Emerging Role of Translational Digital Biomarkers in Home Cage Monitoring Technologies for Preclinical Drug Discovery and Development

Panelists: Matthew Ruiter, Ellie Karlsson, Angela P King-Herbert, Sheba R Churchill, Sean McGuire, ~~Szczepan W Baran~~

Moderator:
Megan LaFollette
Facilitator:
Sally Thompson-Iritani

The North American 3Rs Collaborative

Refine. Reduce. Replace.

NA 3RsC

Collaborating to advance better science – for both people & animals

www.na3rsc.org | contactus@na3rsc.org

NA3RsC partners with you across the field.

NA3RsC's strategy is to identify initiatives with

Strong Evidence

Big Impact

Real-World Practicality

We currently have 6 key 3Rs initiatives.

Rodent Health Monitoring

Microphysiological Systems

Translational Digital Biomarkers

Refinement

3Rs Certification Course

Compassion Fatigue

For each initiative we generally provide

Thought Leadership: expert consensus, real world experiences, & research

Benchmarking Use & Beliefs (e.g., Barriers): surveys & feedback

Education & Practical Resources: presentations, resource hubs, slide decks, SOPs, training courses, FAQs, etc.

The NA3RsC Translational Digital Biomarkers initiative collaborates to **increase adoption** & **regulatory acceptance** of TDB that refine & reduce animals in research.

17 tech providers & end-users are members

abbvie

Actual Analytics™
Capture, analyze and discover

Calico

evotec

gsk GlaxoSmithKline

VERISIMLife

NOVARTIS

Noldus

Stoelting
SINCE 1886

TECNIPLAST

SABLE SYSTEMS INTERNATIONAL

TESSERA THERAPEUTICS
A Flagship Pioneering Company

TSE systems

uid IDENTIFICATION SOLUTIONS

RECURSION

FDA, NIH/NIEHS

We collaborate to

- Establish improved understanding of the **value** of these technologies
- Facilitate optimal **implementation**
- Engage end-users & others interested in learn more about how these technologies can be used to **promote the 3Rs**

We're creating resources for you

Peer-reviewed Manuscript w/ checklist & figures

Educational Resource Page & Regular Posts (in progress)

Present at 5 conferences & webinars

Tech Hub of available systems (in progress)

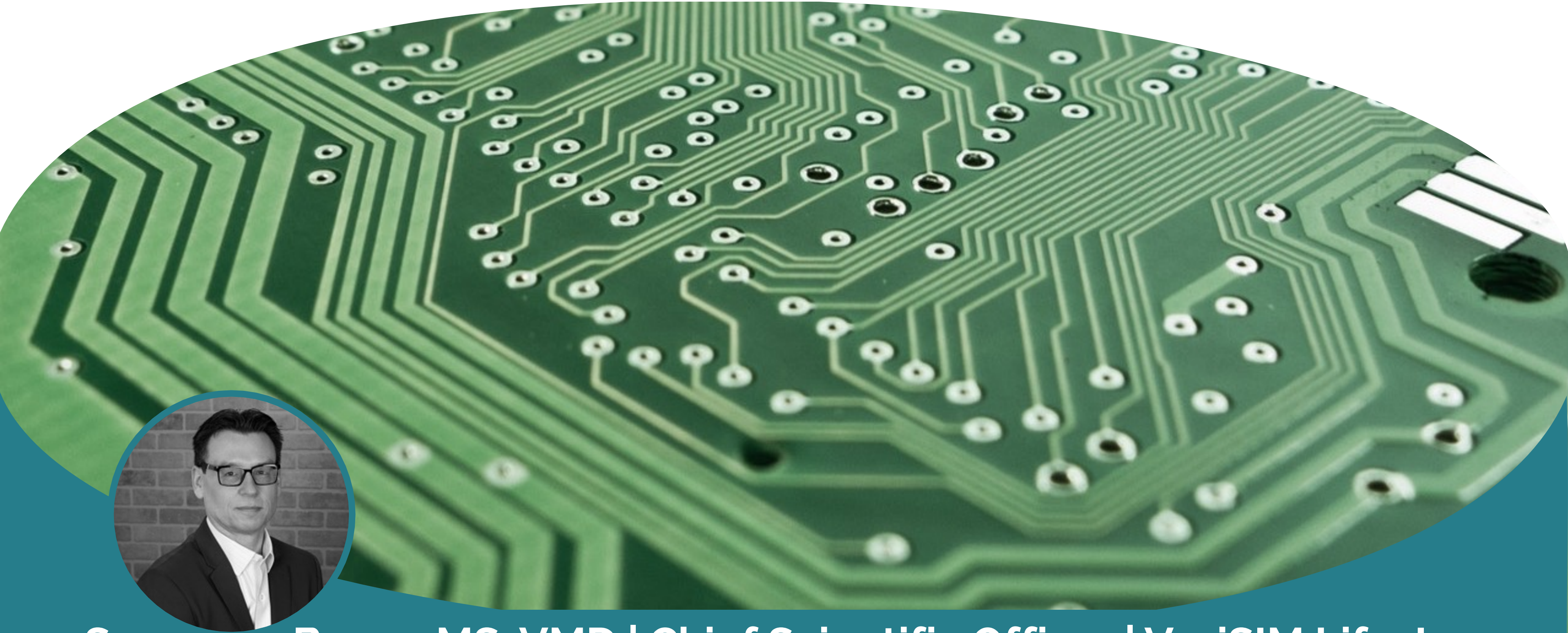
Subscribe to NA3RsC Newsletter for Slide Deck

https://bit.ly/3RC_Newsletter

NA3RsC's AALAS Events

- **Booth #1150**
- ~~**3Rs Reception:** Monday, 5-7pm at Hyatt Pimlico Room~~
- ~~**Translational Digital Biomarkers Roundtable:** Tuesday, 12:30-2pm~~
- **Environmental Health Monitoring Session:** Tuesday, 2:45-5pm
- **Compassion Fatigue Resiliency Session:** Wednesday, 2:45-5pm
- **Refined Mouse Handling Roundtable:** Thursday, 12:30-2pm

