遥测技术在实验动物研究中的应用

Shining Su
DSI Country Manager

DSI简介

- 1983公司成立，一直专注于动物实验用遥测技术研发
- 在北美，欧洲和中国都有自己的办公室
- 30+ 多项专利
- 被市场验认可的金标准
  - Over 1000 peer review articles published that reference DSI
  - Systems in 42 countries

总部位于美国明尼苏达州
圣保罗市

议程

- DSI介绍
- 在实验研究中的应用
  - 心血管系统
  - 呼吸系统
  - 中枢神经系统
- Q&A

DSI™

Where We Started

- 1984 • DSI在建立时只有5个人
- 1985 • 首款植入子仅能测温度，生物电和活动度
- 1989 • 第一款血压植入子上市
- 1994 • 第一款大动物用双压力植入子上市
- 1998 • 第一款小鼠用血压植入子上市

DSI™

Where We Started

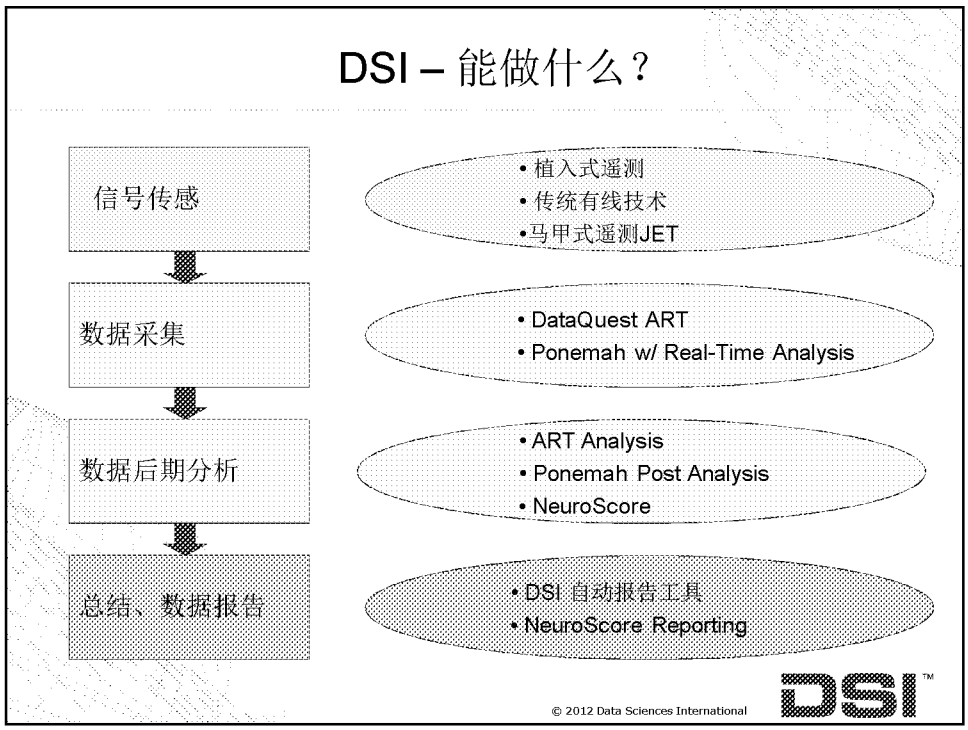
- 2006 • DSI收购了业内领先的 Ponemah 平台
- 2007 • JET™ 上市
- 2010 • PhysioTel™ HD发布，为新一代的小动物植入子系列
- 2012 • PhysioTel™ Digital发布，DSI科学服务组成立
- 2014 • 第一款全植入式连续血糖监测植入子
  • DSI 收购了Buxco 公司

