2020 Russia (Coronavirus COVID-19)

Необходимость многомерных и многофункциональных измерительных систем в лабораторных исследованиях на животных и важность стандартных внешних факторов для содержания животных

GLP-Planet – St' Petersburg
30 June 2020

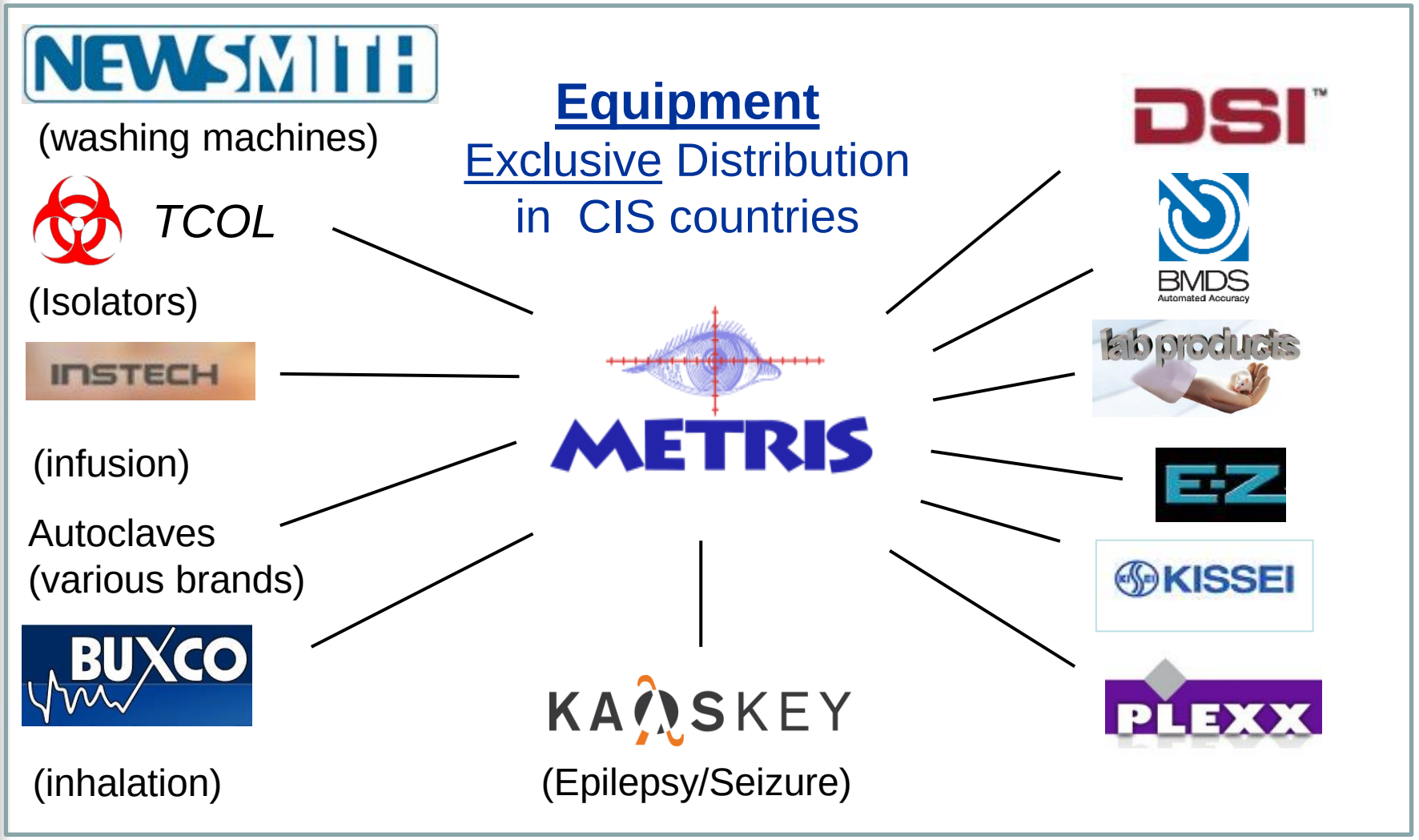
Levon Bachdasarian
Metris BV
Netherlands

Company Overview

- Metris was established in 1994 in Netherlands

- Market presence of 25 years & customers in over 90 countries across Europe, America and Asia
- Metris develops, sells and supports innovative products and solutions to assess laboratory animal behavior & animal vocalizations.
- Metris differentiates itself by finding new solutions that are increasing efficiency, throughput and are completely non-invasive (animal friendly)

Our Strategic Partners



Our Strategic Partners

Research

Scientific Partners
(global alliances)

- *Testing & validation of new equipment*
- *Contract Research*

FMBA & RAMS

SCBMT

RIHTOP

SMU-NN

Product Portfolio

Advanced Analysis Equipment:

- LABORAS (behavior analysis)
- SONOTRACK (vocalization analysis)
- SMARTCHAMBER (controlled environment)
- SLEEPSIGN (sleep analysis)
- DATASCIENCES Telemetry (wireless physiology analysis)
- DSI/Buxco Instruments for respiration study

Product Portfolio

Vivarium Equipment:

- Modular Laboratories (design and realization)
- Animal Housing (Open cages and IVC cages)
- Work benches (Cage change stations)
- Isolators
- Climate Chambers (animal breeding)
- Washing Machines and Autoclaves
- Waste Management Systems
- Animal Identification (RFID based)
- Metabolic Cages

Total Solution vivarium-laboratory-research

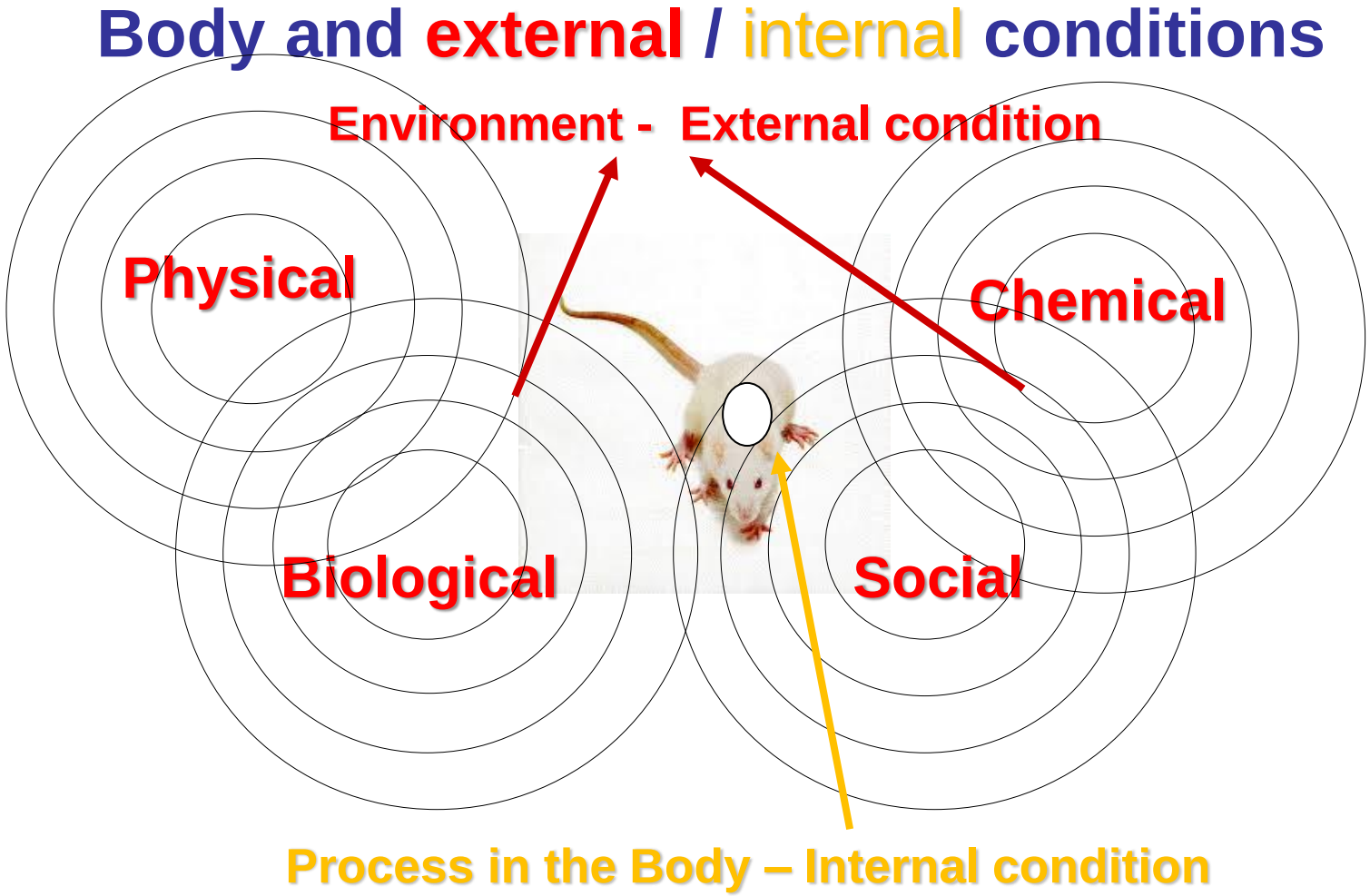
Why a total solution concept?

- Laboratories and vivariums in Russia will have to comply with International standards to enable collaborations and competition with Western companies.

- GLP requirements will require a different way of working, which requires an integrated approach / methodology involving animal housing facilities, equipment and researchers.

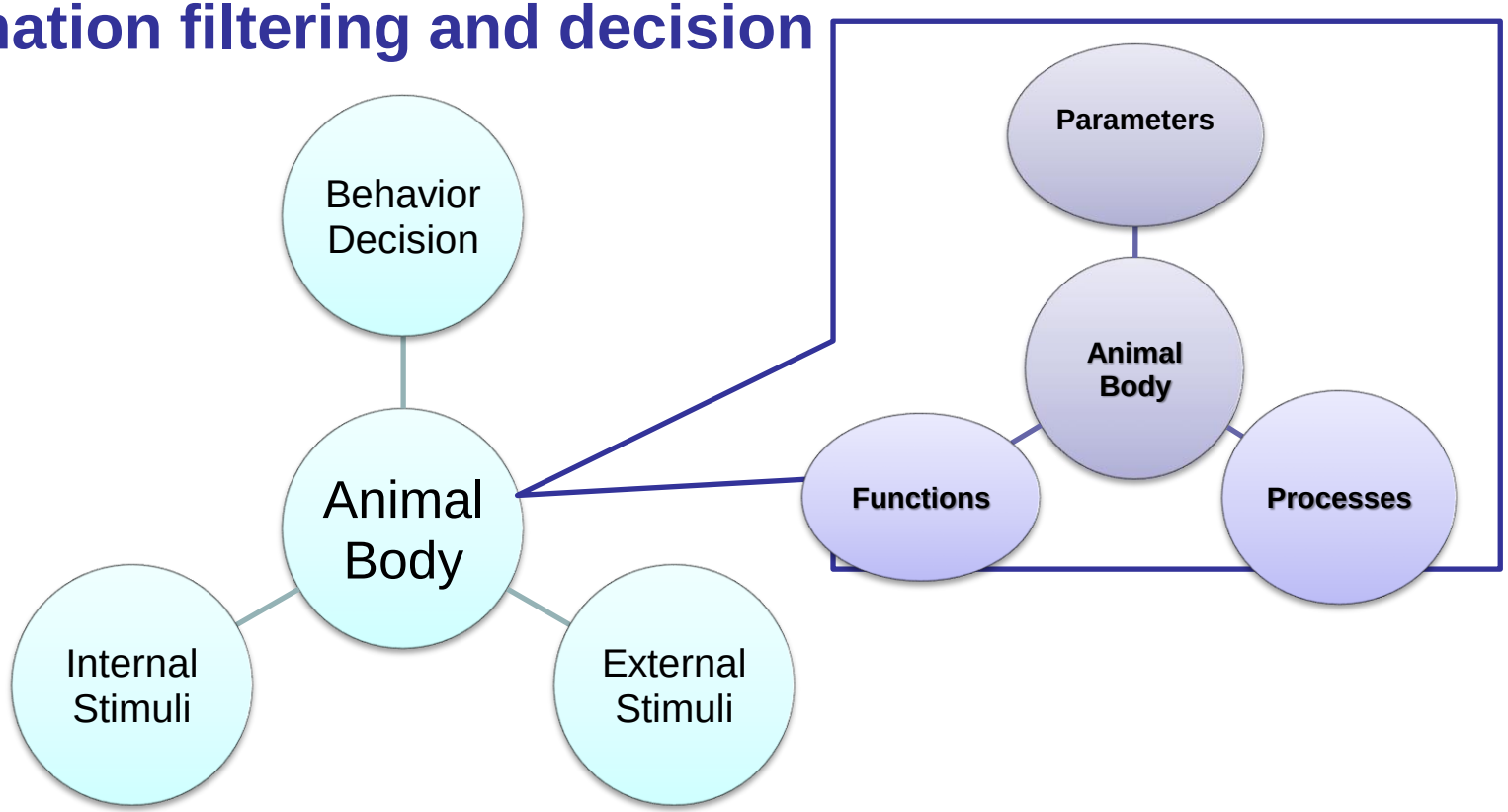
- Complexity of requirements is increased and puts pressure on the agreements!

Physiology-Behavior



Signal influence from environment

Information filtering and decision



BEHAVIOR = Function {Internal stimuli, external stimuli}

Preclinical study

BEHAVIOR =
Function { Internal stimulus, external stimulus}

Environment and Ecology
External factors=constant!
Change internal stimulus?

Pharmacology
Internal factors=constant!
Change external factors?