Introduction to NA3RsC's Translational Digital Biomarkers Initiative



Szczepan Baran, MS, VMD | Chief Scientific Officer | VeriSIM Life, Inc

SB@VeriSIMLife.com www.linkedin.com/in/szczepanbaran

frontiers in Behavioral Neuroscience

REVIEW
published: 14 February 2022
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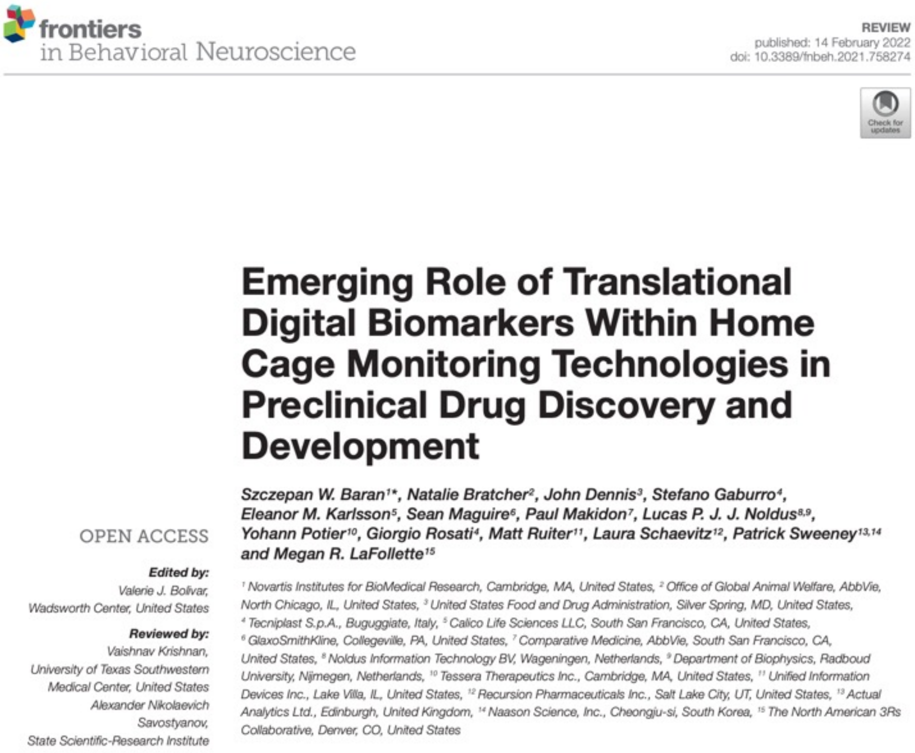
Reference our publication after this talk: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Check for updates

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[1] Novartis Institutes for BioMedical Research, Cambridge, MA, United States, [2] Office of Global Animal Welfare, AbbVie, North Chicago, IL, United States, [3] United States Food and Drug Administration, Silver Spring, MD, United States, [4] Tecniplast S.p.A., Buguggiate, Italy, [5] Calico Life Sciences LLC, South San Francisco, CA, United States, [6] GlaxoSmithKline, Collegeville, PA, United States, [7] Comparative Medicine, AbbVie, South San Francisco, CA, United States, [8] Noldus Information Technology BV, Wageningen, Netherlands, [9] Department of Biophysics, Radboud University, Nijmegen, Netherlands, [10] Tessera Therapeutics Inc., Cambridge, MA, United States, [11] Unified Information Devices Inc., Lake Villa, IL, United States, [12] Recursion Pharmaceuticals Inc., Salt Lake City, UT, United States, [13] Actual Analytics Ltd., Edinburgh, United Kingdom, [14] Naason Science, Inc., Cheongju-si, South Korea, [15] The North American 3Rs Collaborative, Denver, CO, United States

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Edited by:
Valerie J. Bolivar,
Wadsworth Center, United States

Reviewed by:
Vaishnav Krishnan,
University of Texas Southwestern Medical Center, United States
Alexander Nikolaevich Savostyanov,
State Scientific-Research Institute

https://bit.ly/3RC_TDB_Paper

This includes a key questionnaire for technology providers

TABLE 1 | Questionnaire with suggestions of descriptive information to be collected from technology providers to assist end users with selection, onboarding, and resource planning; **(A)** general overview and data accessibility and visualization, and **(B)** digital biomarkers.

	Company A	Company B	Company C
General information			
Technology type (EMF, RFID, Telemetry, Wearable, Video, Other)			
Number of video cameras per cage/system, if applicable			
Location of cameras, if applicable (Side, Top, Other)			
Data storage type (Local, Cloud, Hybrid)			
Type of data (Image, Numerical, Video)			

We have defined key **terminology** to facilitate productive conservations about translational digital biomarkers

Translational Digital Biomarkers

Digital biomarker:

- data collected continuously from unrestrained and un-instrumented animals in their home cage environment.
- These animals should not have undergone minor or major surgery with the exception of radio frequency identification (RFID) chips injected subcutaneously

Translational digital biomarker (TDB):

- an objective, quantifiable measure of physiological and/or behavioral response to disease progression or therapeutic intervention that is collected by means of digital monitoring technologies, including both internal (e.g., injectable or ingestible) and external (e.g., wearable, camera, or electromagnetic field detector) sensors, which is clinically relevant and translate between preclinical studies and the clinic.

Home Environments & Scalable

- **Home cage or home environment:**
  - cages and environment where animals are housed for the majority of their lifetime in the vivarium.
  - Bench top cage or technology: cages and technology (experimental test environments) not designed for permanent housing but where animals are housed for a short (from hours up to few days) period of time.
- **Scalable:**
  - ability to monitor hundreds to thousands of animals within a home environment.

Validation & Verification

- **Analytical validation:** entails evaluation of data processing algorithms that convert technology-collected measurements into outputted metrics (Goldsacket al., 2020).
- **Technology verification:** ensuring, through demonstration of precision, reliability and reproducibility, that a device is measuring and storing data accurately.
- **Clinical validation:** accomplished by demonstrating that technology adequately identifies, measures, or predicts a meaningful clinical, biological, physical, functional state or experience in the specified (1) animal cohort and (2) context of use (Goldsacket al., 2020).

Why should we use translational digital biomarkers in drug discovery & development?

Animal Welfare

↓ morbidity

↓ mortality

↓ handling stress

Objective assessment of welfare & enrichment

3Rs reduction of number of animals via increased translation

3Rs refinement via enhanced monitoring of human endpoints & adverse events & reduced handling

Operational

Automated data analysis

Digitization of data/processes

Incorporation of digital analytics

Assessment of virtually all animals

↓ frequency in-person assessment &

↑ flexibility = ↓ staff burden

Scientific

Noninvasive, objective & quantitative biomarkers in undisturbed animals

Real-time data capture & analytics

Ability to capture variability between day to night, night to night, and day to day variability

Broadly applicable digital biomarkers

Disease specific digital biomarker

↑ frequency of data collection & use of continuous data flows to more accurately & rapidly detect signals

Preclinical biomarkers aligning with clinical biomarkers

Inform experimental planning

Strategic

↑ predictive pre-clinical models

↓ noncompliance risk

Earlier decisions

↑ clinical relevance

Informing first in human (FIH) studies

↑ Operational efficiency

↓ cycle times by shortening pre-clinical phase

Animal assessment tools have improved over time.

1960 → **2022**

62 years

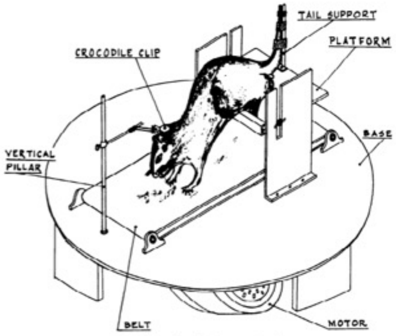
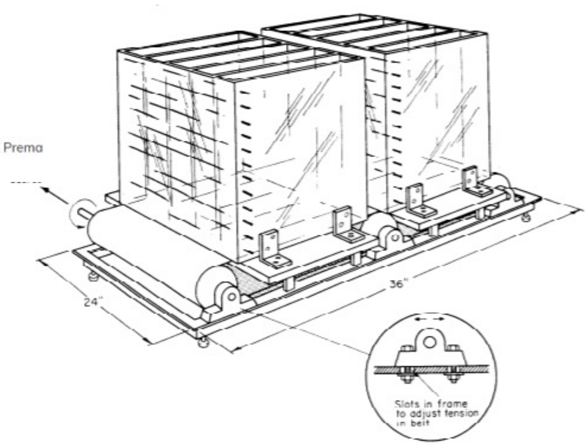


FIG. 1. The forelimbs treadmill.