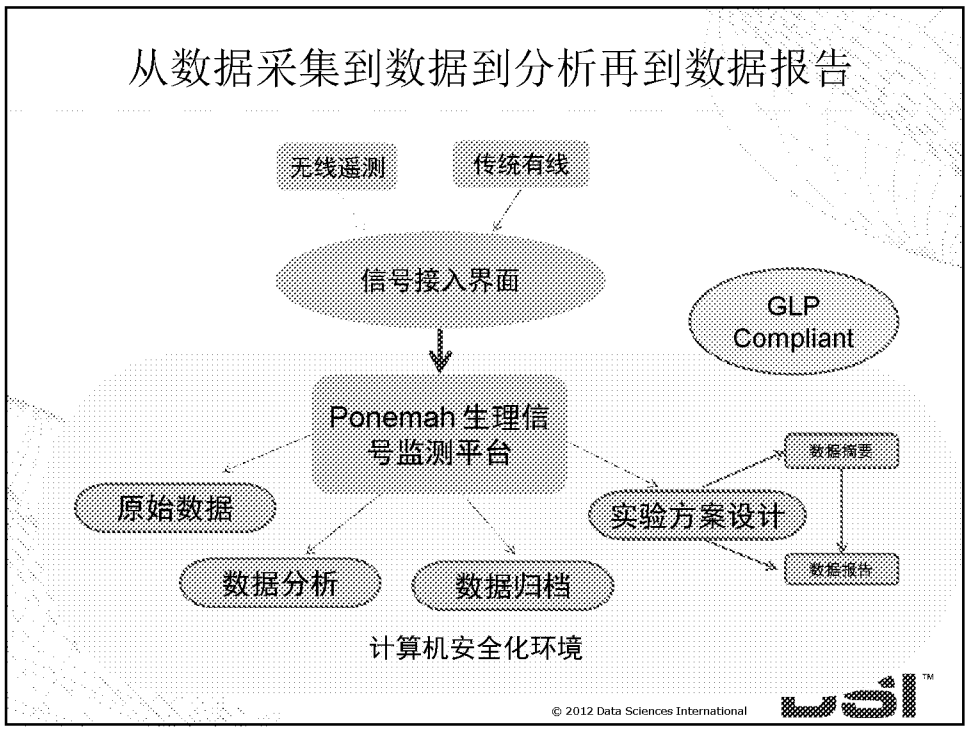
DSI™

DSI Then & Now

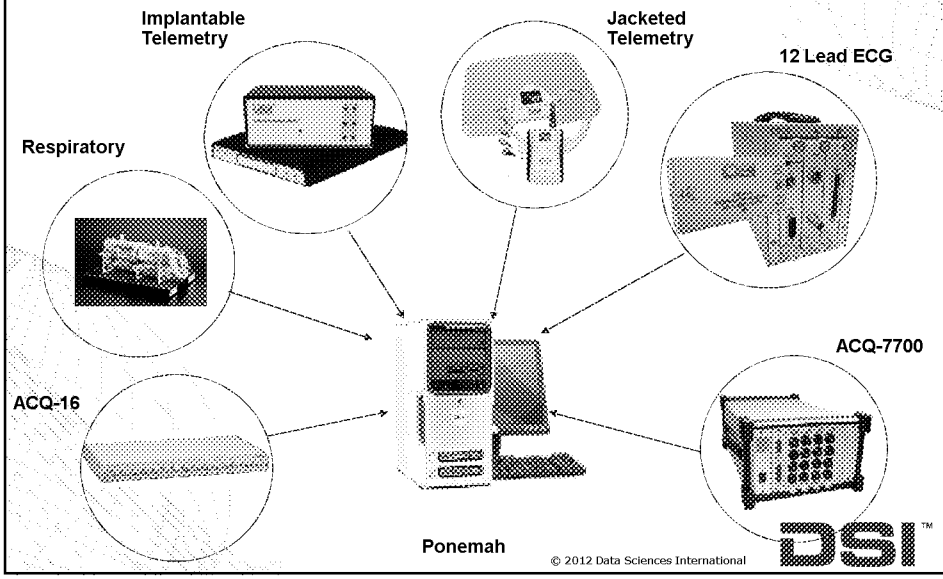
- # 公司人员
  - 1984: 5
  - 2015: 198
- # 产品数量
  - 1990: 115
  - 2014: >2,332
- # 用户数量
  - 1990: 109
  - 2014: >4,531
- # 区域办公室
  - 1984: US Only
  - 2015: 6个国家和地区

DSI™


DSI – 能做什么？
信号传感
数据采集
数据后期分析
总结、数据报告
• 植入式遥测
• 传统有线技术
•马甲式遥测JET
• DataQuest ART
• Ponemah w/ Real-Time Analysis
• ART Analysis
• Ponemah Post Analysis
• NeuroScore
• DSI 自动报告工具
• NeuroScore Reporting
© 2012 Data Sciences International


从数据采集到数据到分析再到数据报告
无线遥测
传统有线
信号接入界面
GLP Compliant
Ponemah 生理信号监测平台
原始数据
数据分析
数据归档
实验方案设计
数据摘要
数据报告
计算机安全化环境
© 2012 Data Sciences International

Ponemah Platform - Multiple Applications



DSI 上海办公室

- DSI亚太区总部设在上海张江药谷，于2007年2月建立。负责亚太区的直接支持和服务
- 团队组成:
  - Account Manager
  - Technical Support Engineer
  - Customer Service

“诚于科学，诚于顾客，诚于自我.”

DSI 国际客户列表

- Covance
- MPI
- Charles River Labs
- SNBL
- Wil Research
- Huntington Labs
- Lovelace Respiratory Research
- Southwest Foundation
- Pfizer
- Abbott Laboratories
- Bristol Myers Squibb
- Glaxo Smith Kline
- Eli Lilly
- Aventis Pharmaceutical
- Bayer A.G.
- Merck
- Banyu
- Hoffman LaRoche
- Novartis
- Schering
- Boehringer Ingelheim
- Ortho McNeil
- Roche Biosciences

DSI 中国客户列表

- Pfizer
- Abbott Laboratories
- Bristol Myers Squibb
- Glaxo Smith Kline
- Eli Lilly
- Aventis Pharmaceutical
- Bayer A.G.
- Merck
- Banyu
- Hoffman LaRoche
- Novartis
- Schering
- Boehringer Ingelheim
- Ortho McNeil
- Roche Biosciences

生理信号检测的常见方法

- 麻醉Anesthesia (chemical restraint)
- 束缚
- 半束缚（Tether）
- 植入式遥测
- 马甲式遥测 (JET)

DSI™

采集到的数据受其他因素干扰吗?

DSI™

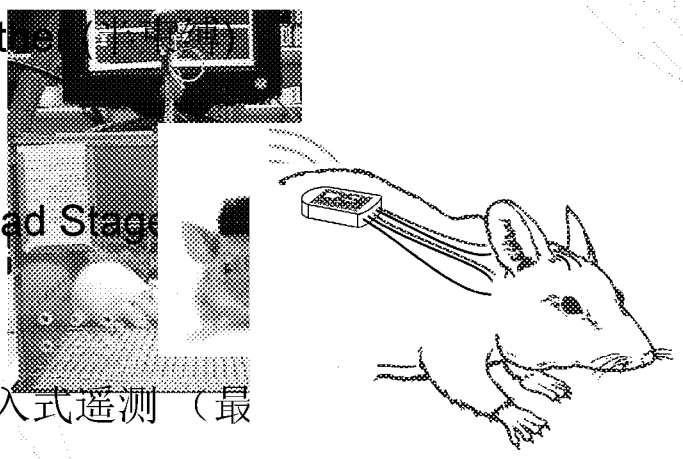
采集到的数据有被干扰吗?

- 麻醉状态 – 麻醉剂影响, 动物无应激反应
- 束缚状态 — 清醒，有应激反应
- 半束缚状态 — 清醒，较小的应激反应
- 遥测 — 清醒，无束缚，无应激反应

