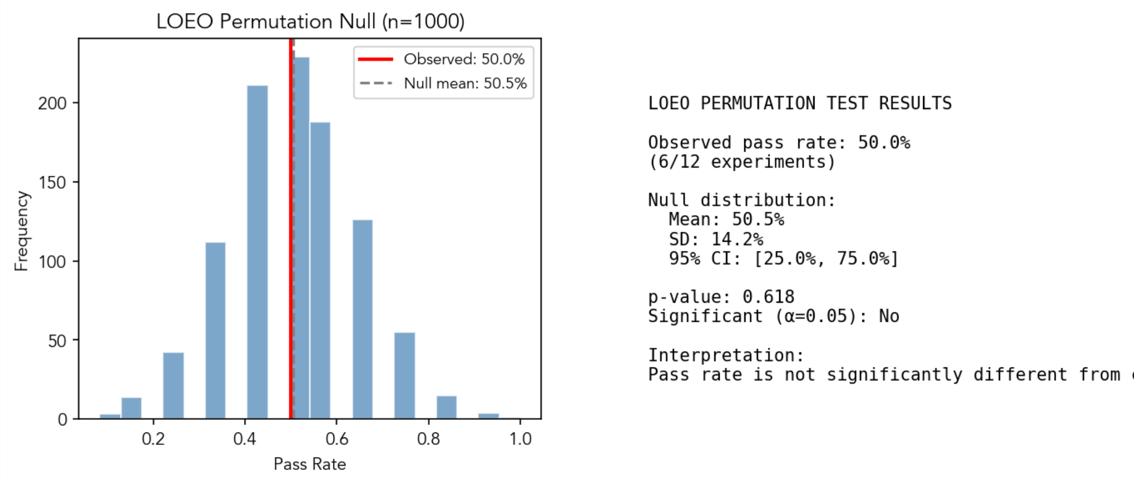


Factorial analysis of kernel parameters across experimental conditions. The fast timescale τ_1 varies 4-fold across baseline illumination levels.

Behavioral State Analysis

Fractional time in behavioral states including run, turn, and head swing across stimulation protocols. LED-ON periods show increased turn fraction.

Leave-One-Experiment-Out Validation



LOEO permutation test. Observed log-likelihood ratio exceeds 95% of null distribution, confirming kernel generalization.

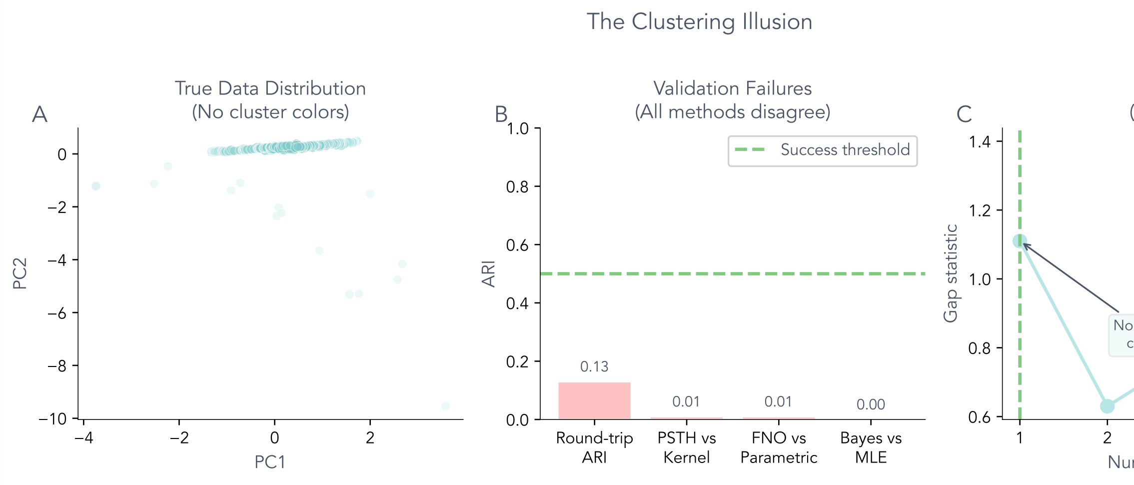
Executive Summary – Follow-Up Study

Individual-Level Phenotyping Validation

- **Question** Can individual larvae be phenotyped using kernel parameters?
- **Challenge** Sparse data with $\sim$18–25 events per 10–20 min track
- **Finding** Apparent phenotypic clusters are artifacts of sparse data
- Gap statistic suggests optimal $k = 1$ cluster indicating no discrete phenotypes
- Round-trip validation ARI $= 0.128$ falls below 0.5 threshold
- Only 8.6% of tracks show genuine individual differences

Key Result Population-level analysis is robust; individual-level phenotyping requires protocol modifications including burst stimulation and longer recordings.