A forelimbs treadmill for small animals.

B Bhatia, N Krishnaswamy, V N Rao, R Venkataraju, and K Prema

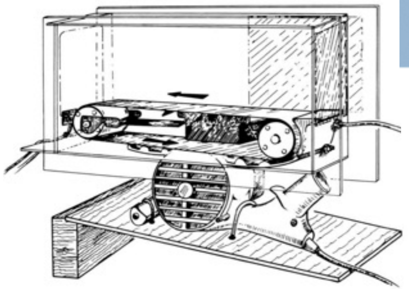
01 MAY 1966 // https://doi.org/10.1152/jappl.1966.21.3.1087



J Appl Physiol. 1969 Jun;26(6):863-4.

An inexpensive motor-driven treadmill for exercising small laboratory animals.

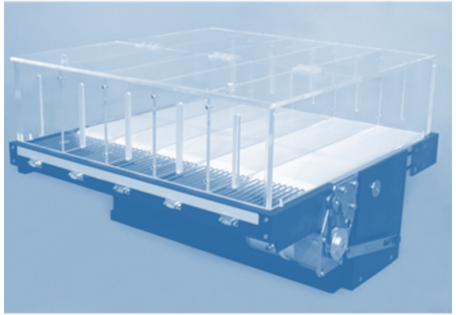
Jette MJ, Windland LM, O'Kelly LI.



J Appl Physiol Respir Environ Exerc Physiol. 1982 Feb;52(2):505-7.

A simply constructed treadmill for rodent exercise studies.

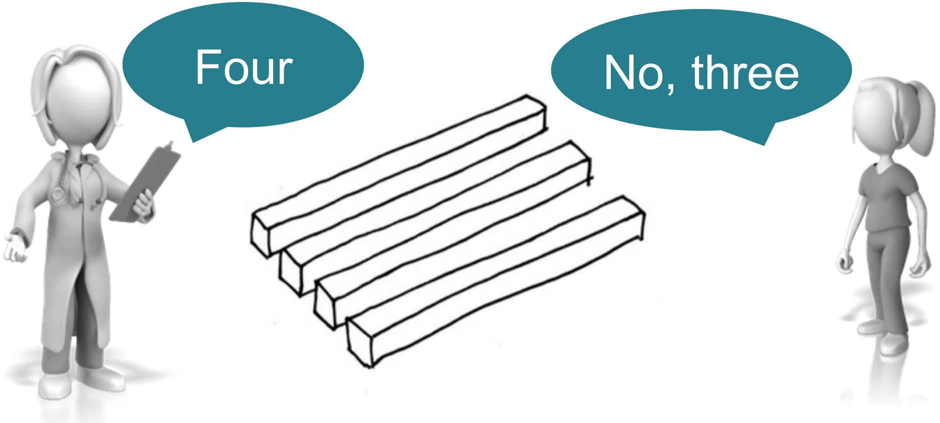
Rubin SA, Mickle D.



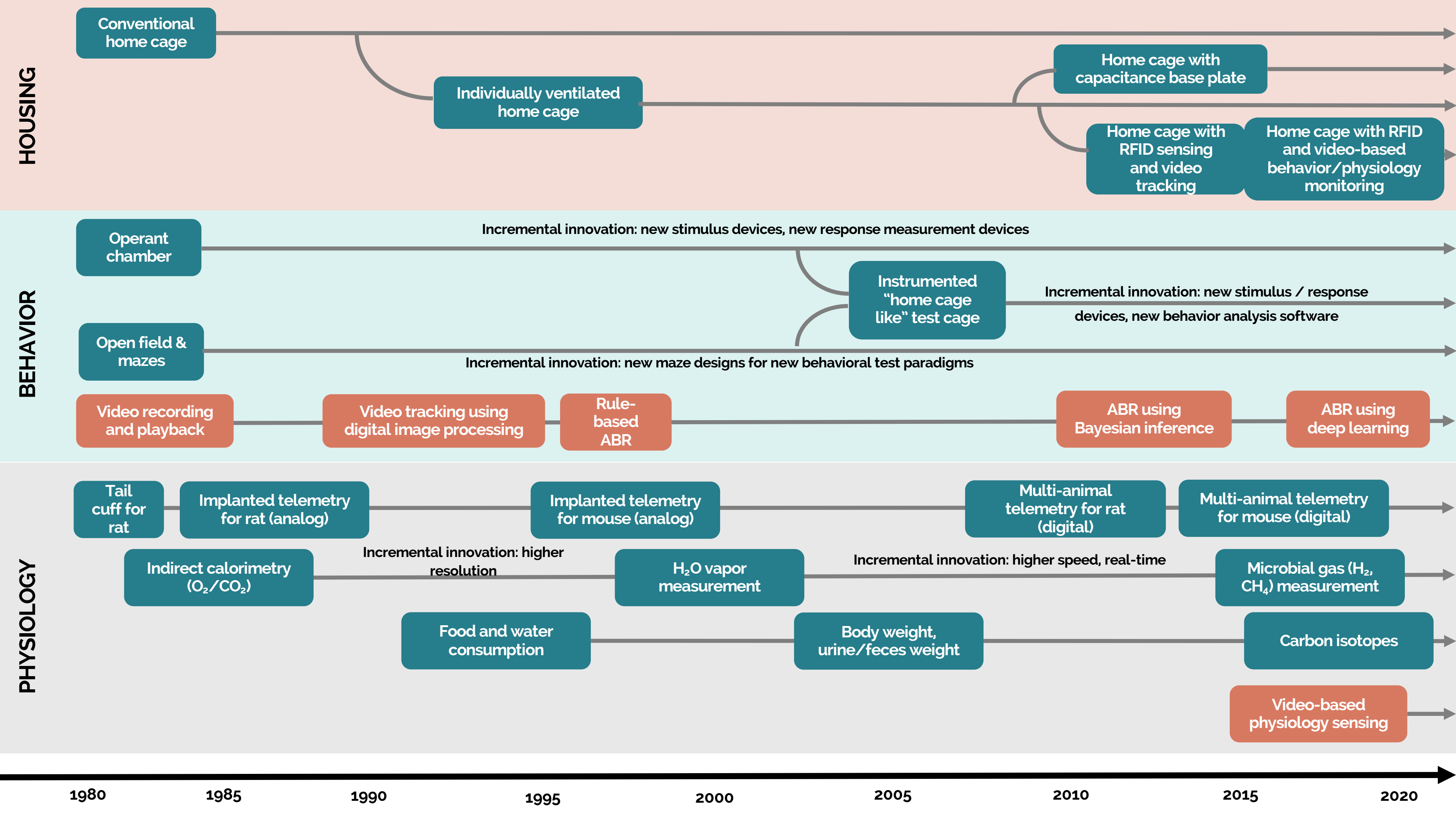
COULBOURN INSTRUMENTS

Removing animals from the home cage can negatively impact animal welfare & data quality through changing animal behavior & physiology

https://bondlsc.missouri.edu/2018/05/10/vivariums-and-the-hidden-metropolis-beneath-bond-lsc/