DSI™

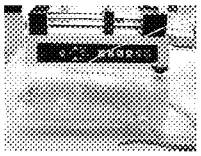
实验研究常用方法

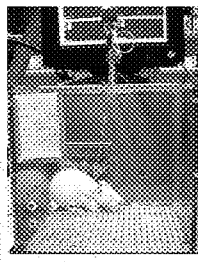
- Tet
- Head Stag
- 植入式遥测（最

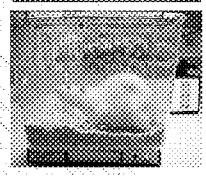


DSI™

不同状态下心率和血压的比较



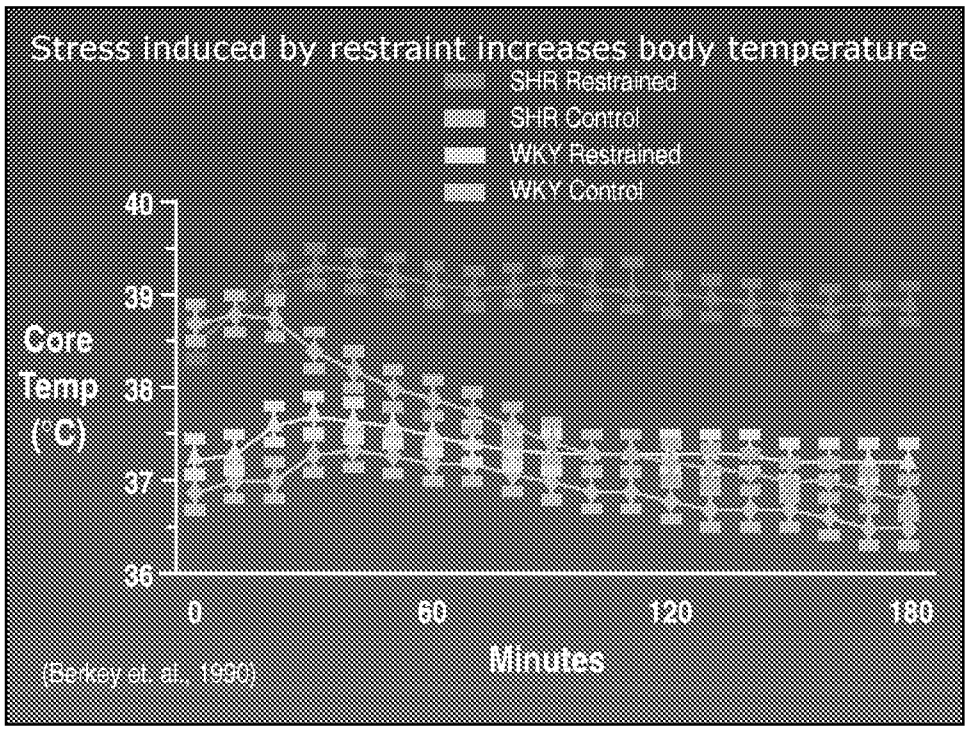


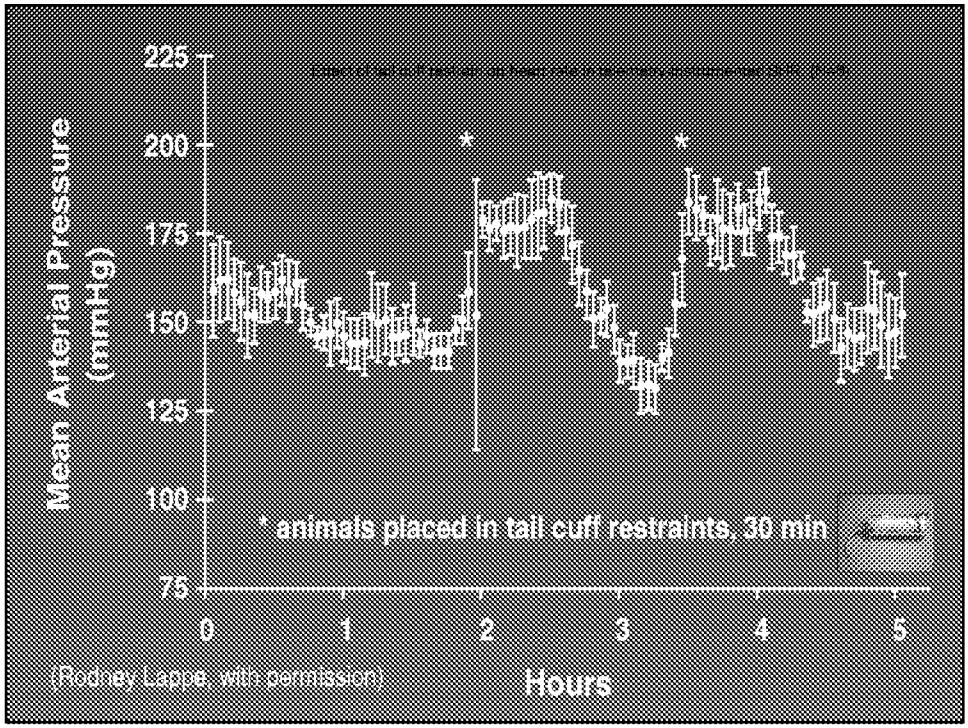


	HR	BP
Restrained	~400 bpm	~140 mmHg
Swivel	~380 bpm	~120 mmHg
Telemetry	~310 bpm	~100 mmHg

Courtesy of UCB Pharma, Belgium

DSI™





AHA Guideline

Recommendations for Blood Pressure Measurement in Humans and Experimental Animals Part 2: Blood Pressure Measurement in Experimental Animals

A Statement for Professionals From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research

Theodore W. Kurtz, MD; Karen A. Griffin, MD; Anil K. Bidani, MD; Robin L. Davisson, PhD; John E. Hall, PhD

ABSTRACT: In experimental animals, as in humans, techniques for measuring blood pressure (BP) have improved considerably over the past decade. In this document, we present recommendations for measuring BP in experimental animals with the goal of helping investigators select optimal methods for BP monitoring in the research laboratory. The advantages and disadvantages of various BP measurement methods are discussed and specific recommendations are provided for selecting the optimal technique depending on the study objective. Although indirect techniques that permit only sporadic measurements of BP may be suitable for some purposes, methods for directly measuring BP are generally preferred because of their ability to monitor the highly dynamic nature of BP in a comprehensive fashion. Selection of the methods to be used should ultimately be guided by the study objectives to insure that the techniques chosen are appropriate for the experimental questions being explored.

Hypertension. **2005;45:299-310**

DSI™

传统麻醉和束缚方法的适用实验

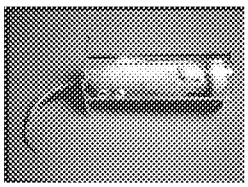
- 急性实验
- 不需要连续检测的长周期实验
- 筛选实验

DSI™

鼠尾压法测定血压

•Physical restraint stress (varied stress response among animals); Questionable accuracy
•Systolic pressure only, no true mean BP
•Few cardiac cycles; Difficulty in assessing BP variability
•Need validation, conditioning =Labor intensive

•Noninvasive/conscious
•Inexpensive to operate
•High throughput
•Repeated measures

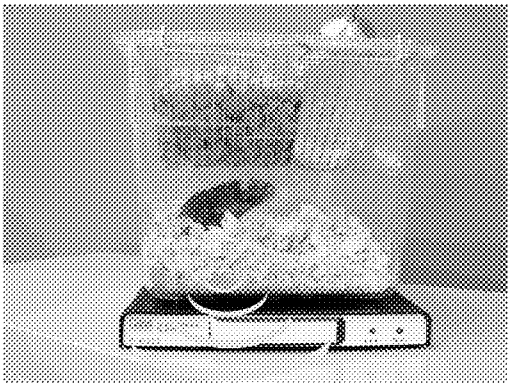


When to use the cuff method?