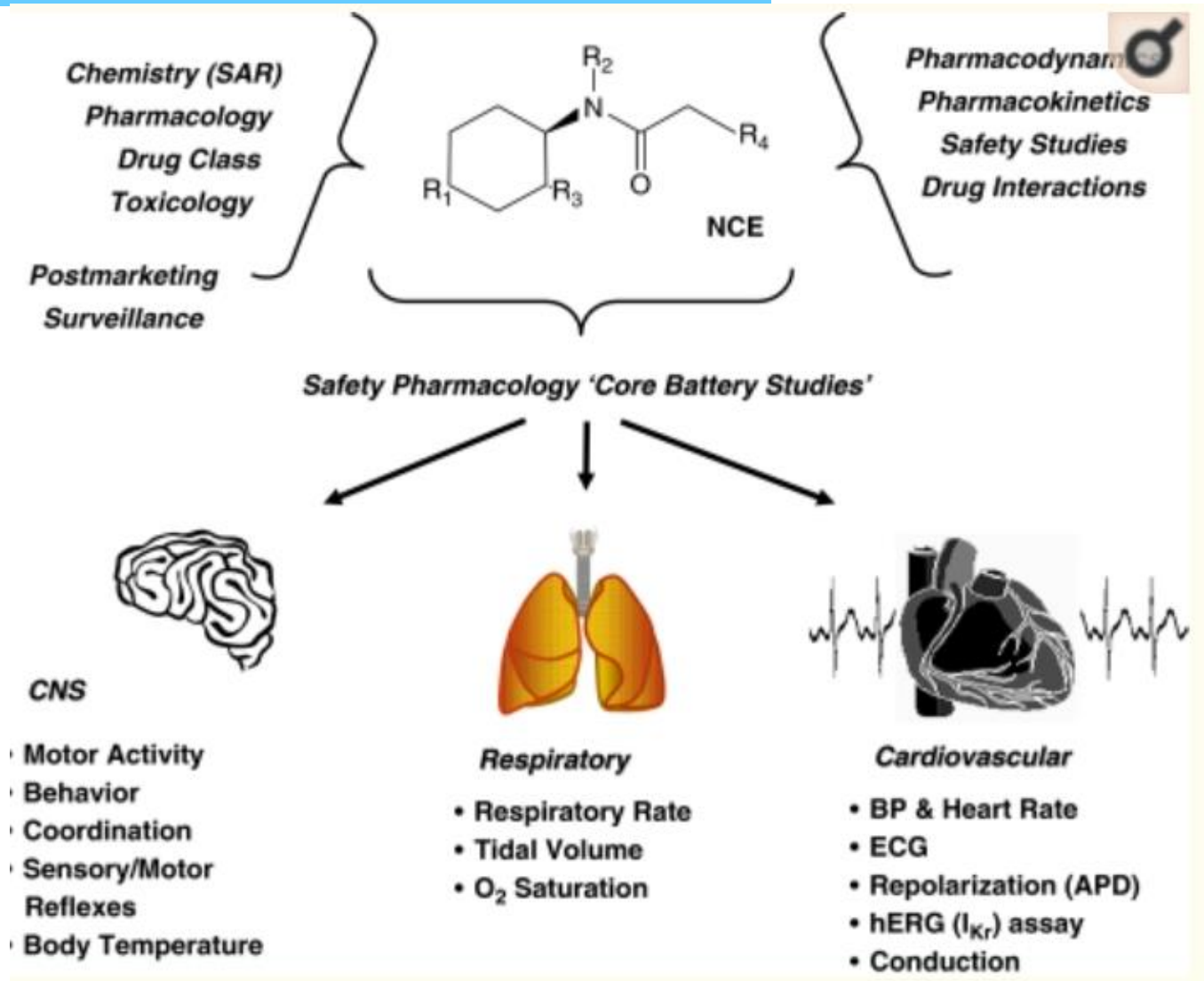
Where:
Internal Stimuli=function {**Internal** factors}
External stimuli=function {**external** factors}

Pre-clinical research

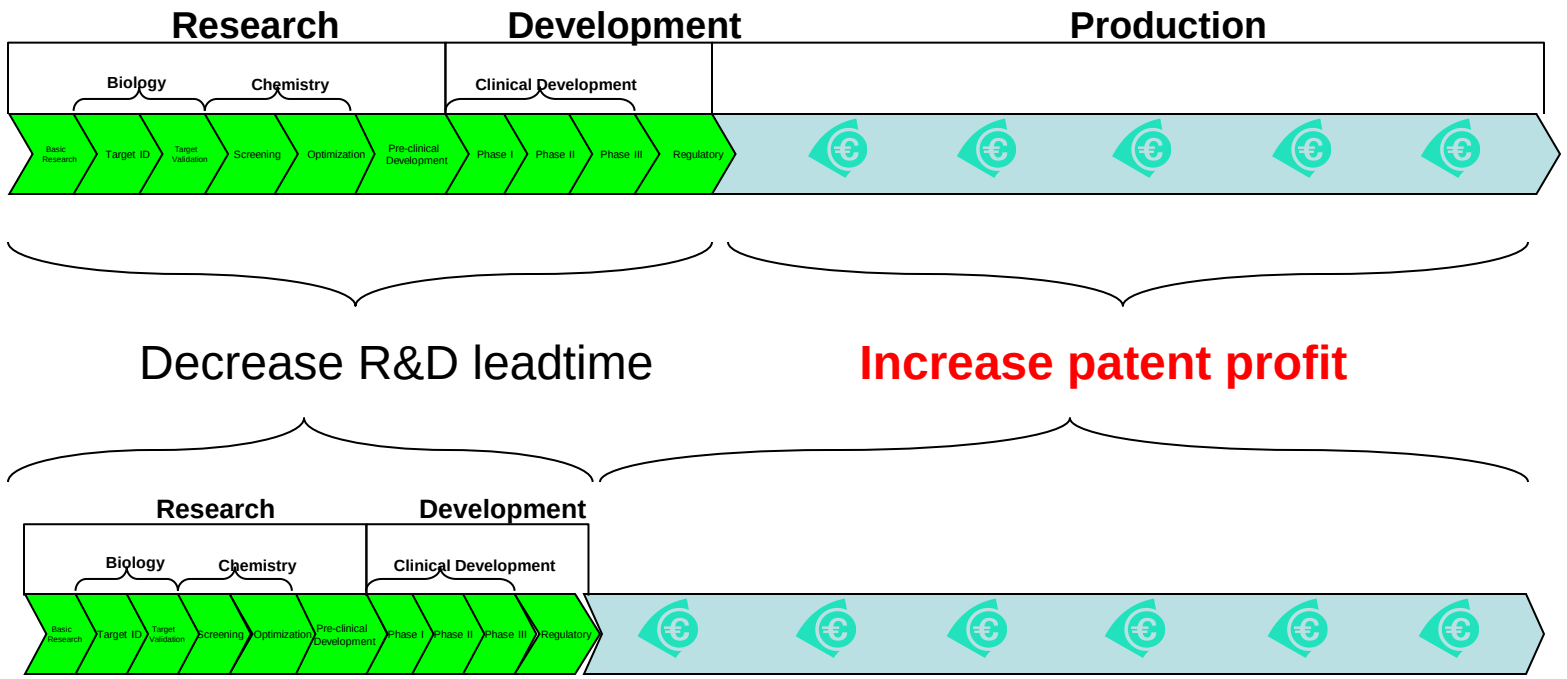
Goals of preclinical studies

- Correct research results
- Proper research statistics
- Useful conclusions from studies
- High Quality Data
- Reduced lead time
- Minimized cost

Pharmacology



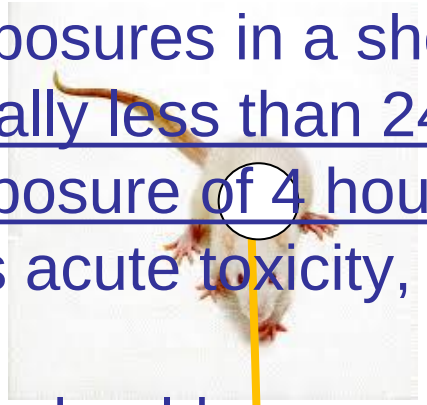
Pre-clinical research



Preclinical experimental studies for COVID-19

Acute toxicity

(epidemic, A pandemic is an epidemic worldwide)
Acute toxicity describes the adverse effects of a substance that result either from a single exposure or from multiple exposures in a short period of time (usually less than 24 hours), or an inhalation exposure of 4 hours.
To be described as acute toxicity,



the adverse effects should occur within 14 days of the administration of the substance.
From the other side the information in the body transmits via neurons and CNS system.

Process in the Body – Internal condition

Preclinical experimental studies for COVID-19

Safety pharmacology

Safety pharmacology specializing in detecting and investigating potential undesirable pharmacodynamic effects of new chemical entities on the physiological functions in relation to exposure in the therapeutic range and above.

Primary organ systems(cardiovascular, respiration, brain, blood)!

Toxicity Studies (all routes)

O Dose range-finding studies

O 14-day toxicity studies: Repeated dermal and ocular studies, respiration

O 28 to 90-day toxicity studies (cardiovascular, liver, brain, blood, CNS)

Chronic Toxicity Studies

6, 12, 18, and 24-month toxicity studies in rodents and non-rodent species (cardiovascular, blood, brain, CNS, metabolism)

Process in the Body – Internal condition

Acute toxicity

Metris BV offers acute toxicity studies by different routes

All studies are performed according to GLP guidelines:

Acute Toxicity Studies (the following routes)

- Inhalation
- Derma
- Ocular
- Blood (multiple methods available)

Safety pharmacology

Metris BV offers Safety pharmacology studies by different routes

Primary organs GLP guidelines

- Cardiovascular System (CV)
- Respiratory System (RS)
- Brain study (EEG)
- Blood (BP)
- Central Nervous System (CNS)

Secondary organ systems of interest are:

- Gastrointestinal System
- Renal System
- Liver system
- Metabolism

Datasciences Telemetry

Animal Physiology Monitoring and Data Collection

- from Wired to Wireless to Integration

- **Implantable Telemetry**
- **Non-implantable Telemetry (JET)**

DSI Business Fields

Research Area

- CNS
- Respiratory
- Metabolism
- Cardiovascular

Equipment offered

- Implantable Telemetry
- External Telemetry
- Tethered Monitoring
- Implantable Pumps
- Plethysmography

DSI-Implantable Telemetry

Implantable Telemetry

Measures combinations of:

Multiple Biopotentials (ECG, EEG, EMG, EOG)

Pressure (Blood Pressure, etc.)

Temperature

Activity

Wireless Monitoring of Conscious, Free-moving Animals

PARAMETERS

- Pressure: BP, Ocular, Bladder, Uterine, Pleural, etc
- Biopotential: ECG, EEG, EMG, EOG
- Temperature
- Respiration
- Motor Activity
- Glucose

Sleep Analysis Software

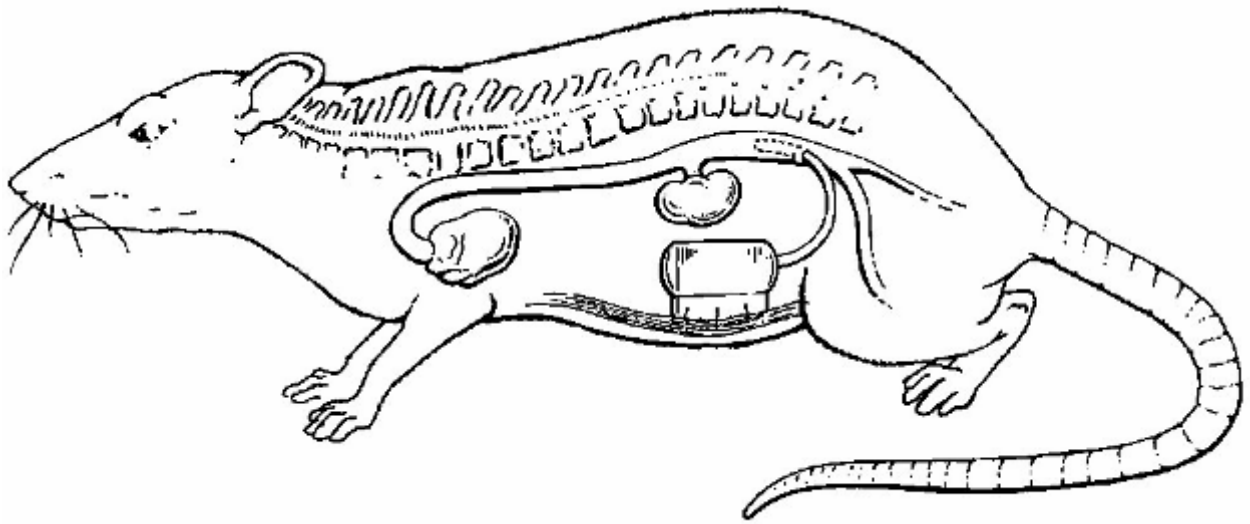
SleepSign® for Animal

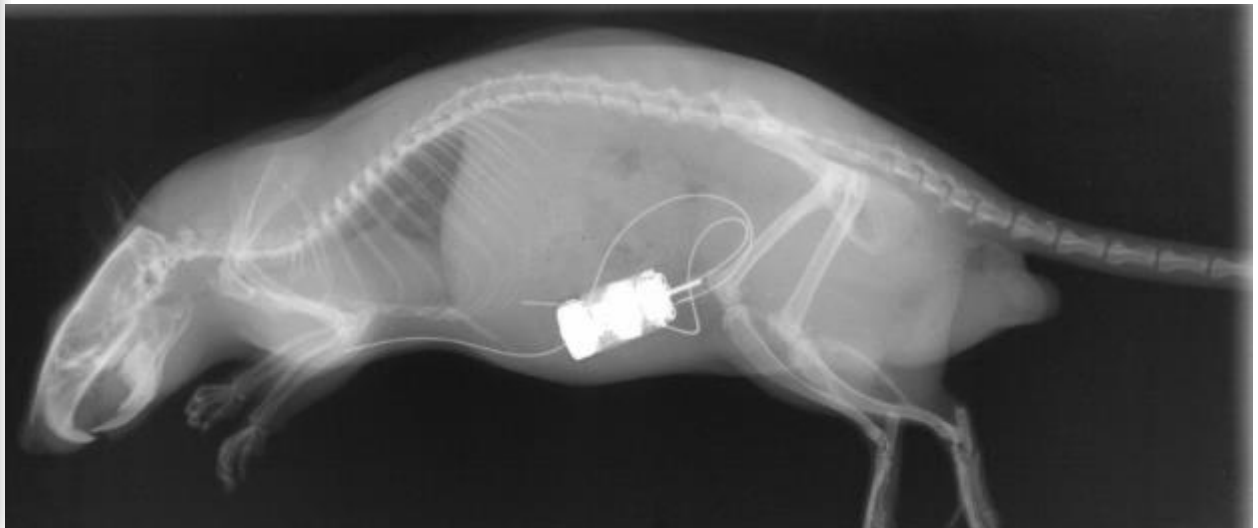
SleepSign

- Based on EMG and EEG signals
- Sleep stages can be scored in a manual mode as well as well as automatically
- Scores pre-assigned sleep stages (such as REM, WAKE, SWS) and up to 3 user defined vigilance stages