(Saibaba et al., 1996; Balcombe et al., 2004; Schreuder et al., 2007; Meller et al., 2011; Gerdin et al., 2012; Lim et al. 2019; Pernold et al. et al., 2019; Baran et al., 2020)


HOUSING
Conventional home cage
Individually ventilated home cage
Home cage with capacitance base plate
Home cage with RFID sensing and video tracking
Home cage with RFID and video-based behavior/physiology monitoring
BEHAVIOR
Incremental innovation: new stimulus devices, new response measurement devices
Operant chamber
Instrumented "home cage like" test cage
Incremental innovation: new stimulus / response devices, new behavior analysis software
Open field & mazes
Incremental innovation: new maze designs for new behavioral test paradigms
Video recording and playback
Video tracking using digital image processing
Rule-based ABR
ABR using Bayesian inference
ABR using deep learning
PHYSIOLOGY
Tail cuff for rat
Implanted telemetry for rat (analog)
Implanted telemetry for mouse (analog)
Multi-animal telemetry for rat (digital)
Multi-animal telemetry for mouse (digital)
Indirect calorimetry (O_2/CO_2)
Incremental innovation: higher resolution
H_2O vapor measurement
Incremental innovation: higher speed, real-time
Microbial gas (H_2, CH_4) measurement
Food and water consumption
Body weight, urine/feces weight
Carbon isotopes
Video-based physiology sensing
1980
1985
1990
1995
2000
2005
2010
2015
2020

Comparison of patients' & animals' monitoring

Patients

Remote:
Home-based unsupervised testing

Remote:
Continuous monitoring

In-clinic:
Instrumented performance testing

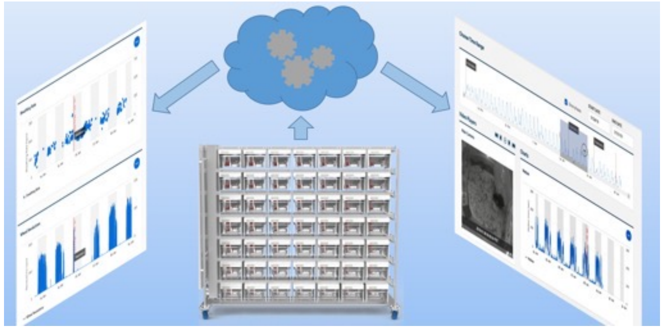
shorturl.at/lnwzB

Reverse Translation

Animals

Outside of home cage

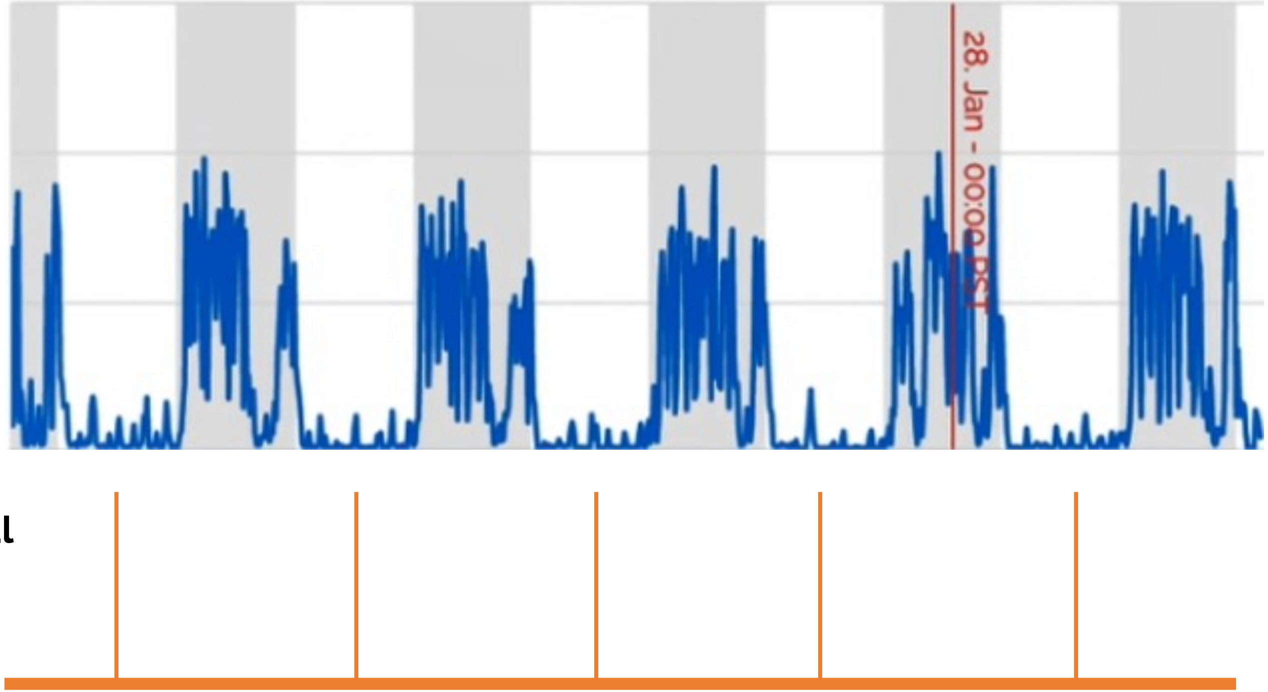
Remote: In home cage



Digital biomarkers can give a holistic view of the animal.

Digital (continuous)

Conventional (episodic)



Data collected remotely within animal home environment

Data collected from conventional assessments outside of home environment

3Rs Impact of Digital Biomarkers

- Refine animal welfare and scientific quality
  - e.g. assess progression of colitis longitudinally in a contactless, objective, continuous, and non-invasive manner (Zentrich et al., 2021).
  - e.g. three-fold reduction in the time the mice have to be kept in the vivarium (Heldring, 2019)
- Reduction
  - e.g. reduce the need for multiple satellite groups of animals that are sacrificed at various points for histopathological assessment of disease progression (Baran et al., 2020)
  - e.g.

Overview of Digital Monitoring Technologies

Matt Ruiter

Unified Information Devices (UID)

uid
IDENTIFICATION SOLUTIONS

Animal Monitoring Technologies – Surgery Vs Non-Surgical Models

Require a major surgery for the implant

No surgery required to collect data (an RFID implant is not classified as a major surgery)

Noninvasive monitoring technologies

- **Beam Break**
- **Video**
- **Disruptive Field**
- **RFID**

What is a home cage?

The Translational Digital Biomarkers Hub defines a Home cage as:

- **Cages and environment where animals are housed for the majority of their lifetime in the vivarium**
- **Bench top cage technology: cages and technology (experimental test environment) not designed for permanent housing but where animals are house for a short (from hours up to few days) period of time.**

Classification by cage type

STATIC CAGING

IVC CAGING

Static caging

- Beam Break – Video – RFID
- Activity, Behavioral, Phenotypes, Physiological parameters
- Companies include
  - Actual Analytics
  - Noldus
  - Sable Systems
  - UID

IVC Cage Rack Technology

IVC home cage monitoring for digital biomarkers and husbandry.