•Gross change in BP (>15-20mmHg)
•Surgery must be avoided

DSI™

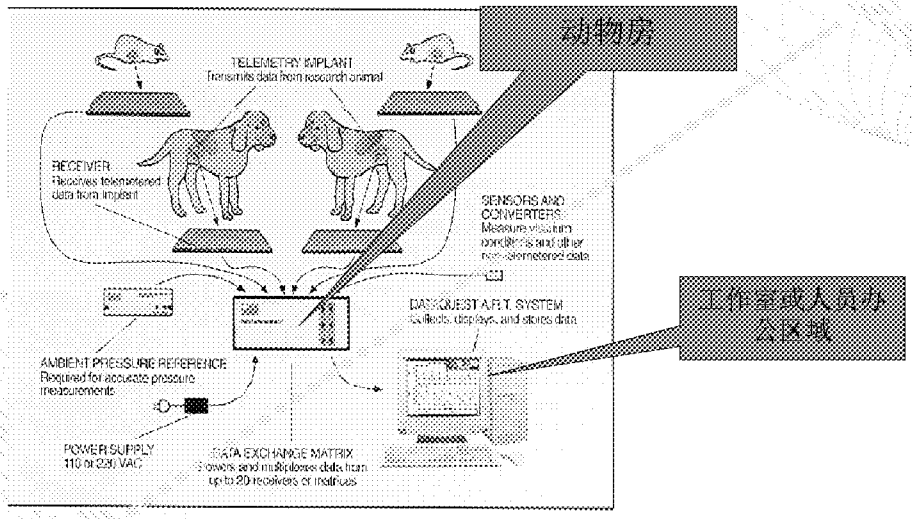
TELEMETRY (“Tele” + “Metron”)



无线检测清醒自由活动动物的生理信号

DSI™

系统在实验的安放



DSI™

遥测技术的优点

- 可以采集清醒的，自由活动动物的数据
- 数据准确度高，可重复率高
  - 没有或很小的动物应激反应
  - 可自身对照，实验动物数比常规方法更少
- 可实现长期检测连续的数据检测
  - 动物可自身对照，洗脱期过后可重复用于后续实验
- 在危险实验中，更好的保护动物和研究人员 （BSL 3&4）
- 更好的动物福利

Telemetry Provides Most Accurate Data

DSI™

符合3 R的要求

- Reduce减少动物用量
  - 用更少的动物得到更好的数据
  - 更优化的实验设计
- Refine优化
  - 新的技术可以获得更多的实验数据
  - 更少的应激反应
  - 马甲式遥测
  - 软件的优势

Better Welfare = Better Data = Better Science

DSI™

举例：标准拉丁方实验设计

Dose Day / Animal	1	2	3	4
1	Control	Dose 1	Dose 2	Dose 3
2	Dose 3	Control	Dose 1	Dose 2
3	Dose 2	Dose 3	Control	Dose 1
4	Dose 1	Dose 2	Dose 3	Control

Note: 75% reduction in number of animals needed w/out affecting statistical power

潜在的不利因素

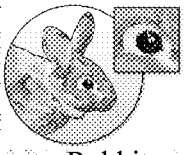
- 需要进行手术 (survival)
- 需要一段时间的手术恢复期： ≥ 7 days in rodents and ≥ 14 days in large animals
- 成本相比传统方法更高

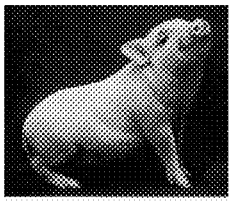
适用于各动物种属

Primates

Pigs

Cattle





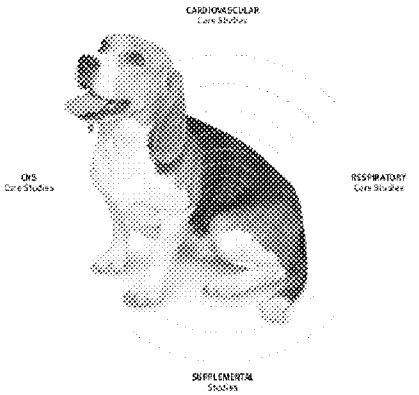
Mice

Sheep

DSI™

DSI 遥测技术可检测的参数

- 压力
  - 系统血压
  - 左心室压
  - 胸膜内压
  - 眼内压
  - 膀胱压
- 心率Heart rate
- 呼吸频率Respiratory Ra
- ECG
- 脑电和肌电
- 温度
- 自助活动度
- 其他…



DSI™

遥测技术的应用领域

- 心血管系统研究
- 呼吸系统研究
- 中枢神经系统研究
- 药物研发
  - 基础研究
  - 药理实验
  - 安全药理实验
- 行为学研究
- 代谢学研究
- 表型研究
- 生物防御研究
- 其他

DSI™

心血管系统研究

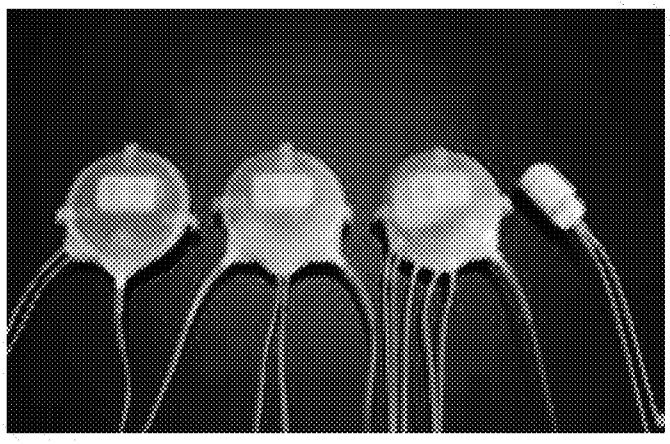
base on ICH Guideline

不同的ECG监测方法的比较

Connection		Benefits	Cons
Surface	Hardwired	Non-invasive Low Cost Easiest to implement and use Familiarity with morphologies	Restrained animal Only good for short term data collection Signal quality due to connection
	JET (Telemetry)	Non-invasive Free roaming, conscious animals Ability to collect more data than HW Relatively low Cost Easy to set up and use	Signal quality due to connection and motion artifacts
Sub Q (Telemetry)		Free roaming, conscious animals Better signal quality than surface ECG Ability to do long term monitoring	Requires minor surgery (w/o pressure) Motion artifact can saturate ECG signal
Epicardiac (Telemetry)		Better signal quality than Sub Q – less motion artifact	Requires more invasive and in depth surgery Concern over leads on heart