- Works with wireless or wired EMG and EEG signals
- In depth analysis using Hypnograms and Trend Graphs
- Various analysis functions, incl. Stage Graphs, Vigilance State Parameter Display, FFT analysis
- Integration with Laboras and Video Data possible

BP/ECG device placed IP in rat





Respiratory Monitoring

Goal: Assessment of respiratory functions in a conscious animal in stress free environment

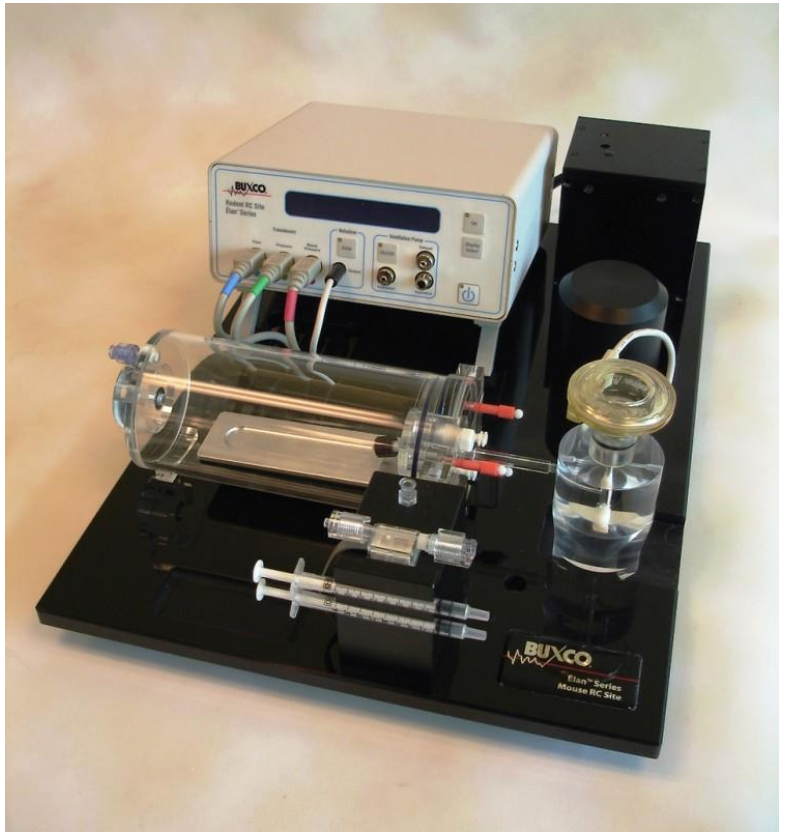
- Whole body Plethysmography (WBP)
- Noninvasive Airway Mechanics (NAM)
- Compliance & Resistance (RC)
- Pulmonary Function Test (PFT)
- Inhalation studies

WBP

Whole Body Plethysmograph Tower from DSI

This system is available for mice,
rats guinea pigs and dogs

NAM and RC

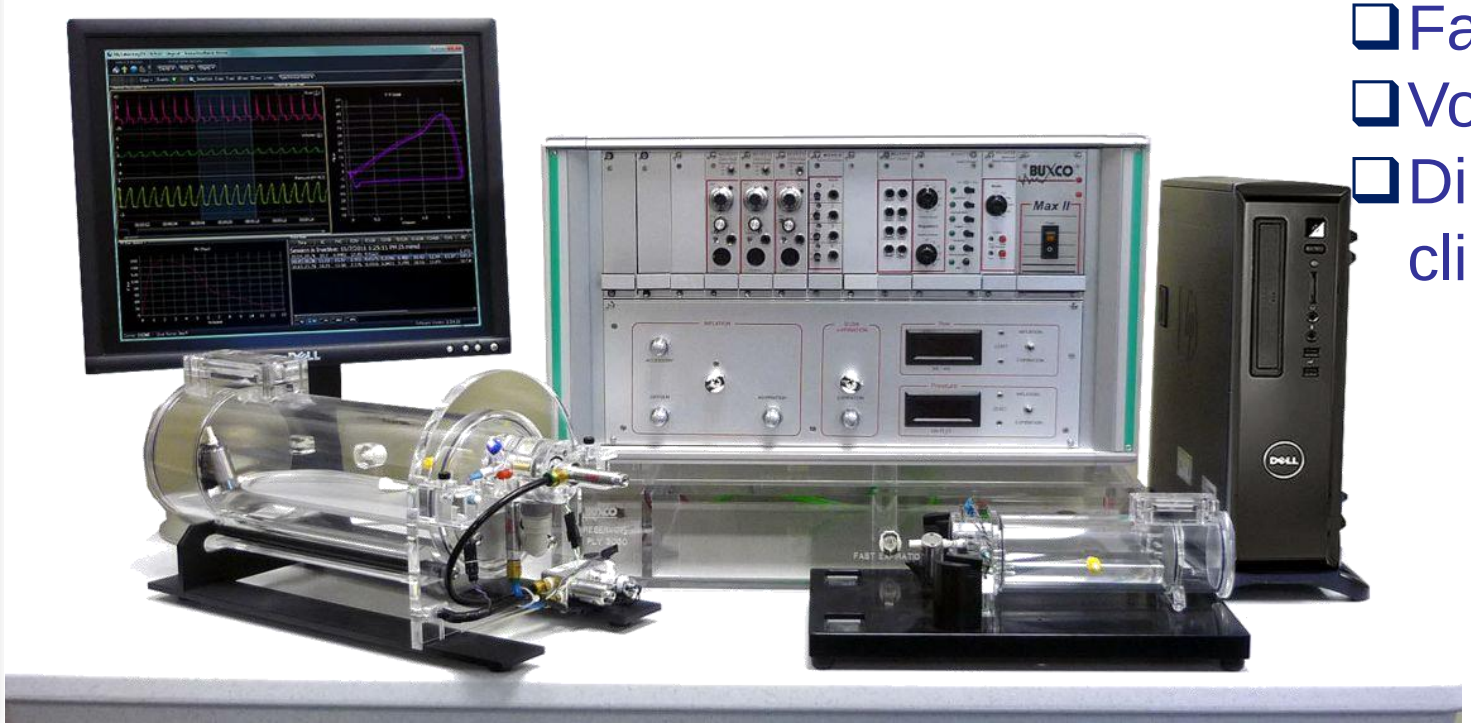


NAM system is available for mice, rats and guinea pigs.

RC system is available for mice, rats and guinea pigs.

Pulmonary Function Testing

Measure flow & mouth pressure during special PC-controlled breathing maneuvers



Gives complete picture of the dynamic lung properties:

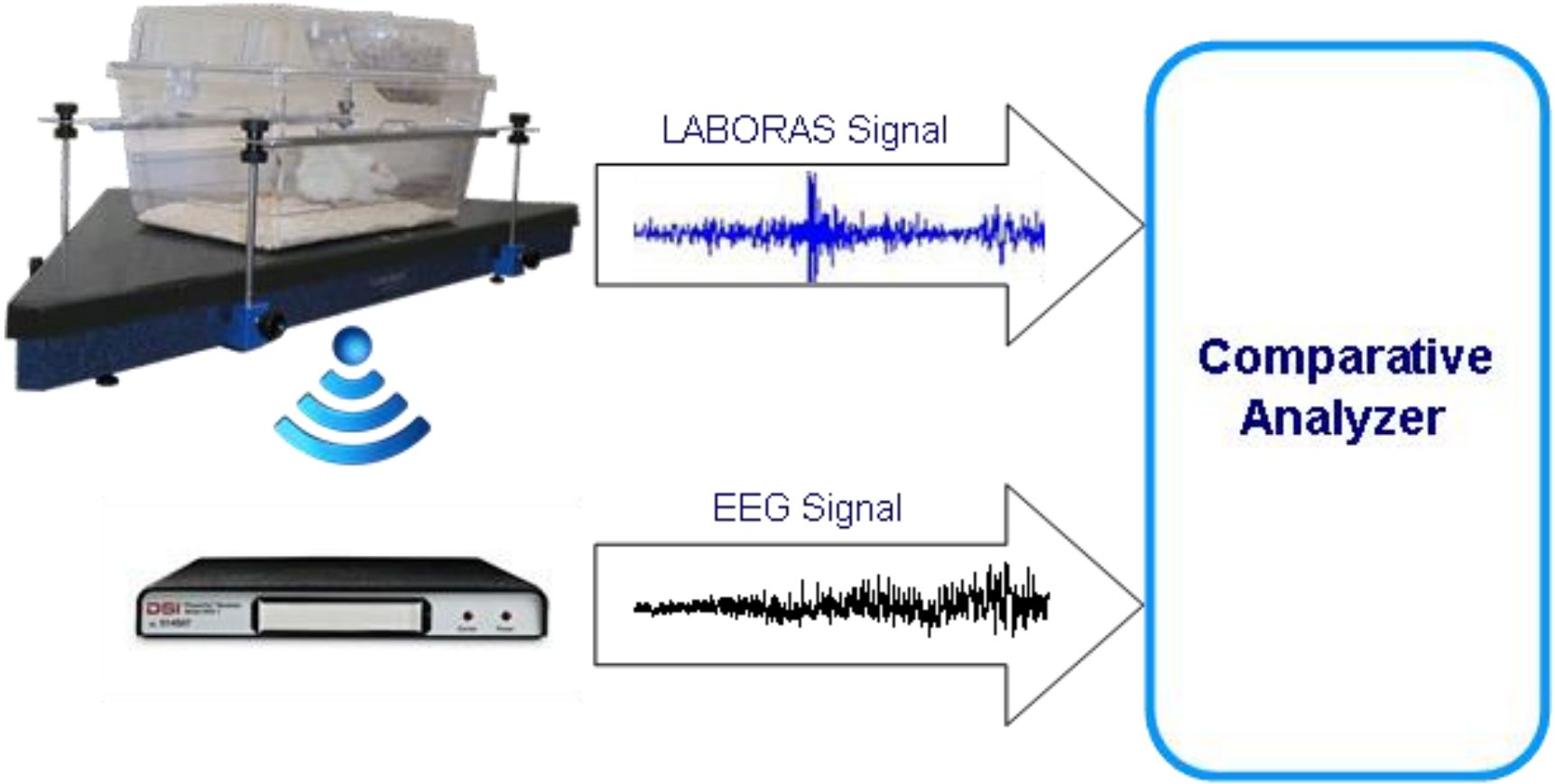
- ❑ FRC and all lung volumes
- ❑ Fast Flow-Volume
- ❑ Volume vs Pressure
- ❑ Directly comparable to clinical data

Inhalation tower & Smoke exposure

- Expose of subjects through the lungs
- Control the duration of the exposure
- Measure concentration & particle size
- Monitors ventilation paramentes

- “Flow past” concentric design
- Top and bottom ports
- Low dead-space nose adapters
- Easy disassembly for cleaning
- slight positive or slight negative pressure configurations