- Technology
  - DVC or RFID
- Data collected
  - Activity, Behavioral, Temperature, Husbandry, food and water

TECNIPLAST innovation through passion

DIGITAL VENTILATED CAGE

inno vive

Innorack® Home Cage Monitoring System

Allentown®

Improving Life – it's in our DNA.®

Understand The Technology to Advance your Research

Research	Husbandry
• Infectious diseases • Vaccine development • Behavioral phenotyping of genetically altered animals • Efficacy and safety of candidate drugs • Studies of circadian rhythms • Learning and memory • Social interactions and behavior • Behavioral Neuroscience • Sleep research • Neurodegenerative disorders • Aging and longevity research • Spinal muscular atrophy • Cancer immunotherapy • Metabolic studies, including diabetes and obesity	• Remote observations and health checks • Reduced animal handling • Improved animal welfare • Humane endpoints - vital parameters can be detected remotely • Health status of animals (temperature & locomotor activity) • Accurate animal census and colony management • Timing of cage changes and other care-taking activities

- **What are the biomarkers you want to collect**
- **What type of cages are required**
- **How do you want to access the data**
- **What is your budget**
- **Compare the technologies**
- **Ask questions**

COMPANIES OFFERING HOME CAGE MONITORING

Columbus Instruments

Noldus

Lafayette Instrument

TECNIPLAST
innovation through passion

uid
IDENTIFICATION SOLUTIONS

Actual Analytics™
Capture, analyze and discover

SABLE SYSTEMS INTERNATIONAL

DSI™
a division of
Harvard Bioscience, Inc.

PHENOSYS
Technology for Behaviour Analysis

emka
TECHNOLOGIES

Current Engagement & Use Cases

Ellie Karlsson, Director, LAR, Calico Life Sciences

Use Case: Study & Humane Endpoints (Oncology)

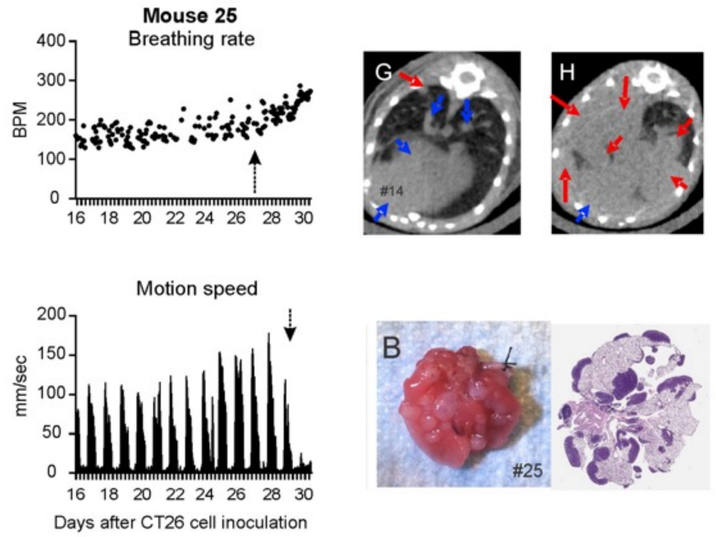
- **Study:** Metastatic lung tumor model in BALB/c and C57BL/6
- **Goal:** Automated monitoring of respiratory rate as a novel humane endpoint to signal the need for increased clinical observations or euthanasia.
- **Resources Required:** Imaging capabilities (microCT)
- **Scientific insights: Tumor-bearing animals developed increased respiratory rates (RR) 1-2 days before decreased locomotion.** Increases RR did not correlate to lung weight. Body weight & temperature measurement did not show significant changes in either tumor-bearing or control animals.

RESEARCH ARTICLE

Automated monitoring of respiratory rate as a novel humane endpoint: A refinement in mouse metastatic lung cancer models

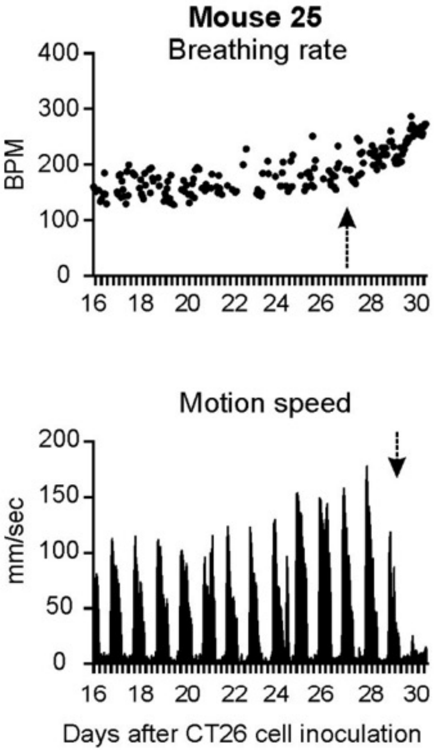
Caroline B. Winn[1], Seo-Kyoung Hwang[2], Jeffrey Morin[1], Crystal T. Bluette[1], Balasubramanian Manickam[3], Ziyue K. Jiang[4], Anand Giddabasappa[4], Chang-Ning Liu[2]*, Kristin Matthews[4]

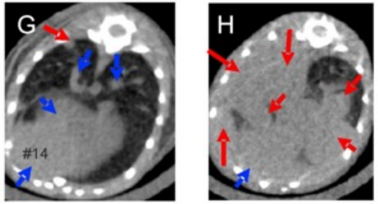
PLOS ONE

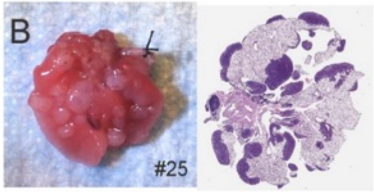


Use Case: Study & Humane Endpoints (Oncology)

- **3Rs Impact:** Refinement of humane endpoints, increases in respiratory rate (1.3–1.5 X) used to provide an objective benchmark can significantly reduce the distress of mice in the terminal stages of metastatic lung cancer.
- **Operational Efficiency:** Adoption of this endpoint criterion allows timely collection of tissues; replace labor intensive imaging assessment with home cage automated observation.

