Development and Application of Machine Learning-Based Digital Biomarkers for Monitoring Spontaneous Seizures in Preclinical Epilepsy Models

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DIGITAL IN VIVO ALLIANCE

Abstract

For this work, we ran a **natural history study utilizing home-cage video data from two mouse models of Dravet Syndrome**, a severe epileptic encephalopathy. Dravet mice and wildtype littermates were weaned into video-integrated cages, where monitoring occurred from postnatal day 21 to postnatal day 50. **To identify spontaneous seizures, machine-based algorithms were trained to detect "taggable" features of tonic clonic seizures, such as loss of righting reflex**. Loss of righting reflex, a reliable feature of loss of consciousness in mice, occurs consistently during spontaneous seizure.

Here we describe the development of the machine learning technology, and the application in spontaneous seizure monitoring and multiplexing other phenotypic readouts (activity, sleep wake cycle, etc.).

Introduction

What are the taggable behaviors associated with seizure in mice?

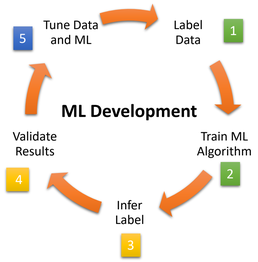
Tonic Clonic Seizure

adapted from Shimada & Yamagata, *J. Vis. Exp.*, 2018

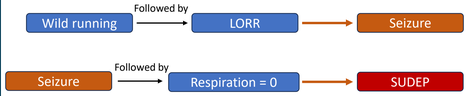
Loss of Righting Reflex (LORR): loss of ability to maintain upright body posture; means of detecting loss of consciousness associated with seizure

This work covers the development of LORR biomarker

Digital Biomarker development is an iterative process between biologists and machine learning scientists.



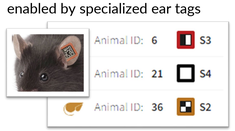
Future work will combine LORR with other metrics to create seizure and SUDEP biomarkers



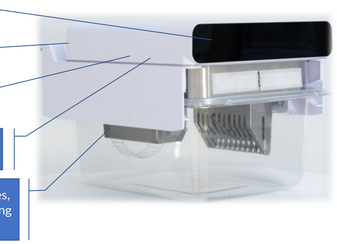
Enabling Technology

Digital home-cages allow for 24/7 recording and behavioral analysis with cloud based digital biomarkers

Individualized animal behavior data enabled by specialized ear tags

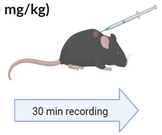


- Digital Cage Card
- Single-board computer
- Two HDR Cameras
- Integrated IR and VIS lighting
- Integrated water bottles, food hopper, and running wheels



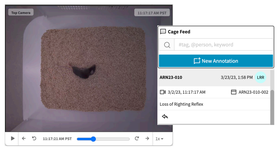
Inducible seizure assay (PTZ) to generate annotated dataset for LORR biomarker training

S.C. PTZ injection (80 mg/kg)

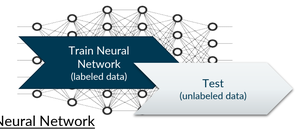


Inducible PTZ seizure assay in WT C57BL6/J mice recorded behavior mice in digital cages for 30 mins.

1 **Manual Annotation of Loss of Righting Reflex (LORR)**



Manual Selection of Labeled Frames



Neural Network

Pros:
- Preserves information from original data
- No need to manually define heuristics

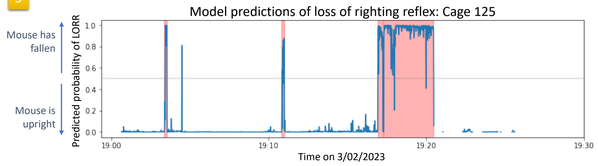
Cons:
- Not explainable

Assess LORR results on video data from PTZ assay and SCN1A natural history study

PTZ Video

3

Red shading : BioMarin's labeled LORRs



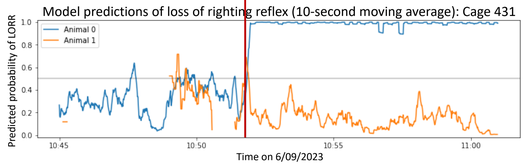
4 Model trained on PTZ-data (tested on PTZ data)