Integration DSI (EEG), ASSYST LABORAS

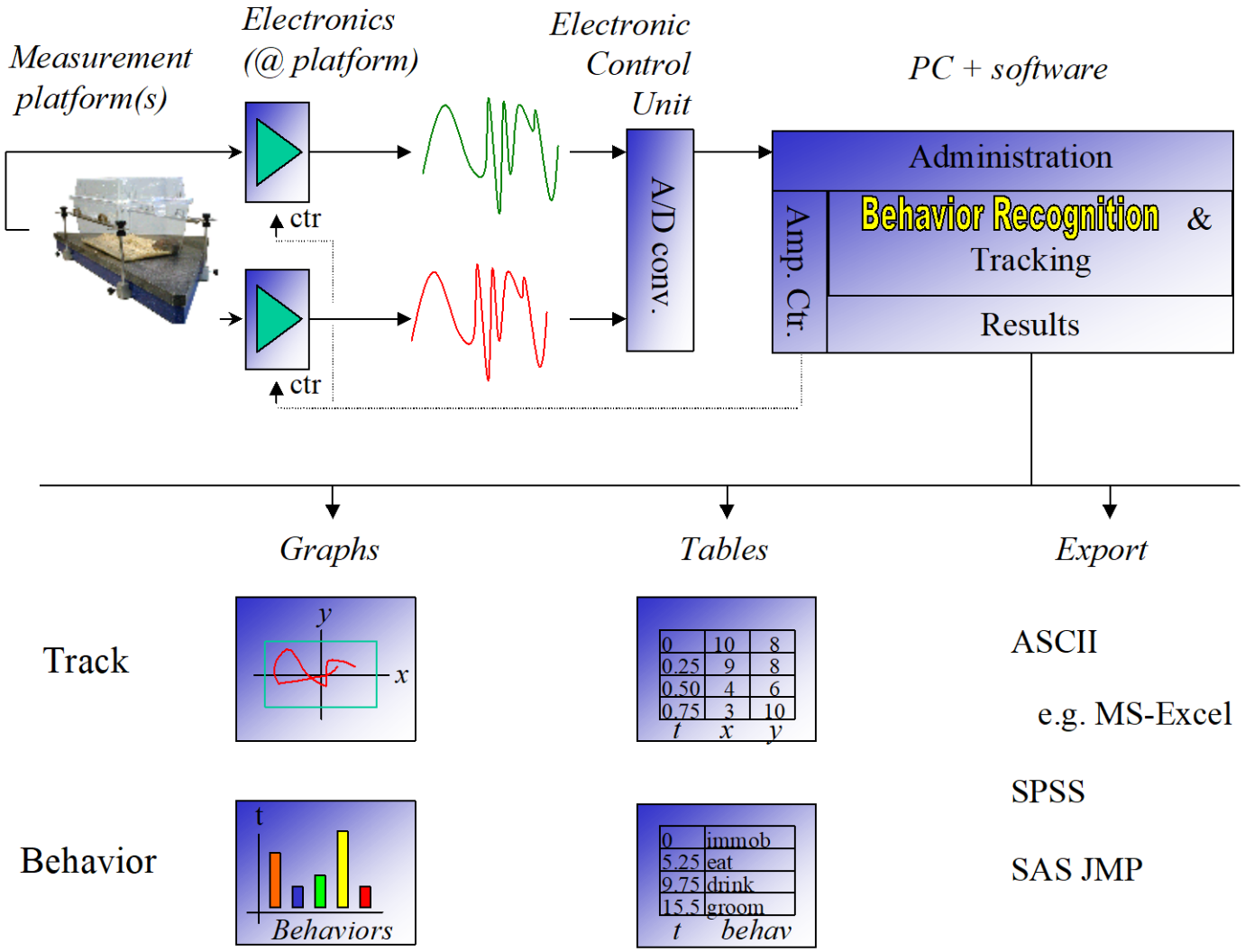


LABORAS

What is LABORAS?

- LABORAS is a fully automatic system for continuous behavior recognition and tracking of small rodents (mice and rats)
- LABORAS replaces, reduces and refines behavioral scoring by human observers
- LABORAS sets a new standard in the area of behavioral observation instruments
- Multi functional and modular

LABORAS Technique



LABORAS technique

Importance of the enegy parameter in behavioral pharmacology

$$\sum E_k = Mv^2/2 + \delta m \omega^2 R^2/2$$

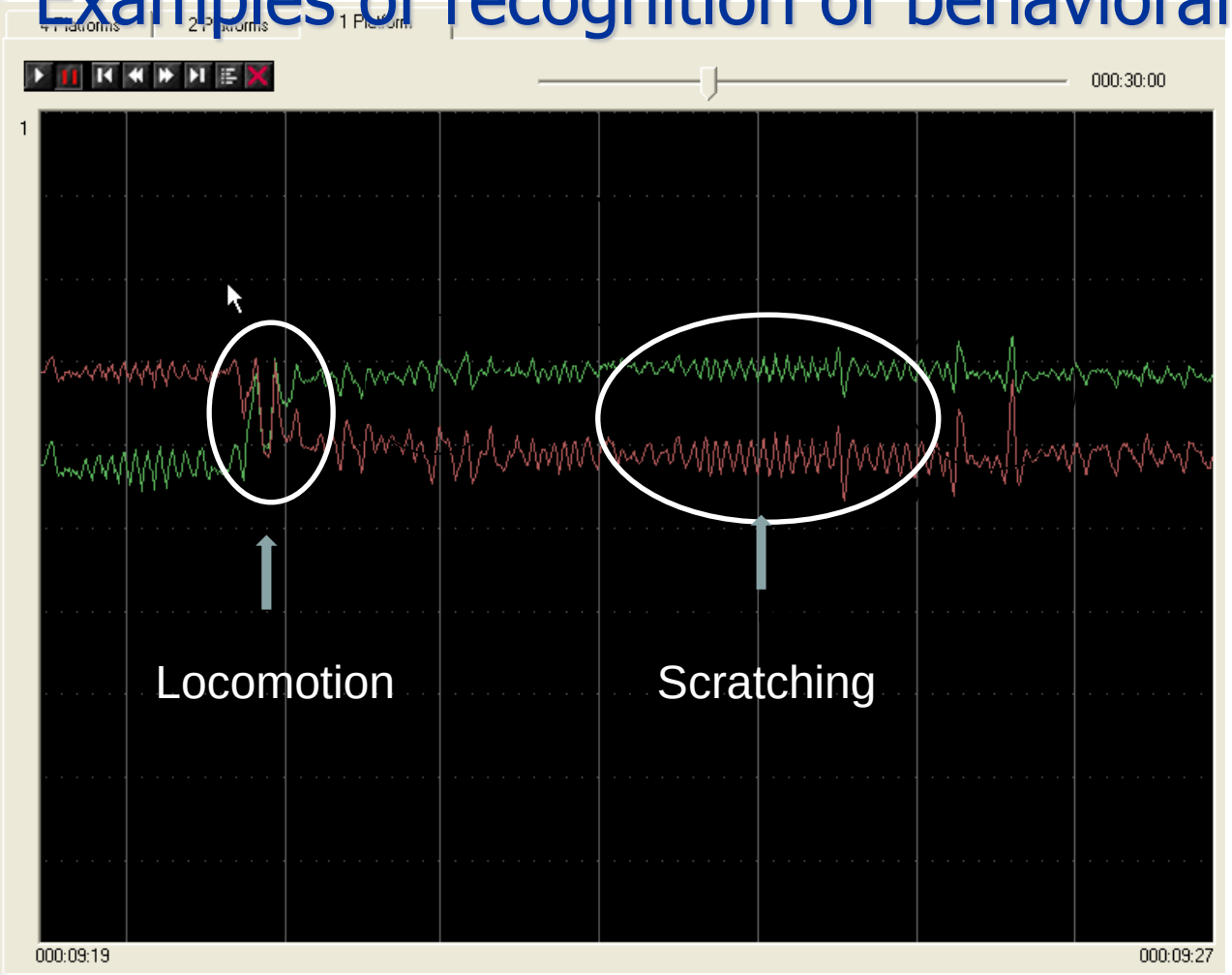
- **Kinetical energy of body**

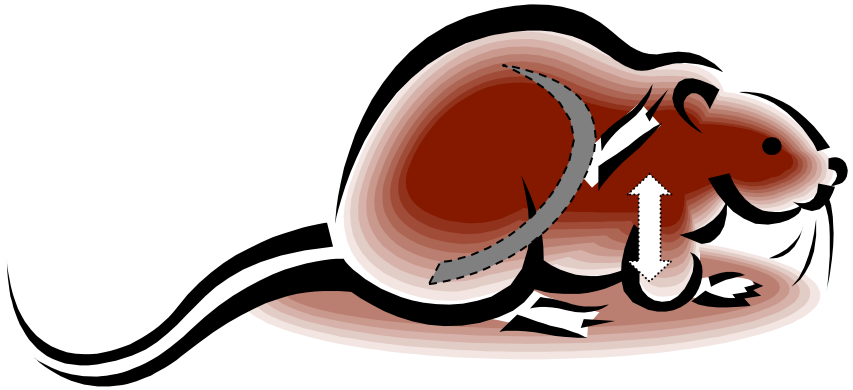
E Locomotion = $Mv^2/2$
V = speed, M = weight of body

E Oscilation = $\delta m\ \omega^2 R^2/2$
ω = oscilation frequency, R = radius of oscilation,
δm = weight of oscilation body part

LABORAS Technique

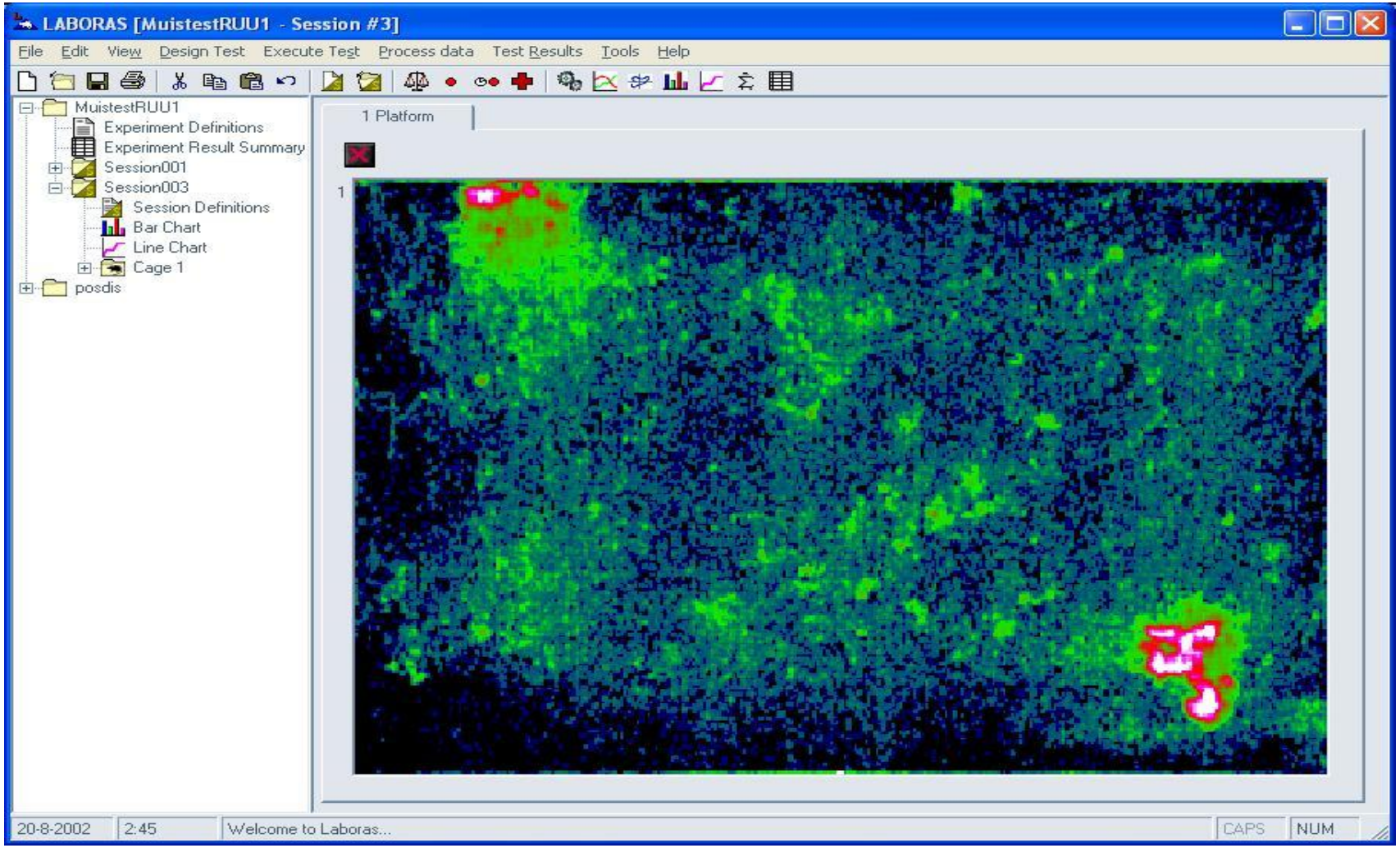
Examples of recognition of behavioral features