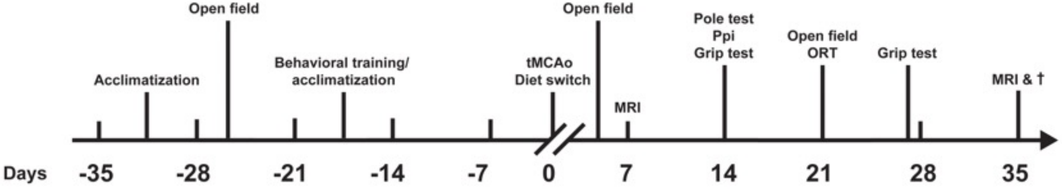






Use Case: Efficacy (Stroke & Behavior)

- **Study:** Movement & walking pattern during stroke recovery in female C57BL/6 mice on a multi-nutrient diet intervention (Fortasyn).
- **Goal:** Quantify parameters of movement, traveled distance, velocity, turnings, and laterality and compare to previously collected traditional measures behavior (Open Field, Pole test), neuroimaging
- **Resources Required:** Researchers with moderate programming background (Python) and traditional behavior assessment; open source trajectory analysis software (Traja)

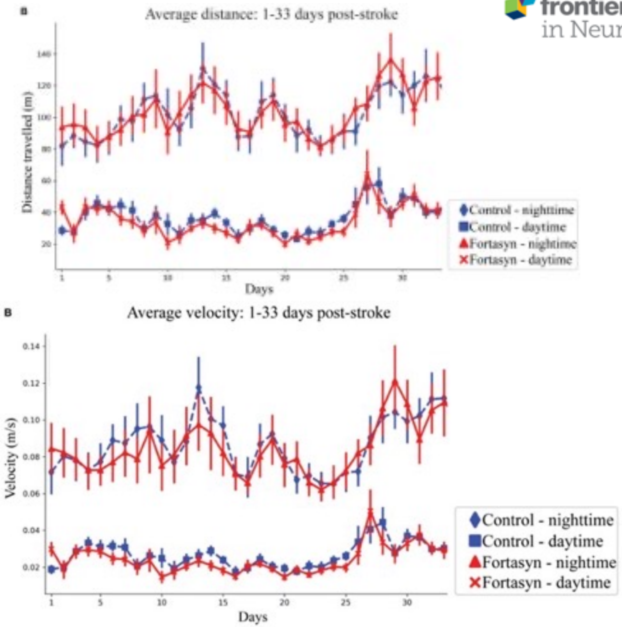


Automated Analysis of Stroke Mouse Trajectory Data With Traja

Justin Shenk†, Klara J. Lohkamp†, Maximilian Wiesmann‡ and Amanda J. Kiliaan‡*

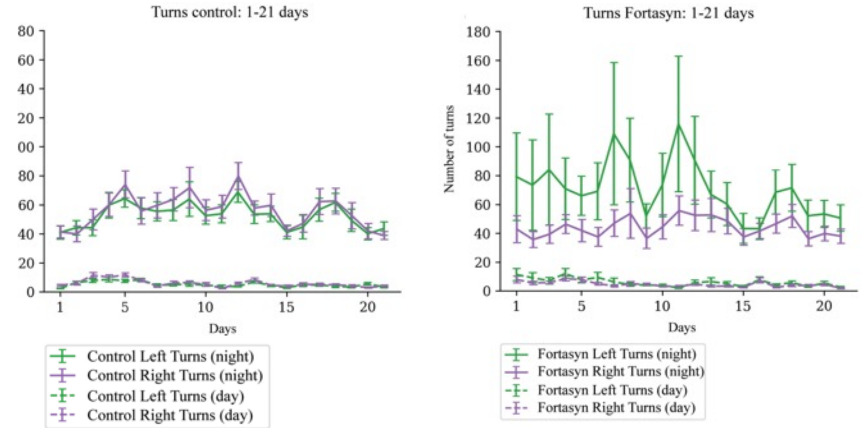
Department of Anatomy, Radboud University Medical Center, Preclinical Imaging Centre PRIME, Radboud Alzheimer Center, Donders Institute for Brain, Cognition, and Behavior, Nijmegen, Netherlands

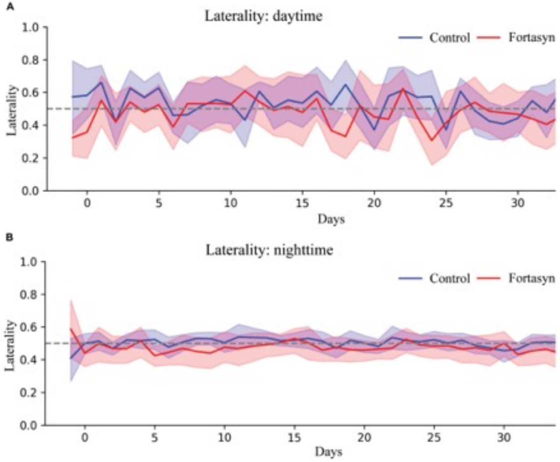
frontiers in Neuroscience



Use Case: Efficacy (Stroke & Behavior)

- **Scientific insight-** Previous studies have clearly shown that Fortasyn has neuroprotective effects after an ischemic stroke. Both groups showed progressive recovery over time, showing an increase of activity, distance, and velocity on short-term and/or long-term after stroke induction.
- **3Rs Impact-** Home cage assessment and minimal handling post-surgery
- **Operations-** Reduced labor for behavioral assessments, automated activity assessment in a surgical model

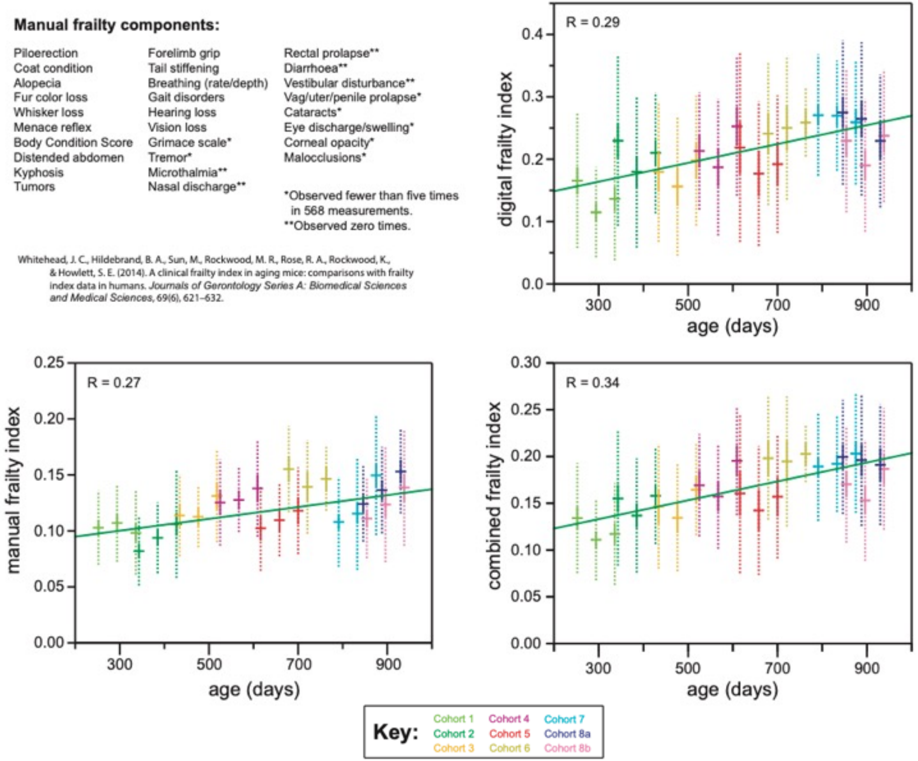




Use Case: Longitudinal Studies (Aging)

Calico

Manual Frailty Index (MFI) and Digital Frailty Index (DFI) versus chronological age



Study: Cross-sectional aging study in male and female Diversity Outbred mice

Goal: Develop non-invasive, automated frailty index based on computer vision and machine learning on home cage video that correlates with chronological age