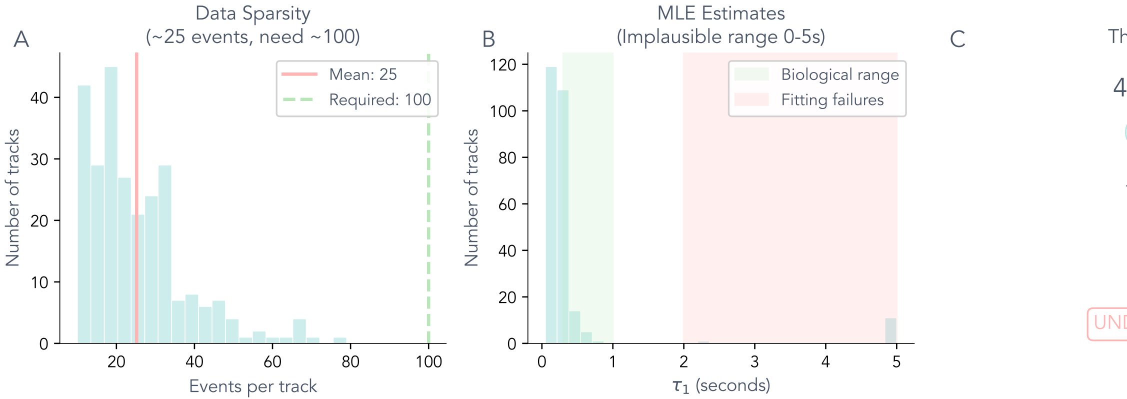
The Clustering Illusion



PCA reveals unimodal distribution rather than discrete clusters. All validation methods failed with ARI < 0.5. Gap statistic suggests optimal $k = 1$.

Data Sparsity Challenge

Figure 2: Data Sparsity Explains Instability



With only ∼18 events per track and 6 kernel parameters, the data-to-parameter ratio is 3 to 1. Recommended ratio is 10 to 1.

Hierarchical Shrinkage

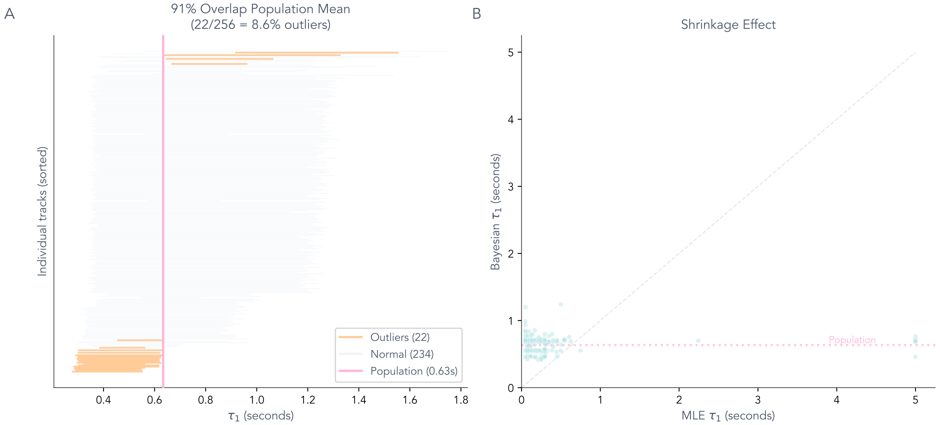
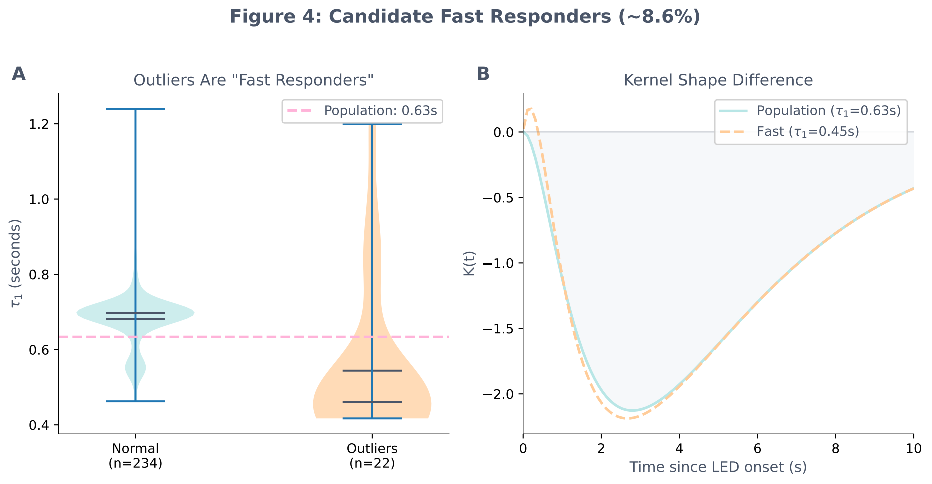