	Predicted non-LORR	Predicted LORR
True non-LORR	188	9
True LORR	7	172

96% of true LORR samples are identified by the model
5% of LORR detections are false positives

SCN1A Video

Annotation on app: hindlimb extension, SUDEP



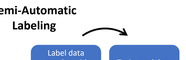
Model trained on PTZ-data (tested on SCN1A data)

	Predicted non-LORR	Predicted LORR
True non-LORR	2108	177
True LORR	152	42

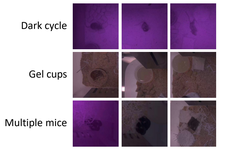
22% of true LORR samples are identified by the model
80% of LORR detections are false positives

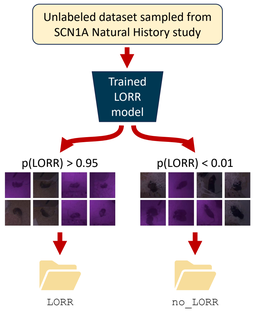
Increase labeled training dataset to tune LORR performance

5 **Semi-Automatic Labeling**



Model performance was low in conditions the model hadn't been trained in, such as:





Improved Model Performance:

Model trained on PTZ & SCN1A data (tested on SCN1A data)

	Predicted non-LORR	Predicted LORR
True non-LORR	2770	68
True LORR	231	272

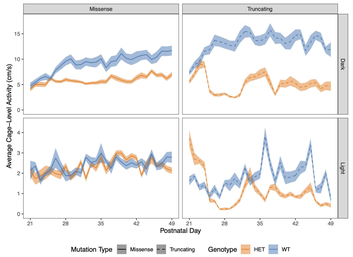
- **54%** of true LORR samples are identified by the model
- **20%** of LORR detections are false positives

Additional rounds of training necessary to increase the recall and precision of our LORR model

SCN1A Natural History Dataset highlights digital biomarker creation, application and discovery process

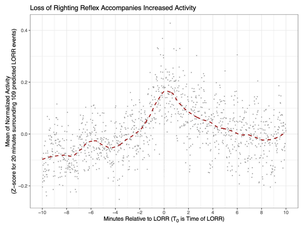
N=65 mice total (~15 per genotype/ strain) weaned 1-3 mice/cage at P21, recorded until P50

Application: multiplex phenotypic readouts-- locomotion data illustrates hypoactivity of SCN1A Hets vs WT mice in dark cycle

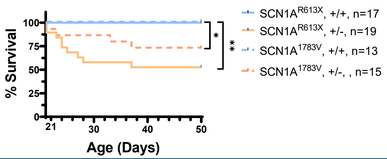


Biomarker discovery can be strengthened and tuned by incorporating data mining techniques

Shown to the right, LORR predictions from SCN1A dataset are often accompanied by increased locomotion, presumed to be "wild running"



Creation: SUDEP Phenotype can be used as substrate for future biomarker development



STARTING POINT
Manual

Watched 288 hours of video at x8 speed to detect 28 seizures in 4 HET mice (36 human hours, approx. 1 work week)

Labor intensive and low-throughput

WE ARE HERE
Semi-Automated

Use LORR model predictions to screen spontaneous seizures in video

- 89% of manually detected seizures are detected by LORR
- 100+ spontaneous tonic clonic seizures detected as of November 2023 (analysis ongoing)

Animal ID	Sex	Genotype	End Age	P21	P22	P23	P24	P25	P26
A3	M	HET			3			1	
A4	M	HET	21		2				
A8	F	HET							
A12	F	HET			11	3			
A15	F	HET	P23			2			

COMING SOON
Fully Automated

- Combine LORR model with other taggable seizure behaviors to increase specificity of biomarker
- 24/7 live individual animal seizure monitoring in group housed home-cage system
- Ability to answer complex biological questions on how spontaneous seizure interplays with other disease phenotypes in SCN1A natural history study and in other preclinical epilepsy models

Digital In Vivo Alliance members work together non-competitively for the purpose of exploring preclinical applications of AI-enabled digital biomarkers from home cage-compatible technologies. For more information, visit DIVA.bio