Resources required: researchers trained in computer vision and machine learning, manual frailty assessment. Aged mice

See our publication:

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

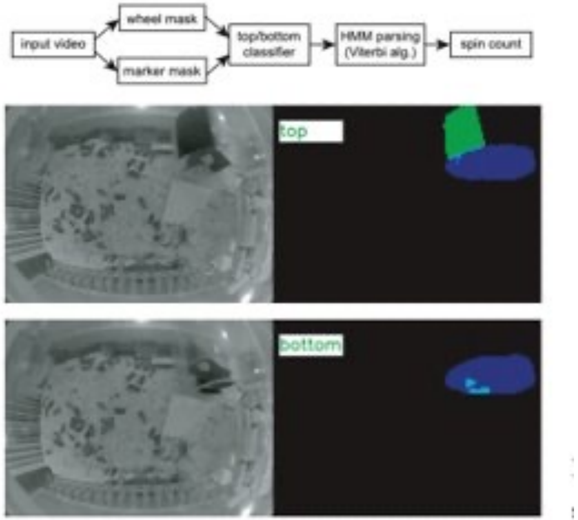
A home-cage, video monitoring-based mouse frailty index detects age-associated morbidity in the absence of handler-induced stress

J. Graham Ruby, Paulo Ylagan, Andrea Di Francesco, José Zavala-Solorio, Robert Keyser, Owen Williams, Sarah Spock, Wenzhou Li, Nalien Vongtharangsy, Sandip Chatterjee, Cricket A. Sloan, Charles Ledogar, Veronica Kuiper, Janessa Kite, Marcelo Cosino, Paulyn Cha, Eleanor M. Karlsson

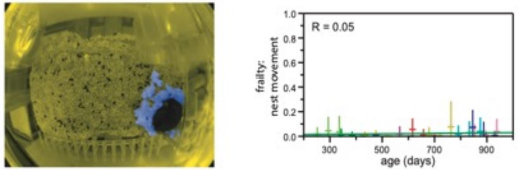
Use Case in Longitudinal Studies (Aging)

- **Scientific insights:** <u>DFI correlated with chronological age, performed slightly better than manual FI.</u> Combination of DFI and MFI increased correlation.
- **3Rs Impact:** Reduced handling of mice, housing in an enriched environment
- **Operational Efficiency:** Studies can be run without highly trained staff with less time

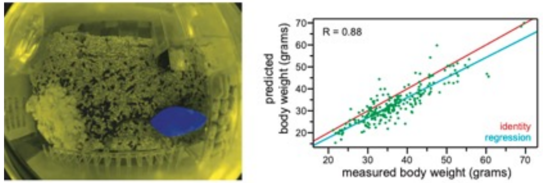
DFI parameters: *wheel distance, gait speed on wheel*



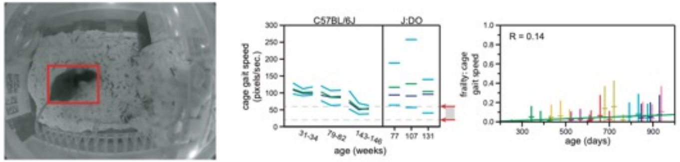
DFI parameter: *nest movement*



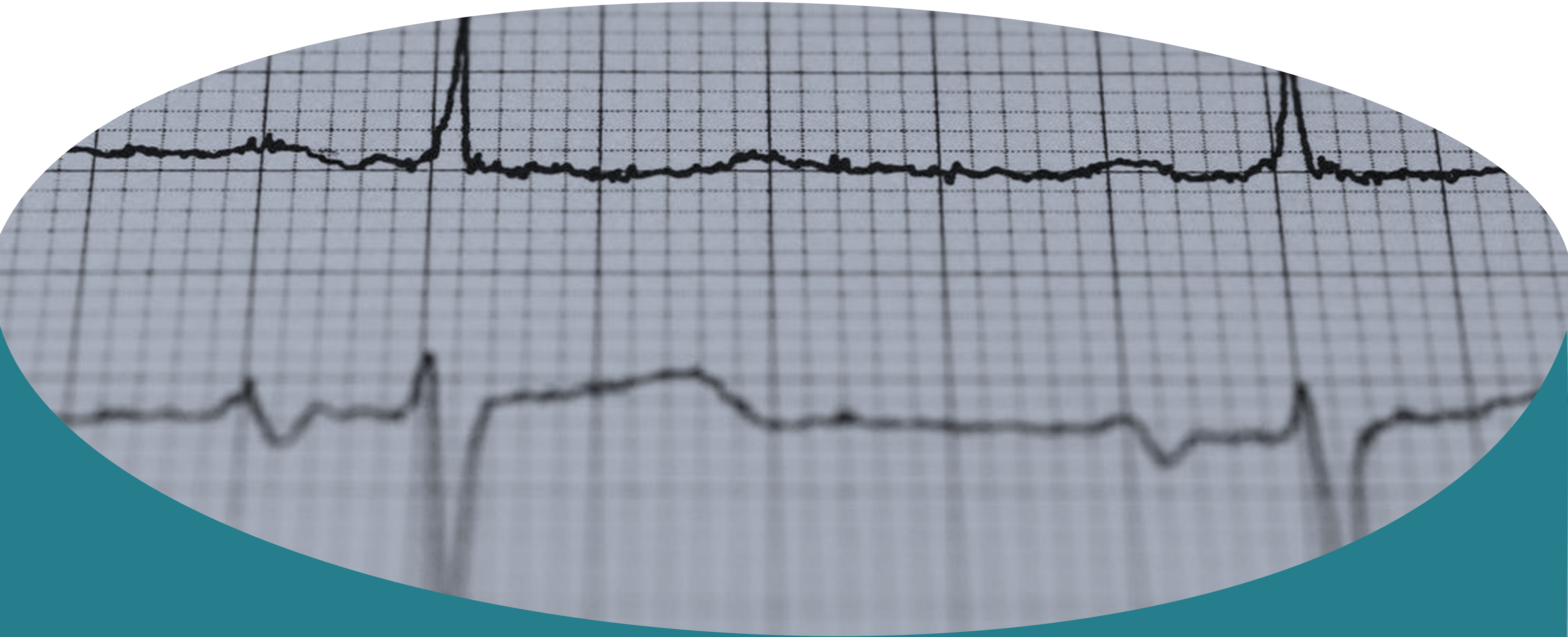
DFI parameters: *body weight change and coat roughness*



DFI parameter: *gait speed on the cage floor*



Data Consistency and Technology Standards



Angela King-Herbert

Head, Division of Translational Toxicology Comparative Medicine Group, NIEHS

Analyzing pilot study data can uncover the potential value of translational digital biomarkers

A number of analysis strategies can be used to determine the added value of TDB.

If the pilot study data suggest TDB may be of value, run a follow-up complete study to verify reproducibility.

Preliminary data may suggest that TDB can provide complementary or more meaningful data.

To be valuable, it will be necessary to show that these data can be reproducibly obtained from multiple studies.

For data consistency, conduct a follow-up study using the exact same study design (including procedure schedule).

Include one or more therapeutics with known efficacy.