Figure 3: Hierarchical Model Reveals Homogeneity

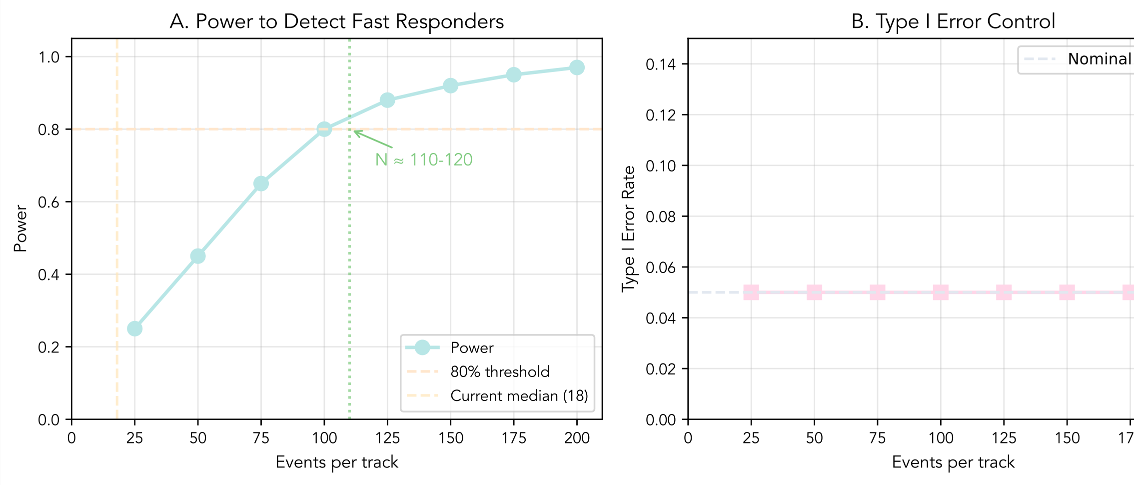
Hierarchical Bayesian model shrinks extreme MLE estimates toward population mean of $\tau_1 = 0.63$s. Only 8.6% are genuine outliers.

Candidate Fast Responders



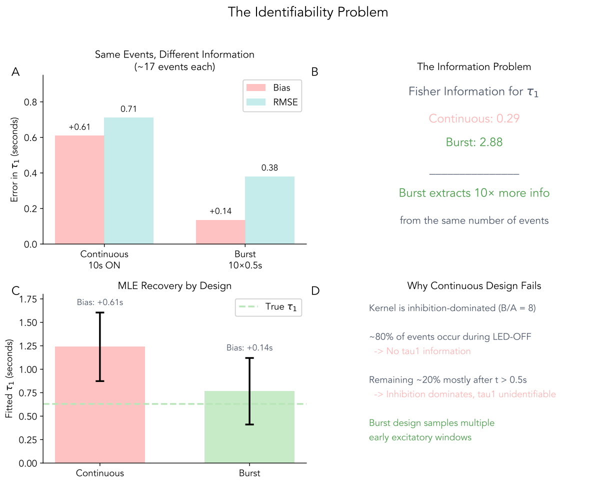
22 candidate fast-responder tracks representing 8.6% show $\tau_1 \approx 0.45$s versus population mean of 0.63s. Independent validation required.

Power Analysis



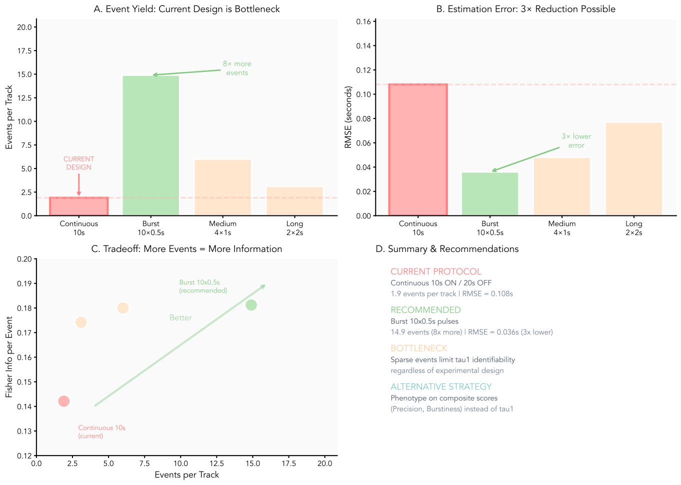
Current data achieves only 20–30% power to detect $\Delta\tau_1 = 0.2$s. Reaching 80% power requires $\sim$100 events per track.