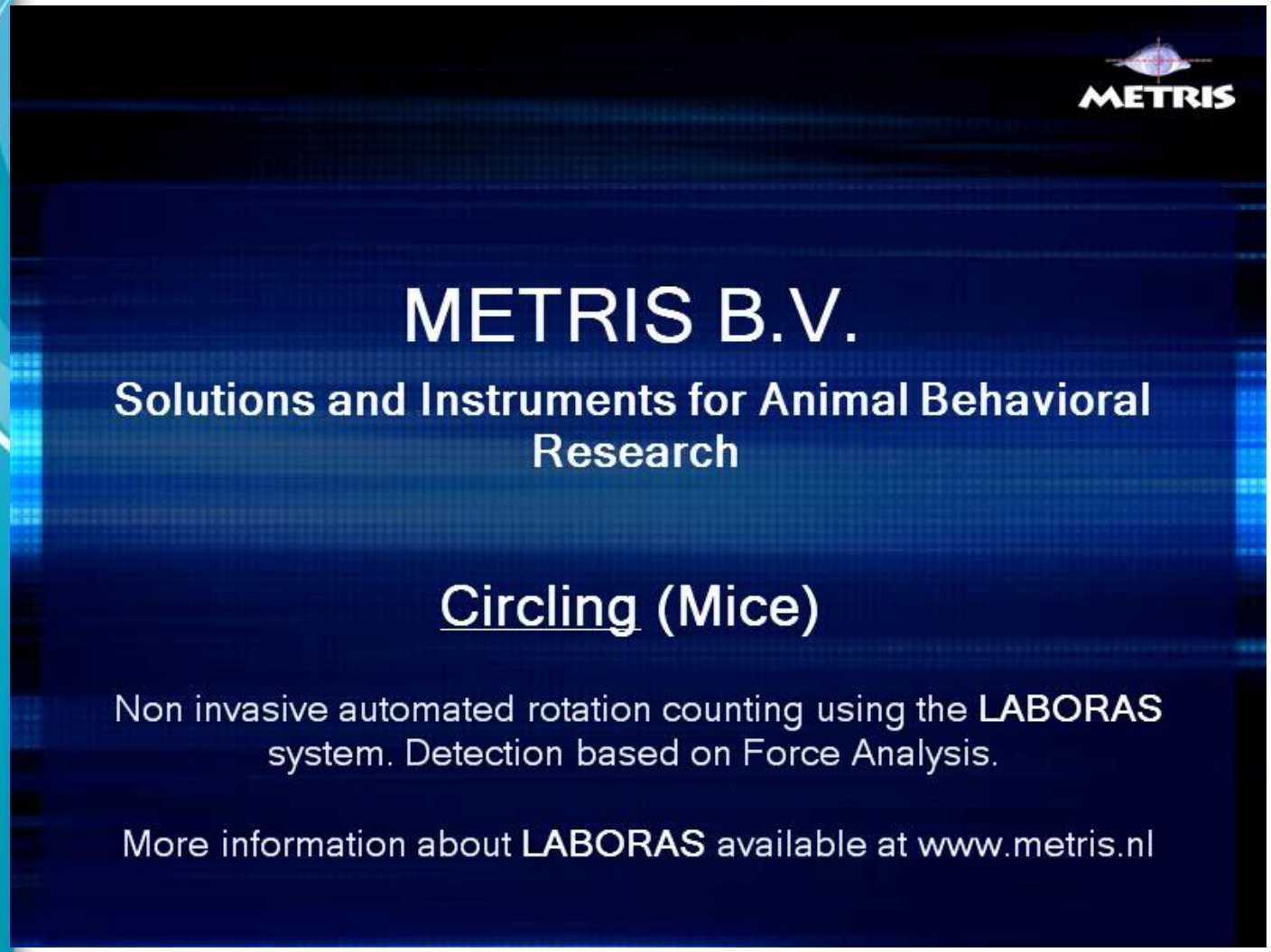


Fast up and down movement of the hind foot, rubbing the side of the body, neck and face.

Position Distribution



Circling (mouse)



Detection of behaviors

LABORAS automatically distinguishes more than 18 different rat and mouse behaviors

Normal behaviors
(mouse & rat)

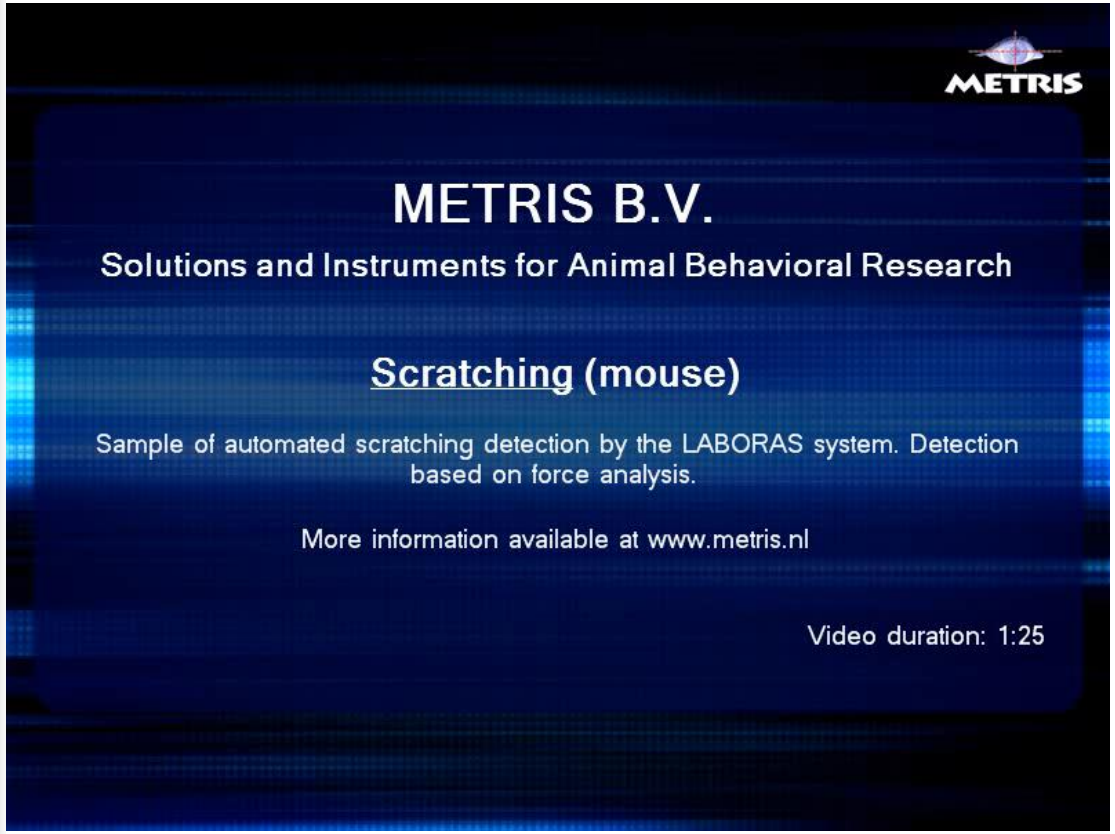
- Locomotion
- Immobility
- Rearing
- Climbing (mouse only)
- Eating
- Drinking
- Grooming

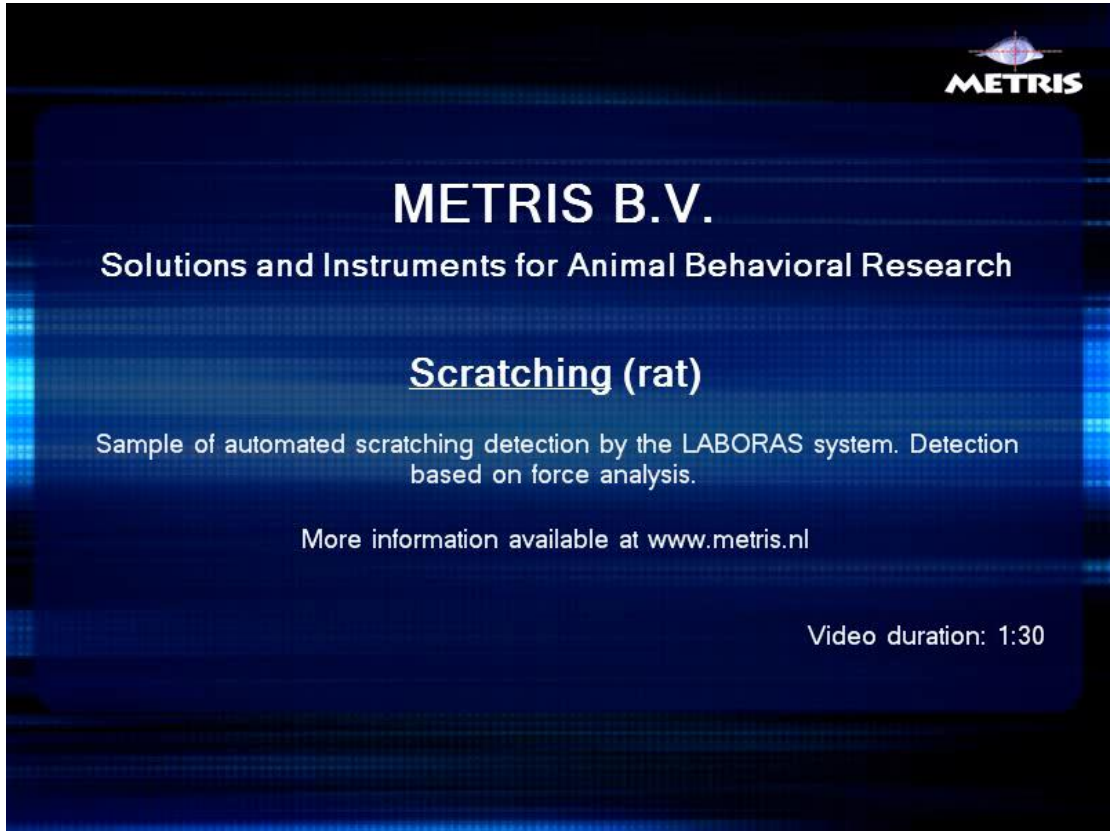
Special behaviors

- Mouse
  - Scratching
  - Seizures - tonic-clonic convulsions, barrel-rolls, Seizures Racine P4 and P5)
  - Freezing & Startle
- Rat
  - Hind limb licking / Formalin test
  - Purposeless chewing
  - Wet dog shakes
  - Headshakes / Head twitches

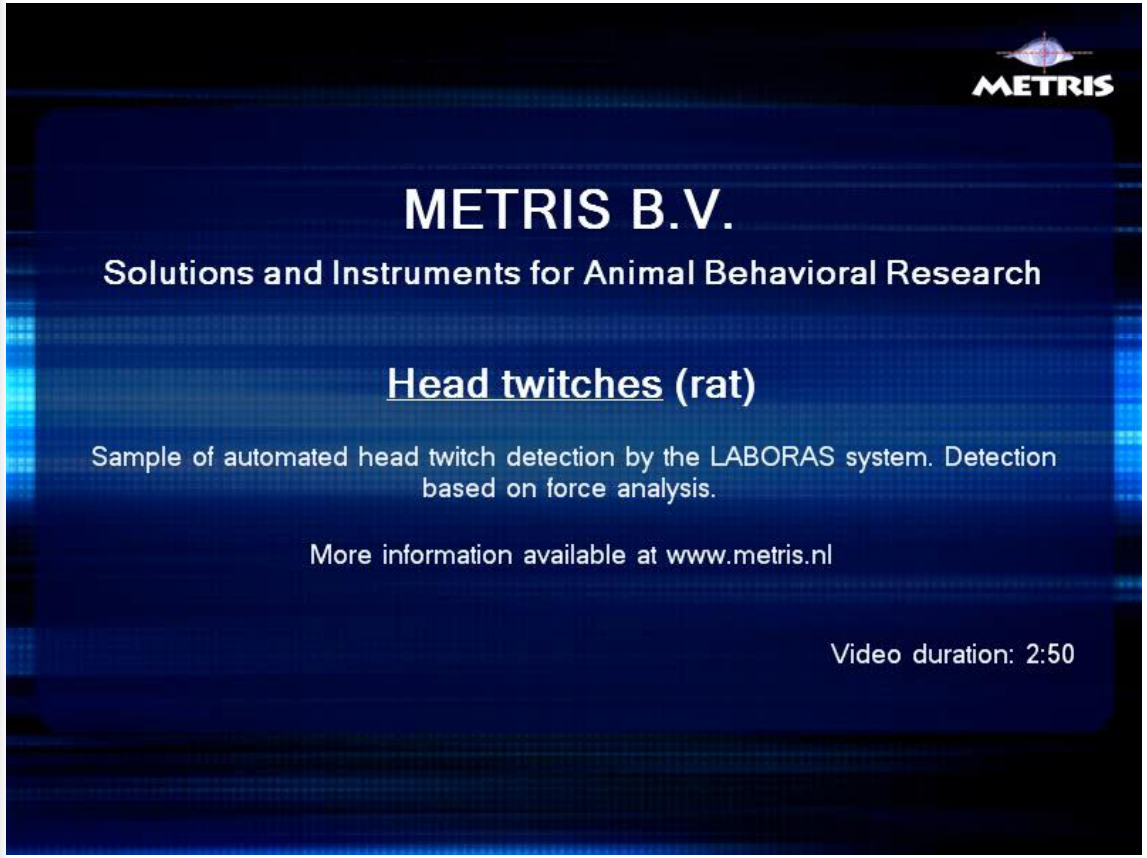
- Estimation of energy use

Scratching (Mice/Rats)