DSI™

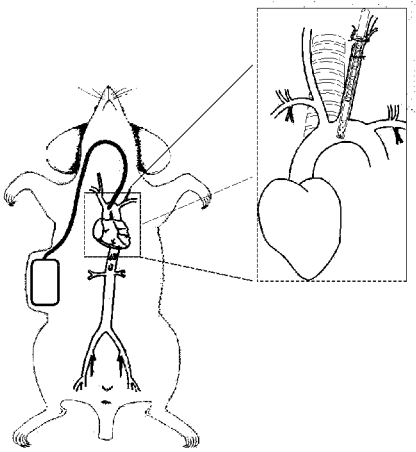
植入式遥测



DSI™

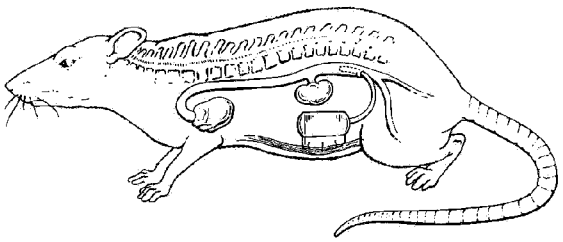
小鼠血压测定

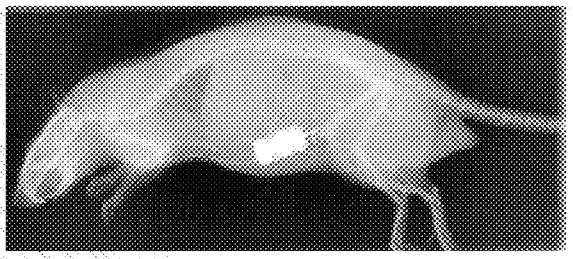
- 最小体重可至18g
- 左颈总动脉插管
- 植入子主体皮下放置



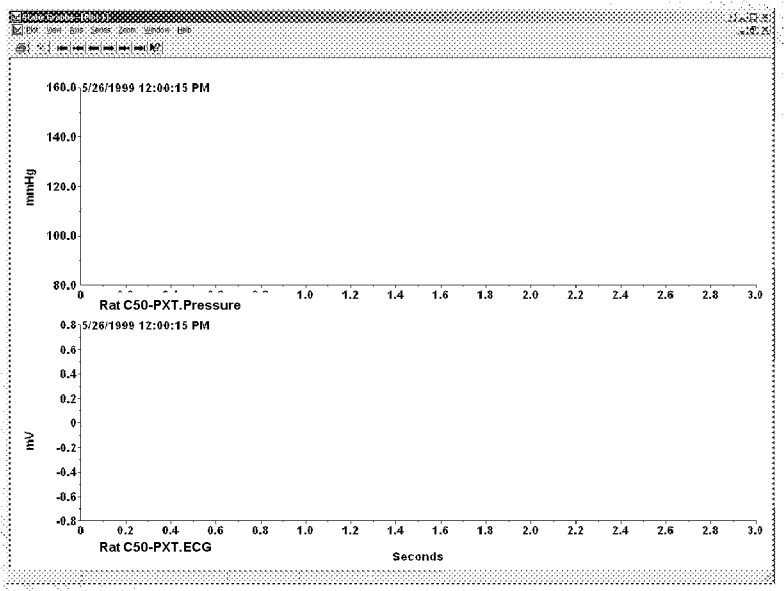
DSI™

DSI Transmitters

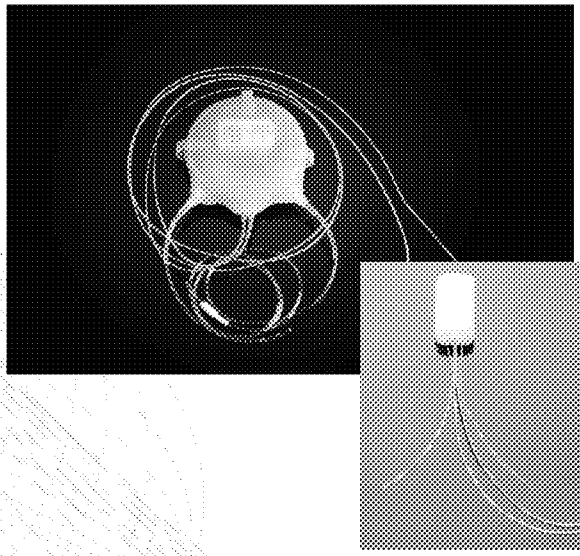




DSI™



Dual Pressure

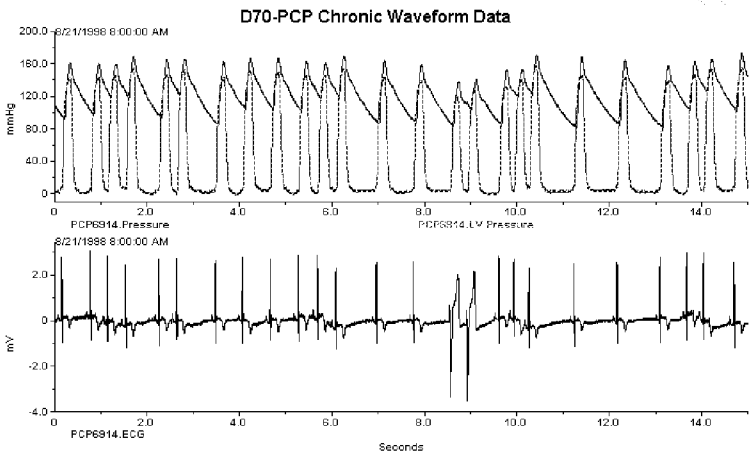


Measures:

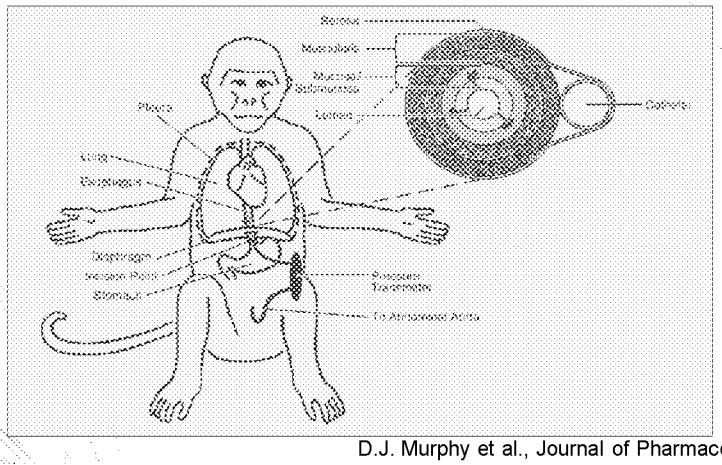
- **2 Pressures**
- **ECG**
- **Temperature**
- **Activity**

植入式遥测

- 可同时监测同一动物的多种参数



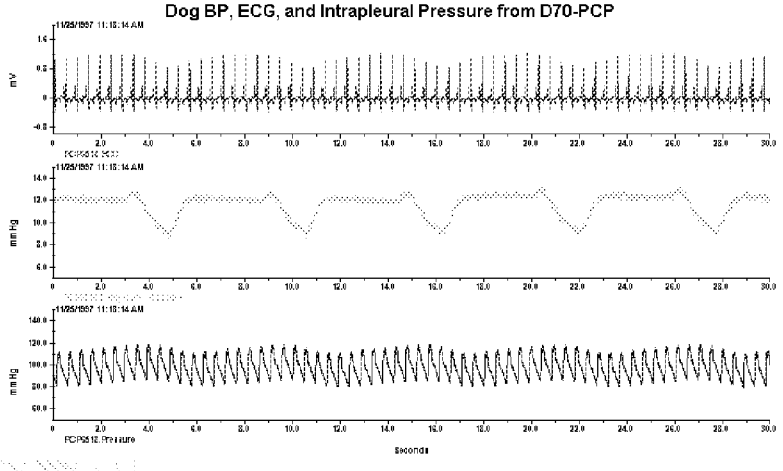
Measurement of Respiratory Function in Conscious Monkey



D.J. Murphy et al., Journal of Pharmacological and Toxicological Methods 46 (2001) 13–20

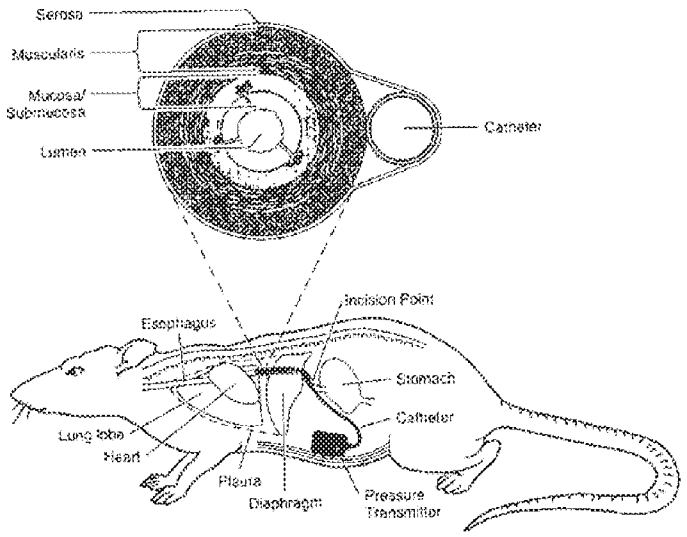
DSI™

BP, ECG, 胸膜内压



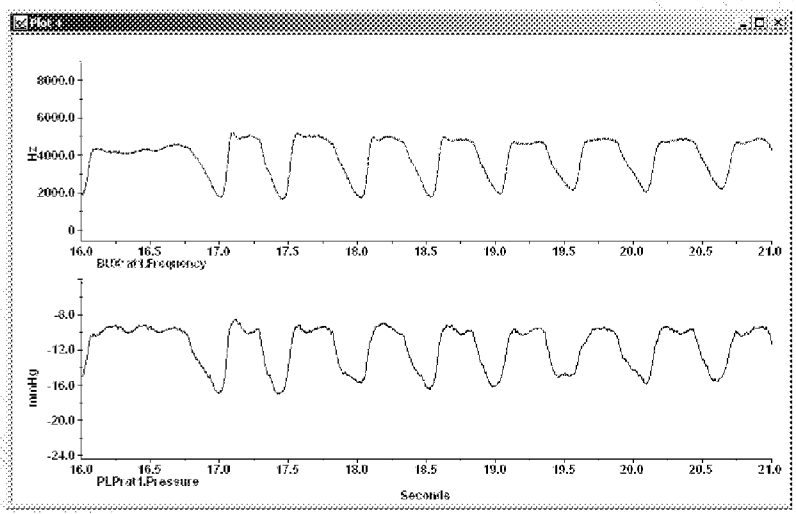
DSI™

遥测技术测定胸模内压



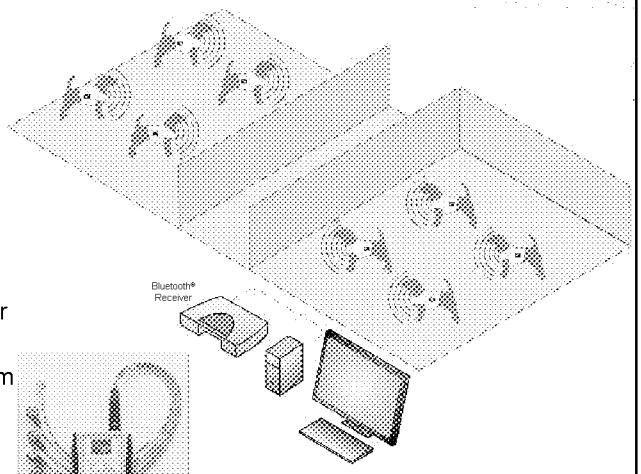
Murphy, Renninger, & Gosset, 1998

大鼠胸模内压验证



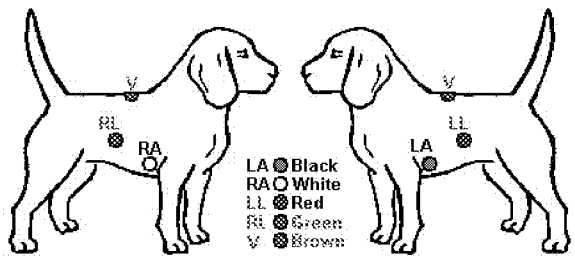
Jacketed External Telemetry (JET)