To ensure reproducibility, use the same statistical strategy to analyze both studies.

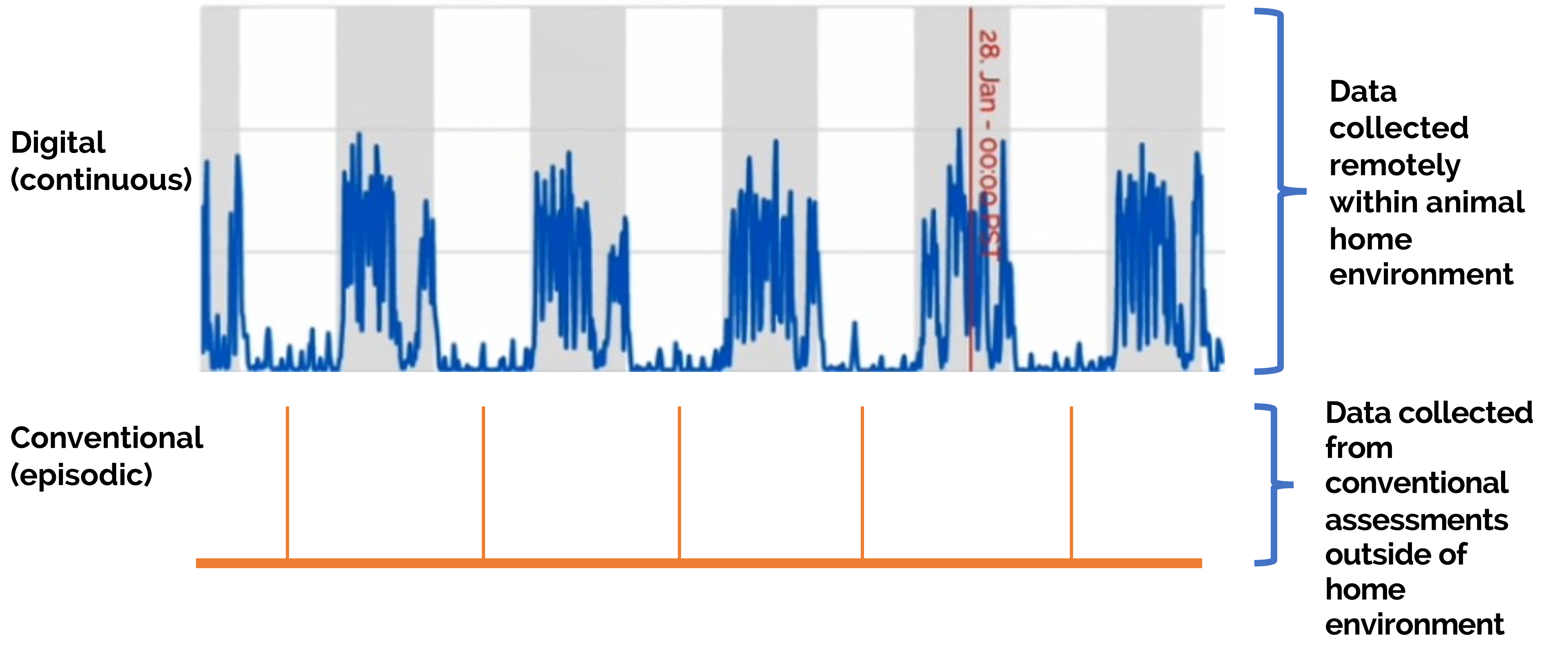
If collaborations are anticipated, ask a collaborator to replicate your findings.

The ability to replicate findings across highly variable laboratory settings will further serve to confirm the reproducibility of TDB.

Scalable DB technologies present an opportunity to capture meaningful, objective data leading to actionable insight into animal welfare, animal tracking, study design optimization, and control on sources of variations.

These technologies present an opportunity to measure novel DBs and digitize existing biomarkers.

Continuous digital biomarkers can give a holistic view versus a snapshot.



Continuous digital biomarkers allow the measurement of spontaneous behavior & subtleties that may go unnoticed by gross cage side observations.

Use rigorous technology standards: Pertinent & timely data

- Pertinent and timely data are required for a translational biomarker to inform clinical and preclinical researchers in a usable manner.
- To achieve and standardize such a translational biomarker requires a great deal of time and resources in order to establish its credibility as a measurement.

There is a variety of diverse technology

- There are a **variety of devices that** currently address **different aspects of animal welfare,** all measuring **varying sets of digital biomarkers.**
- These devices are used to provide data to inform scientists, managers, and technicians of various aspects of *in vivo* health, welfare, disease status, and treatment efficacy.

Use rigorous data standards for data storage & protection

Design an architecture that promotes the ability to: store, retrieve, and interact with large amounts of data.

When onboarding TDB, use a vetting process that includes pilot studies & data management plans

Barriers and Solutions to Implementation and Adoption

Sheba Churchill | Staff Veterinarian, Charles River Laboratories

Barriers and Solutions to Implementation and Adoption

Barriers	Solutions
IT and infrastructure to support technologies	Early engagement with IT, through understanding of internal infrastructure at start of planning.
Cybersecurity	Early engagement with cybersecurity team
Non-IT resource requirements	Involvement of vivarium leadership and scientist in the planning of technology. Investment in training around the new technology.

Barriers and Solutions to Implementation and Adoption

Barriers

- Communication between technology provider and end-user
- Consideration and/or understanding of technology impact on *in vivo* model or biology
- Consideration and/or understanding of changes in animal housing on *in vivo* model or biology

Solutions

- ID main point of contact for tech provider and end-user.
- ID publications demonstrating the benefits of the tech with specific performance data.
- ID publications with similar tech, use pilot studies, talk with other end-user to understand the cost, benefits, and impacts to a model.

Barriers and Solutions to Implementation and Adoption

Barriers

- Social housing and data gaps
- Data quantity
- Timeline: decision → engage → running studies

Solutions

- Determine if social housing will cause data gaps. Engage data scientist early.
- Map out data flow and develop data storage infrastructure, maintenance, access strategy including data retention policy.
- Map out realistic timeline and share with all stakeholders.

Barriers and Solutions to Implementation and Adoption

Barriers

- Technology verification and validation
- Study design

Solutions

- Establish guidelines for how novel digital biomarker technology should be validated; as an example, methodologies to compare digital measures to more traditional measures.
- Involve dedicated data scientists upfront to improve study design by taking into account the n number (cage or animals, depending on the technology) and relative power calculation for the outputs to be expected.

Barriers and Solutions to Implementation and Adoption

Barriers

- Regulatory application of a novel biomarker
- Fear of change

Solutions

- Engage health authorities early to identify context of use and qualification criteria and co-develop publications.
- Educating teams about digital monitoring technologies, 3Rs benefits, and study approach.

Barriers and Solutions to Implementation and Adoption

Barriers

Collaboration

Solutions

- Internally, establish mechanism or group to aggregate experiences of studies with these technologies. Examples include industry wide, establish precompetitive groups with various stakeholders such as the Translational Digital Biomarkers Initiative within NA3RsC to share their experiences and serve as a knowledge repository with a goal of establishing more universal approaches to these emerging technologies.

TDB Paper

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Email me: meglafollette@na3rsc.org