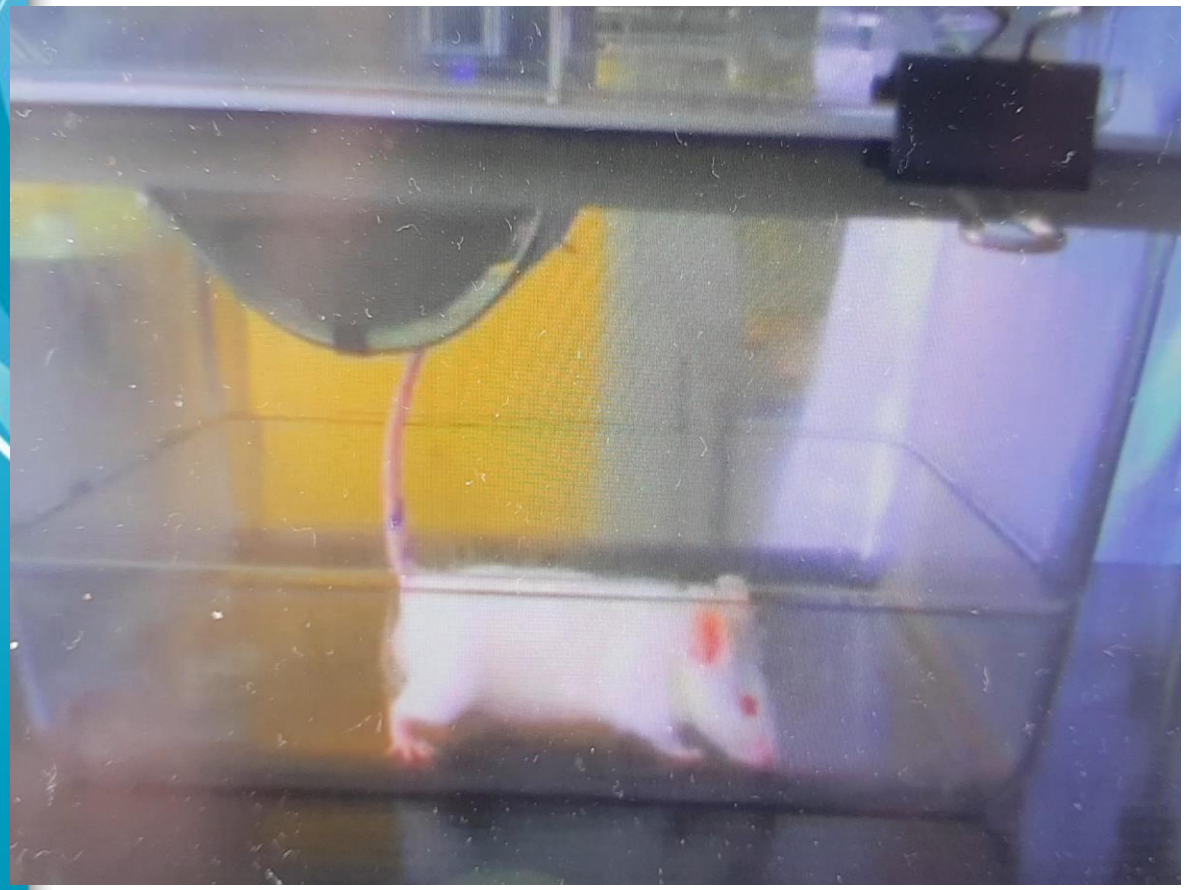


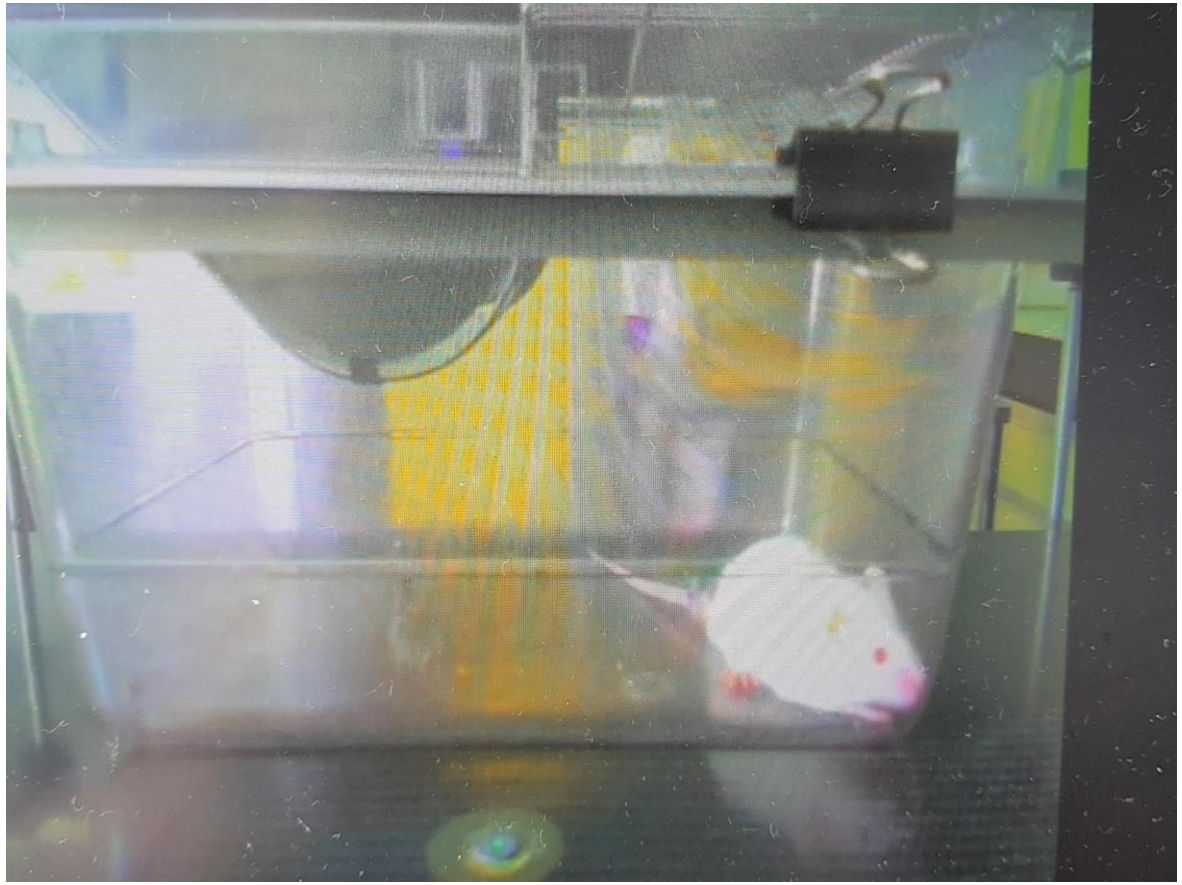


Head Twitches (HT) - rats &
Wet Dog Shakes (WDS) - rats



Seizure-mice





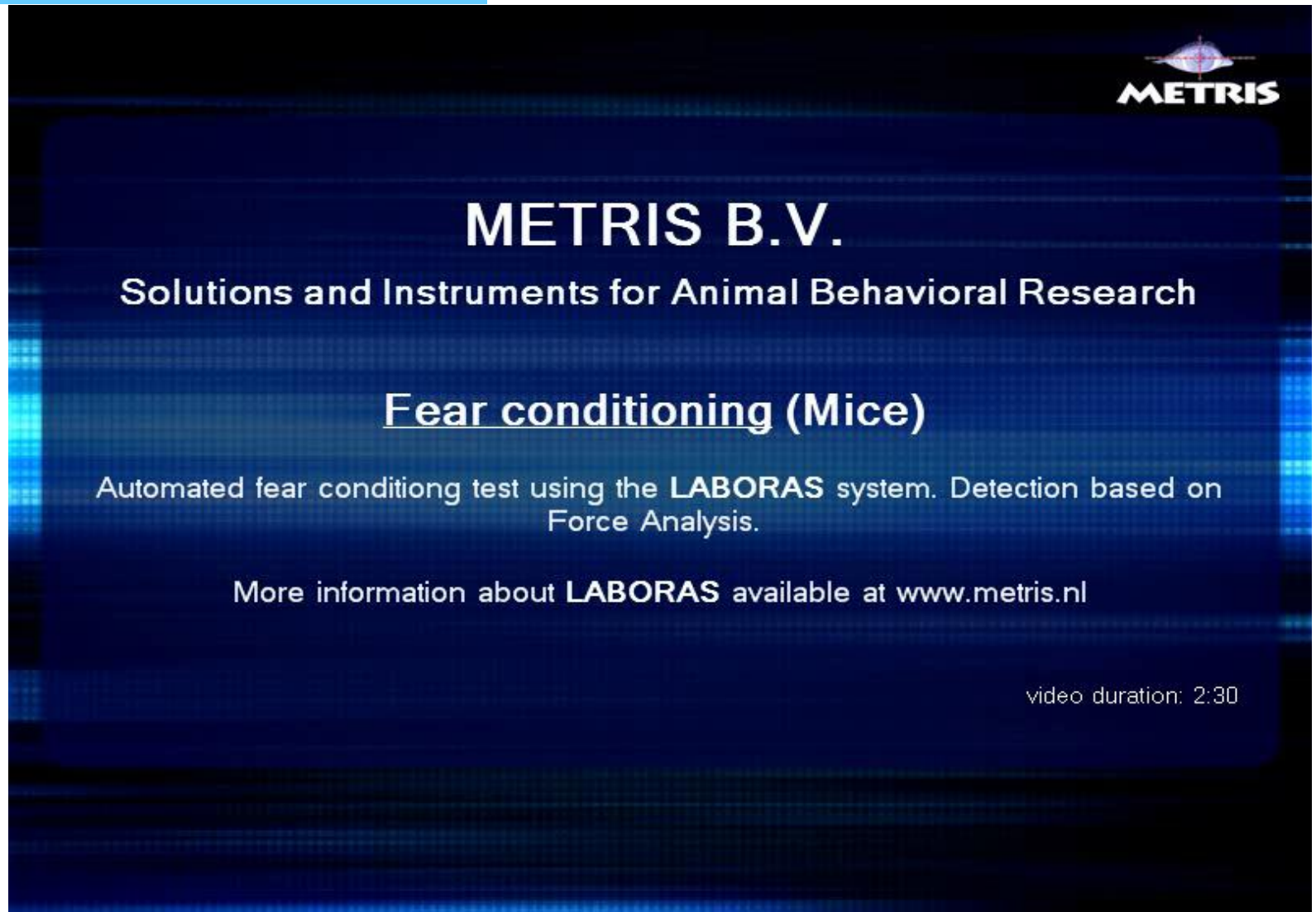
Seizure and Freezing in Mice

Freezing behavior

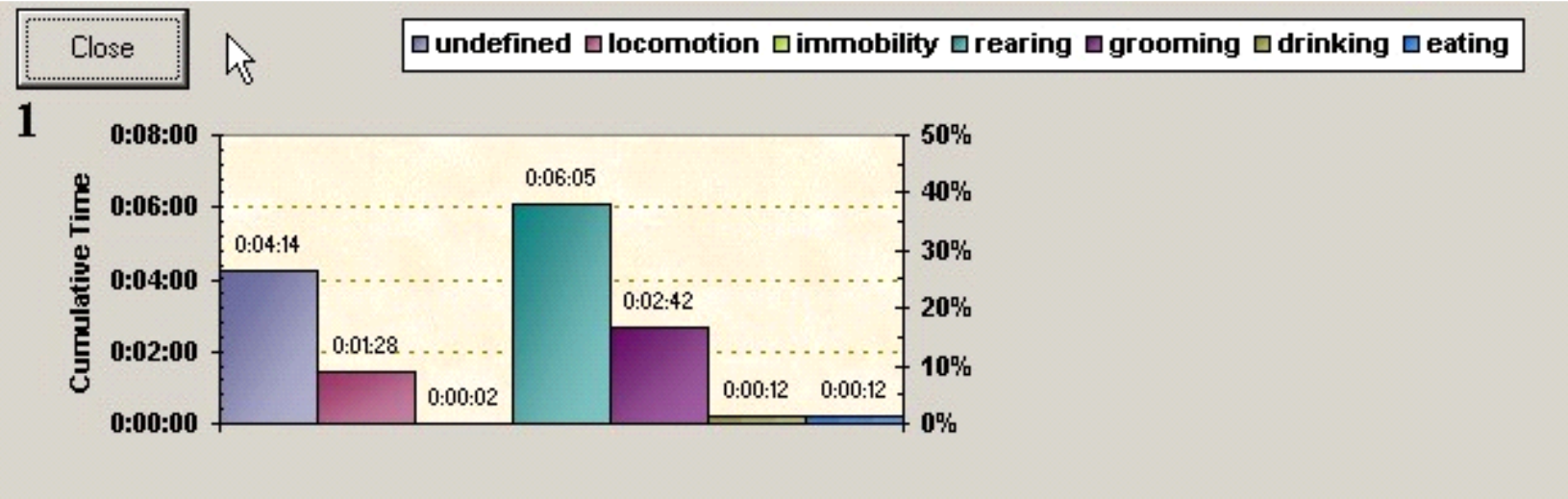
Laboras Immobility detection = (no position changes, but allows for small movements such as sniffing etc.)

Laboras Freezing detection = (No position changes, No other movements!)

Startle & Freezing (mice)