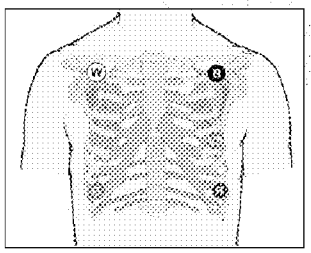
- Telemetry Device
  - Bluetooth communication
  - Individual i.d.
  - Up to 10 m transmission
  - Non-invasive or minimally invasive
  - Rechargeable by user
- Up to 36 animals per room
- ECG, RIP, and BP



DSI™

ECG电极放置位置



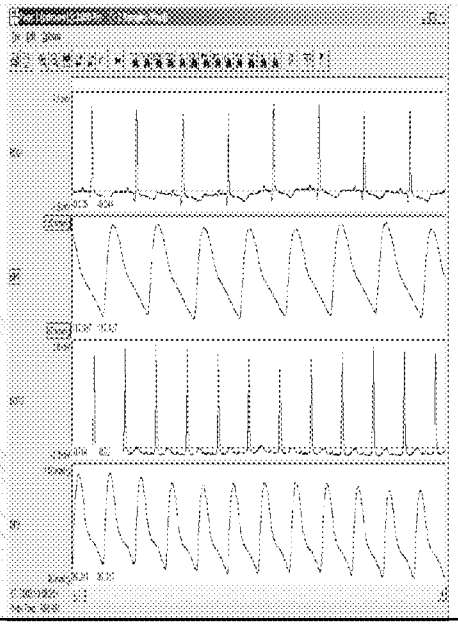


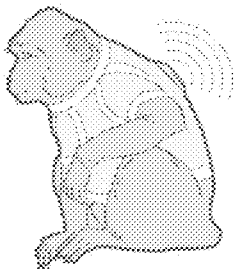
Primates

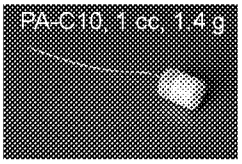
Lead I, II, III, aVR, aVL, aVF, VLead

DSI™

JET with BP (minimally invasive)







DSI™

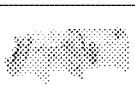
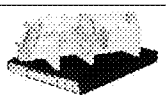
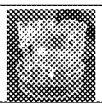
呼吸系统研究

呼吸实验研究中的主要术语和参数

- 流量: mL/sec of air into and out of the respiratory tract during each breath.
  - Peak Inspiratory Flow – PIF
  - Peak Expiratory Flow – PEF
  - Breaths per minute-BPM
  - Tidal Volume – TV
  - Minute Volume – MV
- 压力: cm H2O; signal typically comes from a pressure transducer.
  - Resistance - RI
  - Compliance - Cdyn
- 其他重要演算参数 (derived from pressure)
  - 顺应性Compliance (Cdyn) - change in volume divided by the change in pressure (dV/dP).
  - 气道阻力Resistance (RI) - change in pressure divided by the change in flow (dP/dF).

DSI™

小动物呼吸系统实验研究的常用方法

	露头式呼吸腔	露头式呼吸腔+遥测	非补偿型整体式呼吸腔	补偿型整体式呼吸腔
				
优势	高质量信号，后期数据分析比较容易	高质量信号，可做支气管收缩实验研究	适合监测时间较长的实验，动物应激反应较小，不需前期训练	可得到真实的潮气量和分钟通气量;动物应激反应较小，不需前期训练
弱点	动物在束缚状态，有一定的应激反应，需要实验前对动物进行训练	动物在束缚状态，有一定的应激反应，需要实验前对动物进行训练。需要做手术	信号较小,比较容易受影响，后期数据分析需要更多的工作	信号较小,比较容易受影响，后期数据分析需要更多的工作
采集到的信号	流量 (thoracic displacement via diff. Pressure)	流量 (via diff. Pressure) Pleural Pressure	流量 (via diff. Pressure)	环境压力; 流量 (via diff. Pressure) 温度，湿度
得到的参数	BPM; IT; PIF, ET; PEF; TV, MV	BPM; IT; PIF, ET; PEF; TV, MV Resist.; Compliance	BPM; IT; ET; Penh; relative (PIF; PEF); TV; MV	BPM; IT; PIF, ET; PEF; Penh; TV; MV
			+遥测，可同时监测BP, ECG, body temp.	+遥测，可同时监测BP, ECG, body temp.