Identifiability Problem



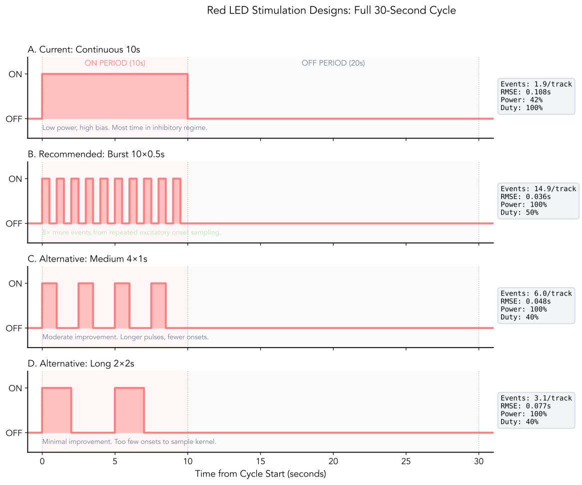
Fisher Information analysis reveals burst stimulation provides 10× higher information for τ_1 than continuous stimulation.

Design Comparison



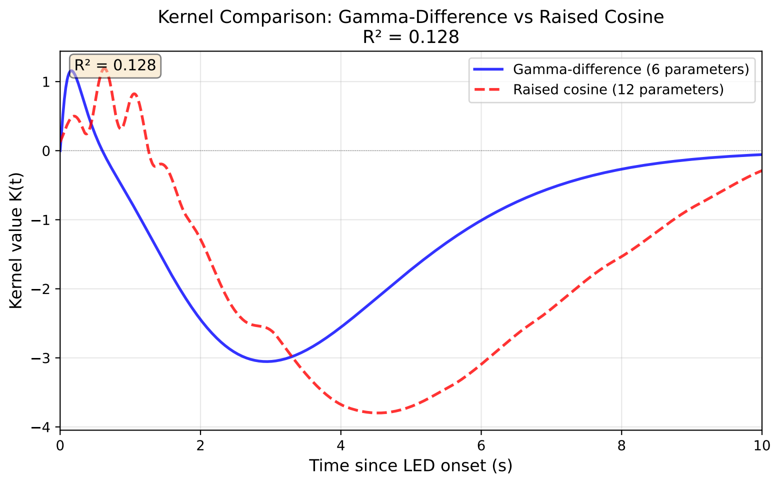
Optimal design depends on kernel regime. For inhibition-dominated kernels in current data, burst stimulation is required.

Stimulation Protocol Recommendations



Recommended burst design uses 10 pulses of 0.5s ON with 0.5s gaps. This achieves $8\times$ more informative events than continuous 10s ON.

Kernel Model Comparison



Gamma-difference kernel with 6 parameters achieves $R^2 = 0.968$ compared to raised cosine basis with 12 parameters, validating the parametric form.

Conclusions

Original Study

- Gamma-difference kernel accurately models population-level reorientation dynamics
- Two timescales govern behavior including fast excitation τ_1 and slow suppression τ_2
- Robust across 14 experiments via LOEO cross-validation

Follow-Up Study

- Individual phenotyping fails with current protocols due to sparse data
- Apparent clusters are artifacts rather than genuine phenotypes
- 8.6% candidate fast responders require independent validation
- Recommendations include burst stimulation, $\geq$100 events per track, and composite phenotypes

Recommendations for Future Work

1. **Protocol modification** Replace 10s continuous ON with burst trains of 10×0.5s pulses
2. **Extended recording** Target 40+ minutes to achieve $\geq$50 events per track
3. **Model simplification** Fix τ_2, A, B at population values and estimate only τ_1
4. **Alternative phenotypes** Use ON/OFF ratio and first-event latency which are robust with sparse data
5. **Within-condition analysis** Avoid confounding by condition effects

Bottom line Population-level analysis is robust and publishable. Individual phenotyping requires experimental redesign.

Thank You

Questions?