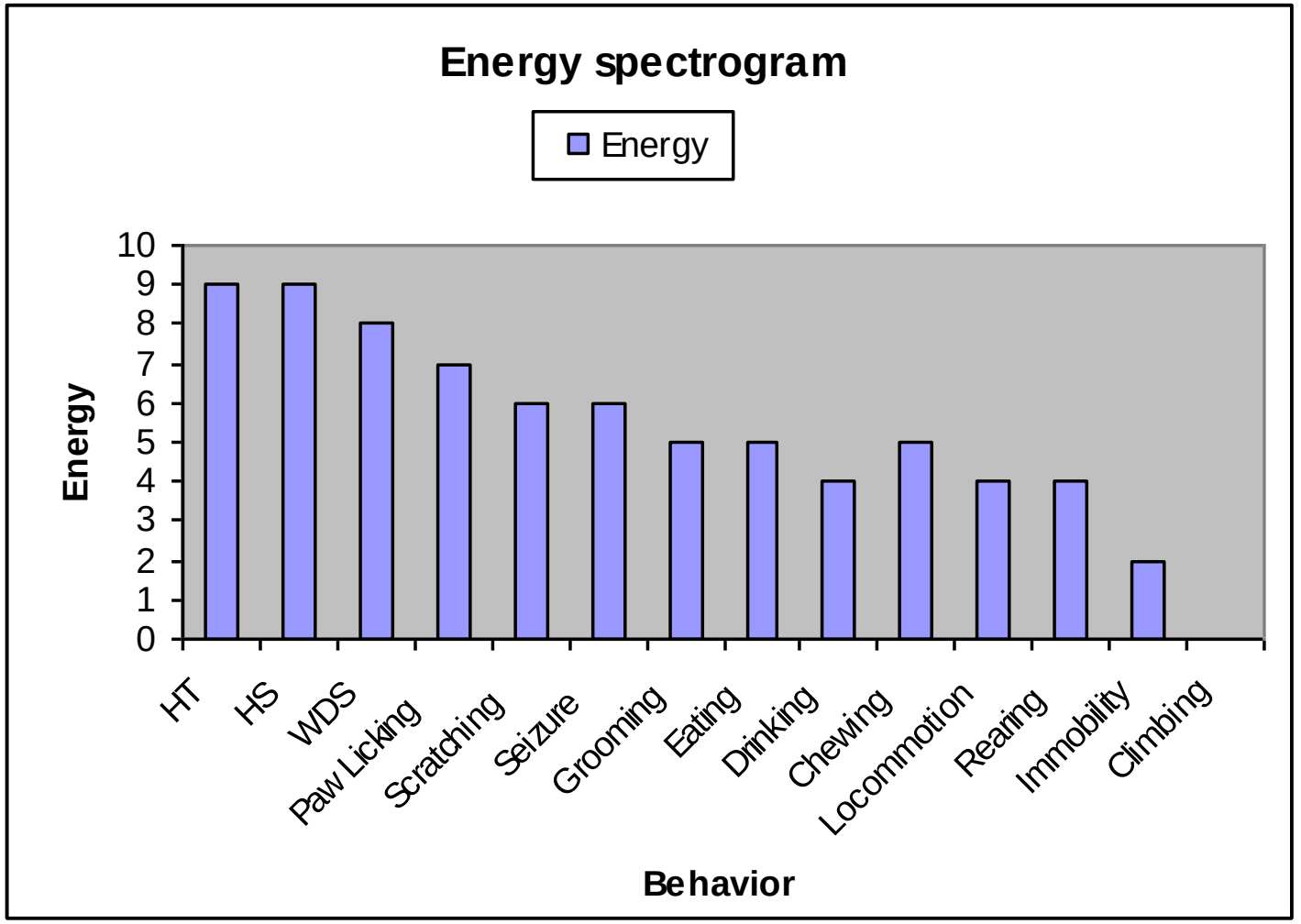


Examples of data presentation



	A	B	C	D	E	F	G	H	I	J	K	L	M
1	WINDOW	START	END	CAGE	ANIMAL	TREATM	UNDEF_D	LOCOM_D	IMMOB_D	REAR_D	GROOM_D	DRINK_D	EAT_D
2		TIME	TIME				[s]	[s]	[s]	[s]	[s]	[s]	[s]
3													
4	1	0:00:00	0:10:00	1	2	1	165.57	23.27	23.65	49.78	323.17	13.78	0.78
5	2	0:10:00	0:20:00	1	2	1	103.83	5.74	231.36	18.06	241.01	0	0
6	3	0:20:00	0:30:00	1	2	1	252.72	5.14	105.65	2.42	234.07	0	0
7	4	0:30:00	0:40:00	1	2	1	0	0	600	0	0	0	0
8	5	0:40:00	0:50:00	1	2	1	13.53	0	586.47	0	0	0	0
9	6	0:50:00	1:00:00	1	2	1	148.76	9.05	226.05	31.67	184.47	0	0
10	7	1:00:00	1:10:00	1	2	1	168.57	0	188	0	243.43	0	0
11	8	1:10:00	1:20:00	1	2	1	110.88	0	218.71	0	270.41	0	0
12	9	1:20:00	1:30:00	1	2	1	140.19	2.48	429.9	0	27.43	0	0
13	10	1:30:00	1:40:00	1	2	1	150.66	1.17	393.76	0	54.41	0	0
14	11	1:40:00	1:50:00	1	2	1	203.78	8.55	203.1	21.68	162.89	0	0
15	12	1:50:00	2:00:00	1	2	1	147.56	0	384.73	0	67.71	0	0

E (Oscillation) / E (Locomotion) spectrogram

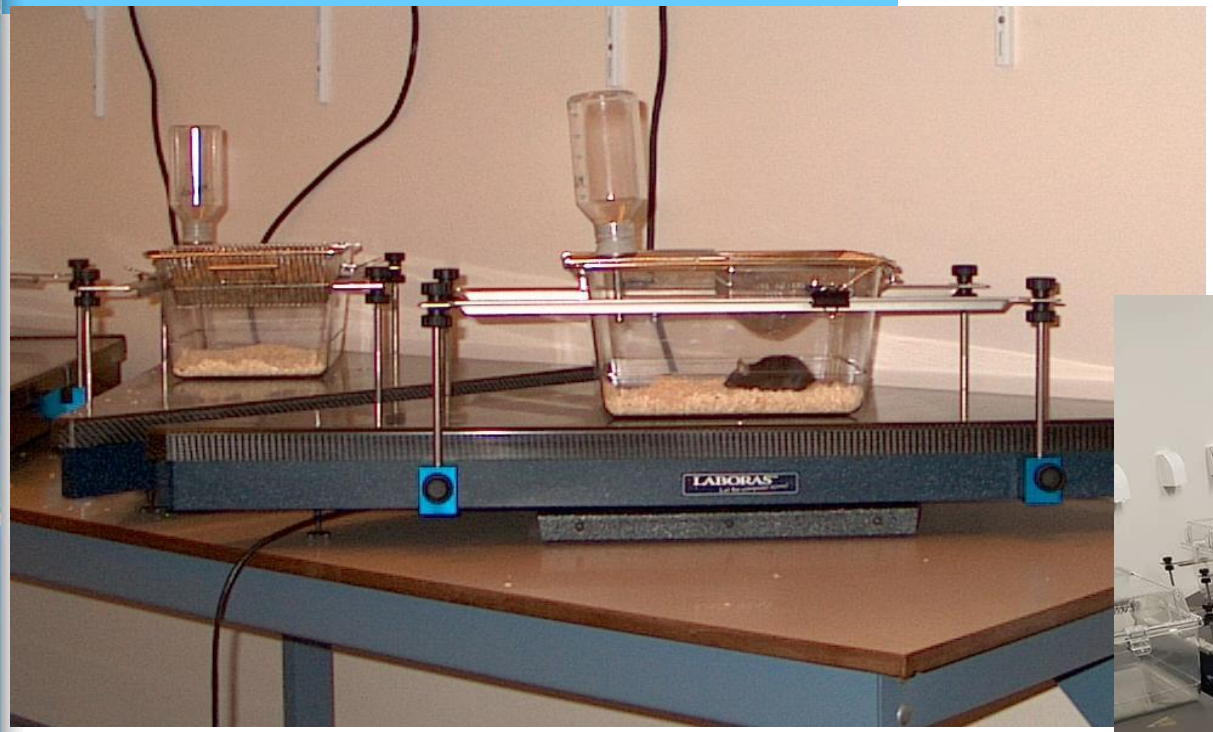


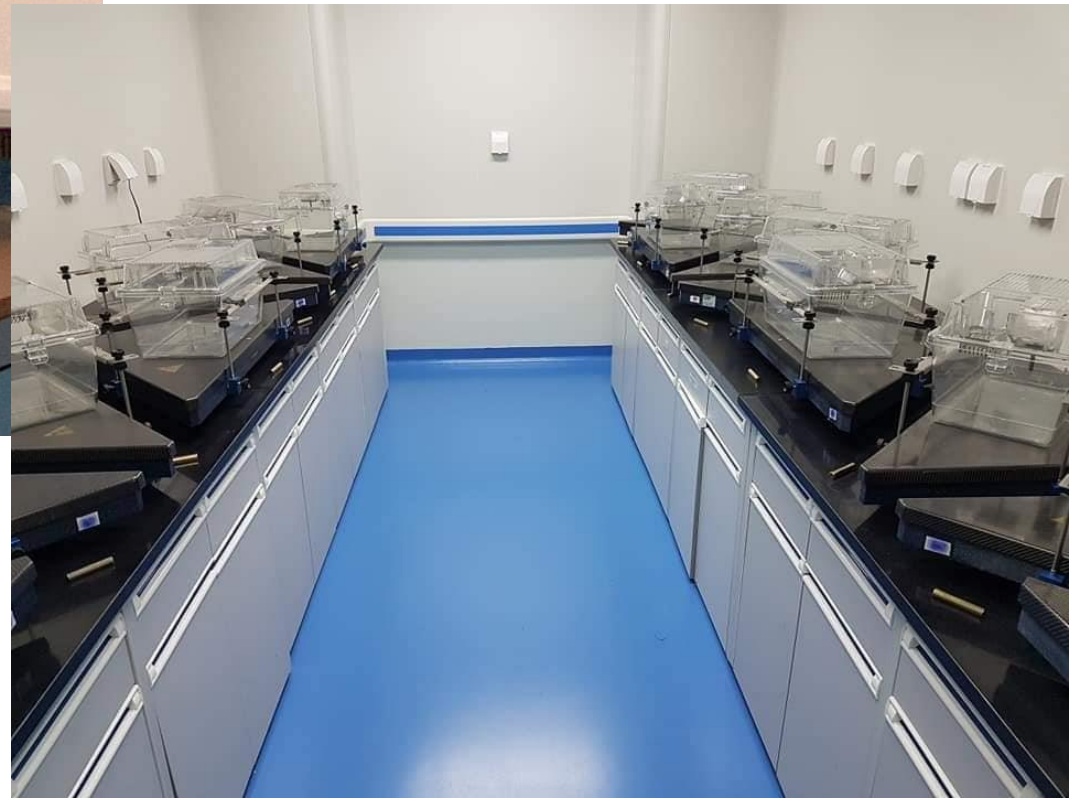
Applications LABORAS

- **LABORAS application areas are:**
  (behavioral assessment in)
  - Drug Development
  - Safety Pharmacology
  - Ecology and Hygiene
  - Toxicology
  - Phenotyping
  - Lab. animal science

- **Typical customers are**:
  - Pharmaceutical Corp
  - Academic Institutes
  - Hospitals & Universities
  - CRO's (Contract Research Org.)
  - Lab. Animal Suppliers
  - Governmental Organizations

LABORAS





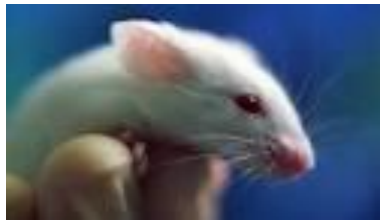
SONOTRACK functionality

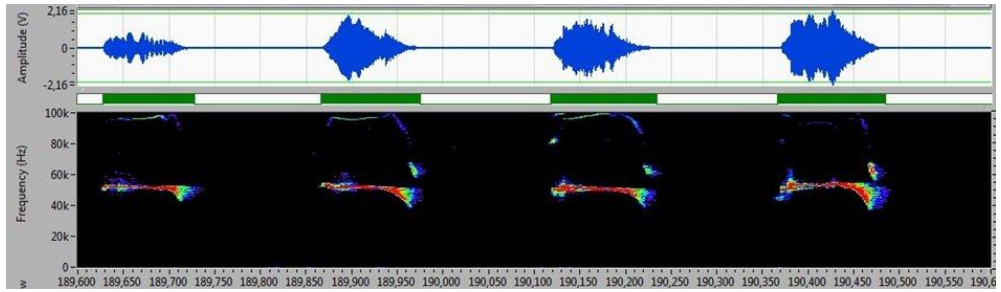
USV Recording, Playback and Analysisn (15KHz-125KHz)

-1, 2 or 4 channel Full Spectrum USV recording
- Advanced Manual and Automatic analysis
-1 or 2 channel USV playback (optional)

Examples of USV

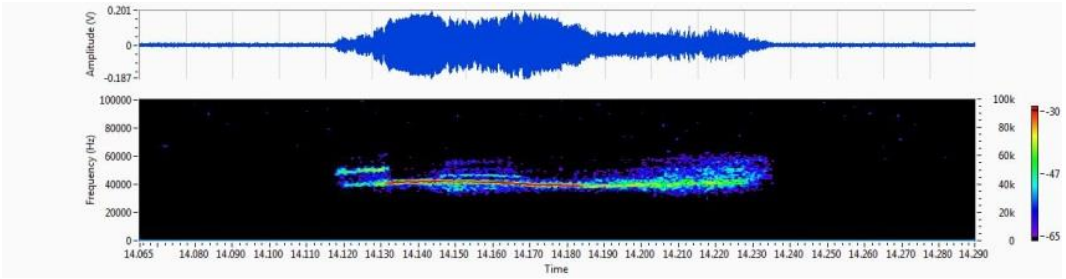
- Mouse





- Marmoset

- Hamster



- Rat

SONOTRACK Applications

- SONOTRACK can be used to monitor animal well-being and interaction between animals based on the ultrasonic vocalizations of the animals

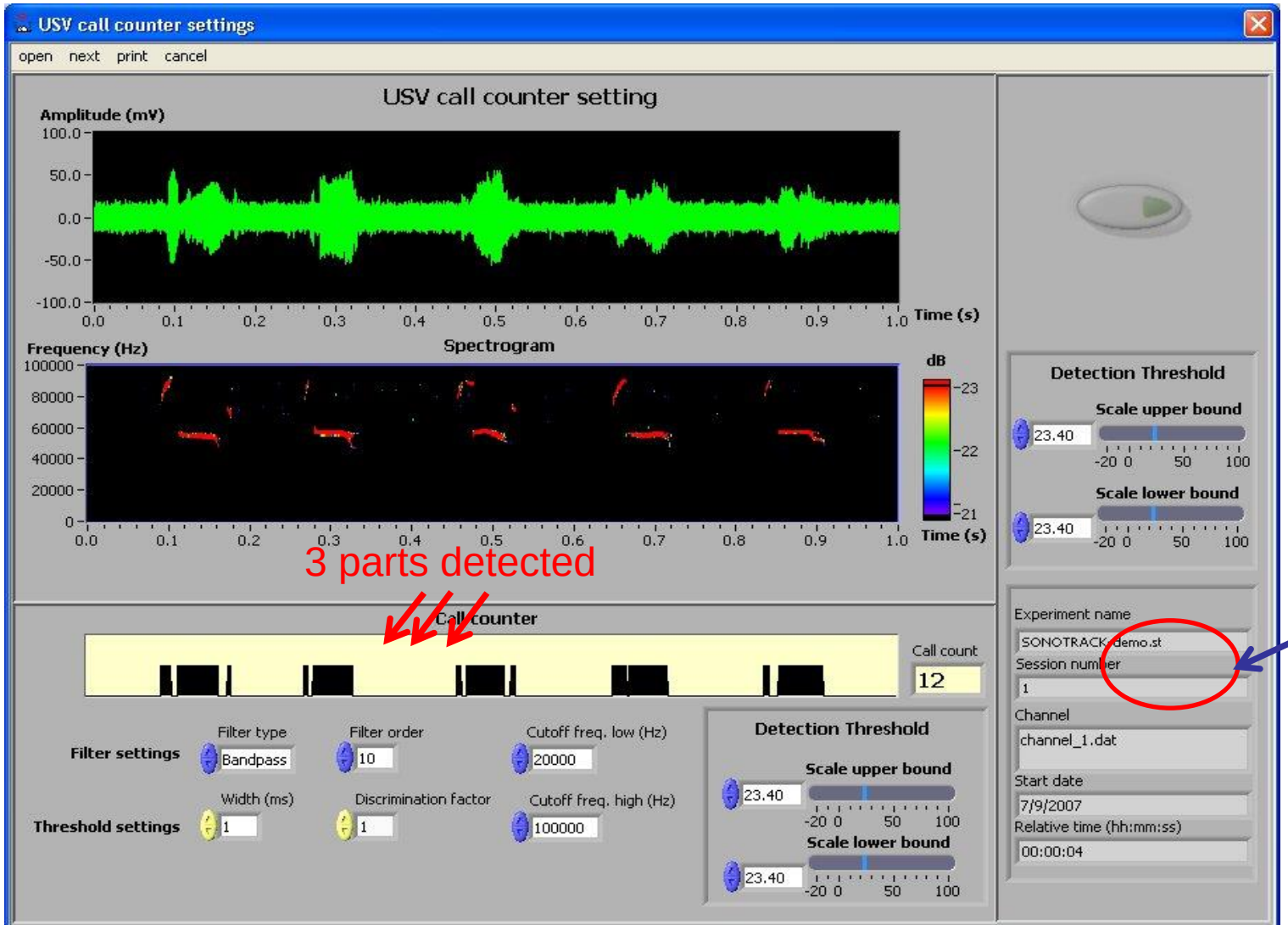
- Typical research areas:
  - Pain Research
  - Anxiety Research
  - Stress Research
  - Brain and Memory Studies
  - Depression Studies
  - Sexual Interaction
  - Social interaction (mother-pup, male-female, etc.)
  - Developmental toxicity
  - Animal Welfare Studies

Modular and Multi-purpose system with

many

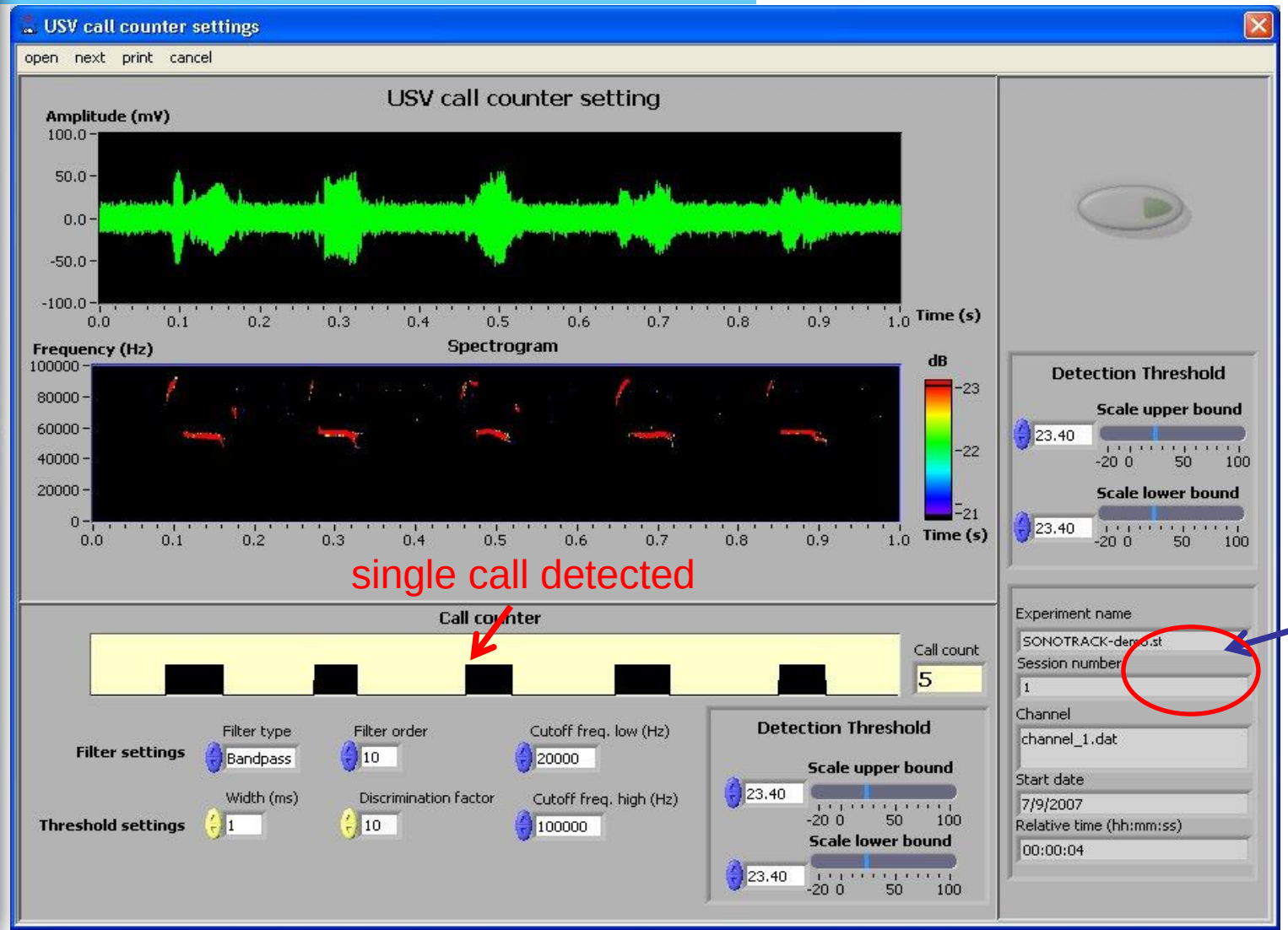
different research applications

Automatic Analysis Features



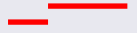
Automatic Callcounter (set to detect individual parts of calls)

Automatic Analysis Features



Automatic Callcounter (set to detect parts of calls single calls)

Automated Call Classification

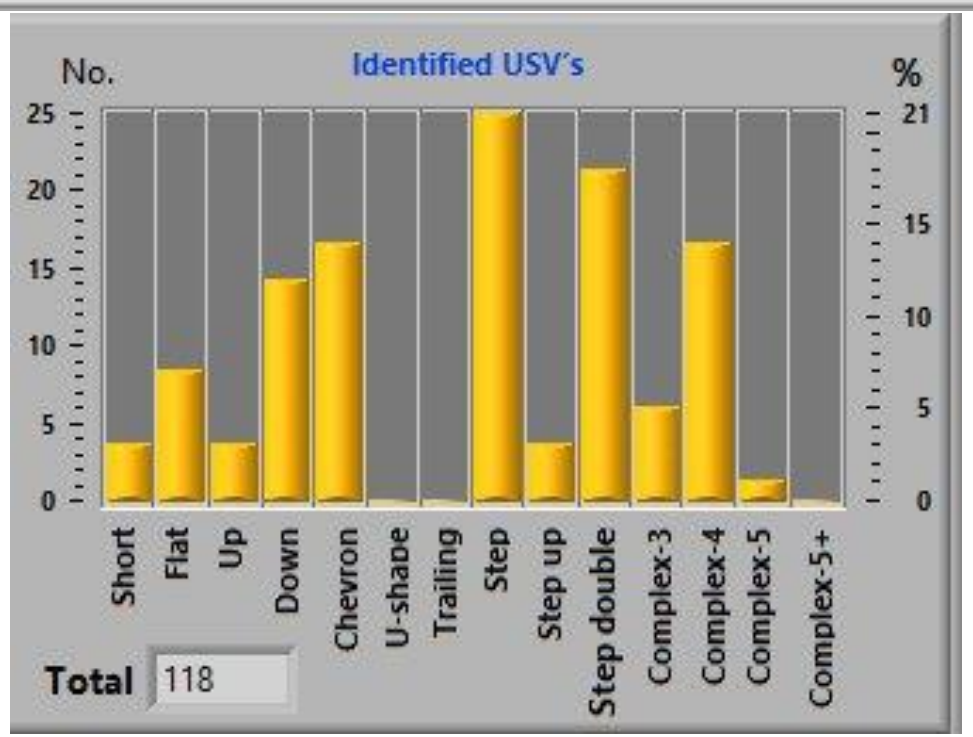
Continouos USV mouse		Discontinuous USV mouse	
Short (very short duration)		**Trailing** (flat with short interrupt)	
Flat (frequency constant		**Step up** (freq. step up)	
Up (frequency increase)		**Step down** (freq. step down)	
Down (frequency decrease)		**Step double (split)** (2 frequency steps)	
Chevron (freq. up & down)		**Complex 3** (mix of 3 components)	
Reversed Chevron (freq. down and up)		**Complex 4** (Mix of 4 components)	
		Complex 5 (mix of 5 components)	

Automated Call Classification Statistic

Part 4: Number and percentage of USV per call type

Identified USV´s

Short	Flat	Up	Down	Chevron	U-shape	Trailing	Step down	Step up	Step double	Complex-3	Complex-4	Complex-5	Complex-5+	Total
3	8	3	14	17	0	0	25	4	21	6	16	1	0	118
3	7	3	12	14	0	0	21	3	18	5	14	1	0	100%



Sound Attenuation Chambers

- Sound Attenuation Chambers strongly improve the quality of the recordings
- Metris SmartChamber™ has the following advantages:
  - (Ultra)sound isolation
  - Elimination of echo's
  - Magnetic field isolation
  - Build in Sonotrack microphone (placed at optimal position)
  - Ultralow noise ventilator (mounted outside measurement chamber)
  - Dark-Light cycles
  - Integrated Video (displayed on tablet)
  - E-Tablet control of light and ventilator and door

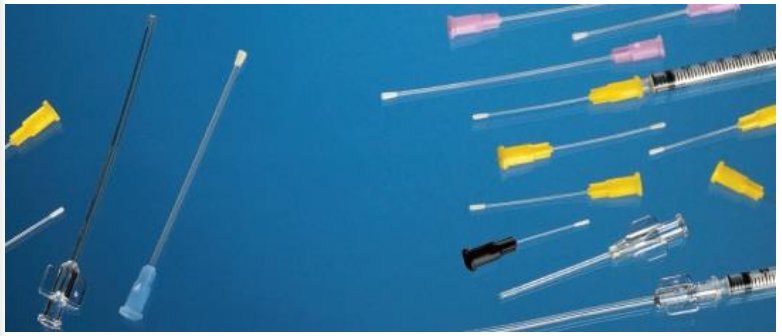
Automated Blood Sampler (ABS) INSTECH

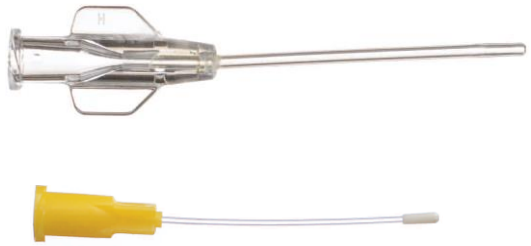
The flexibility to work with a range of species, from mice and rats to large animals

The ABS2, Instech autosample
A short collection path, to minimize mixing and collection times

Less than 5 µL of blood wasted per sample, to minimize hemodilution

Feeding Tubes and Pumps





Precision rotary fluid joints to allow free movement of tethered animals

SWIVEL MOUNTS

Arms to attach swivels to various types of animal cages

TETHERS

Harnesses, buttons and other devices to connect a catheterized rodent to a swivel

CATHETERS

A full range of finished catheters designed for rodent anatomy and connection to Instech devices

PINPORTS

Miniature ports for quick, aseptic access to externalized catheters and tubing sets

FEATURED **PRODUCT:**

OrchesTA model 100 syringe pump. A state-of-the-art clinical-grade pump for rodent toxicology studies.

FEATURED **PRODUCT:**

Harvard Pump 11 Elite. A graphical interface and improved flow performance enhance this workhorse infusion pump line.

Study duration COVID-19

Estimation time Coronavirus (COVID-19) study, statistic and medicine				
Preclinical study	Duration(days)	Min time	Duration for parallel study	Duration for no parallel study
Acute Toxicity Studies in critical states	14-21			
Safety pharmacology	14-90			
Toxicology experiments	21-120	need	120 days (4 month)	231 days (8 month)
Chronic Toxicity Studies	180-720	rec	720 days (24 month)	951 days (31 month)
Clinical study	Duration(days)	Min time	Duration for parallel study	Duration for no parallel study
Acute Toxicity Studies in critical states	14-40			
Safety pharmacology	14-21			
Toxicology experiments	7-120	need	120 days (4 month)	181 days (6 month)
Chronic Toxicity Studies	180-1080	rec	1080 days (36 month)	10260 days (42 month)
blood/ immune test	60-90			
Imunne system/ Coronavirus (COVID-19) spreading spectral analysi	90-180	need	180 days (6 month)	270 days (9 month)
Epidemiology study and analysis	180-360			

Russia - 2020

Thanks

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www.metris.nl

www.datasci.com

www.instechlabs.com

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Meet Some Of Our Customers