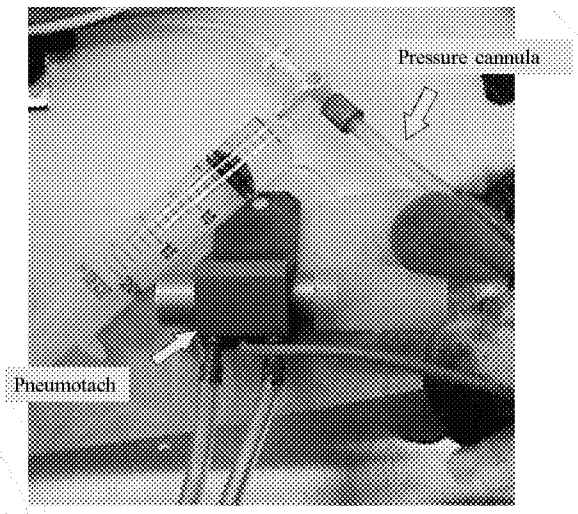
DSI

大动物呼吸系统实验研究的常用方法

	麻醉方法	面具（束缚）	头盔（束缚）	遥测PCTR	JET RIP
					
优势	最经典的呼吸实验研究方法，高质量信号，后期数据分析比较容易	清醒动物，适合短时间数据采集，信号质量好，	清醒动物，适合短时间数据采集	清醒自由活动动物，长时间检测。同时可整合CV实验	清醒动物，可长时间监测.同时可整合CV实验
弱点	麻醉模型。一般一次只能采集1只动物的数据	束缚状态–R需要实验前进行训练，很难同时采集多只动物	束缚状态，需要前期训练，信号容易受影响，后期数据需要更多的工作	需要手术，活动时数据易受干扰。在后期数据分析时需考虑不同统计方法	需要前期训练，自由活动数据不好，后期数据分析需要更多工作
采集到的信号	流量 (via diff. Pressure), 胸膜内压 (via esoph. Pressure). + pulse oximetry	流量 (via diff. Pressure)	流量 (via diff. Pressure), 胸膜内压	电阻抗	相对流量 (respiratory inductive plethysmography)
得到的参数	BPM; IT; PIF, ET; PEF; TV, MV, Resist., Compliance	BPM; IT; PIF, ET; PEF; TV, MV	BPM; IT; ET; Penh; PIF; PEF; TV; MV; +telemetry - Resist.; Compliance	BPM; IT; PIF, ET; PEF;TV; MV	BPM; IT; PIF, ET; PEF; Penh; TV; MV
	monitor BP, ECG, body temp.		+telemetry - monitor BP, ECG, body temp.		

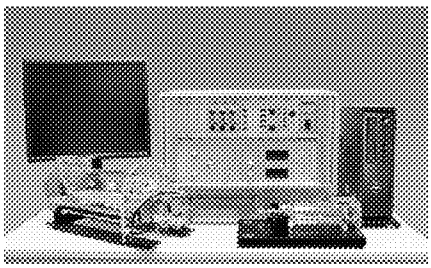
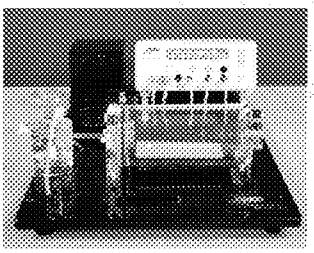
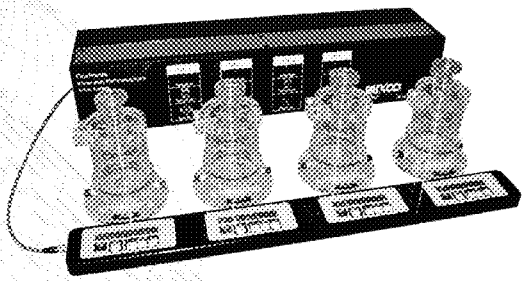
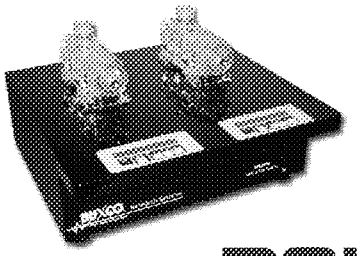
DSI™

经典模型 (麻醉)



DSI™

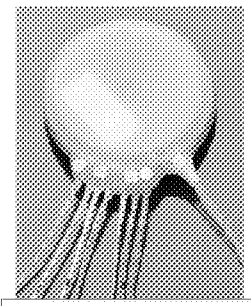
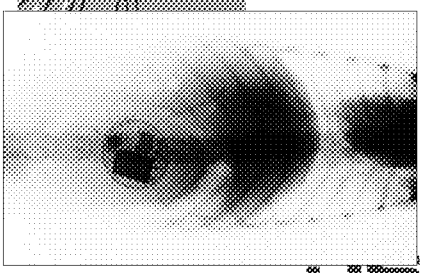
呼吸实验研究仪器

DSI™

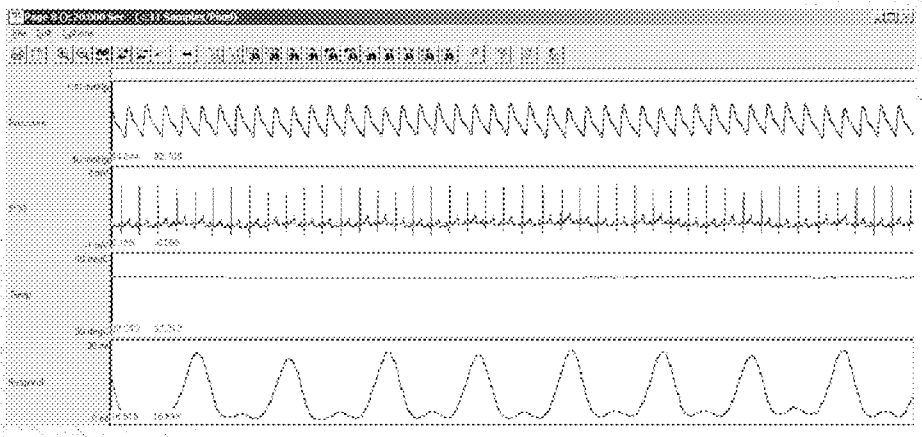
植入式遥测 D70-PCTR

- BP
- ECG
- 温度
- 呼吸
  - 频率
  - 潮气量
  - 分钟通气量
- 活动度

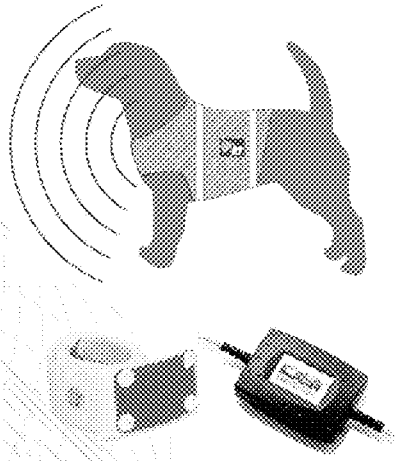
DSI™

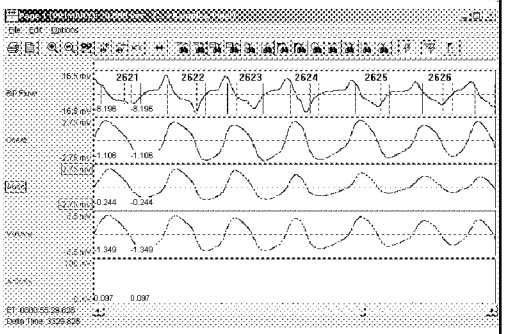
BP, ECG, 温度和呼吸



DSI™

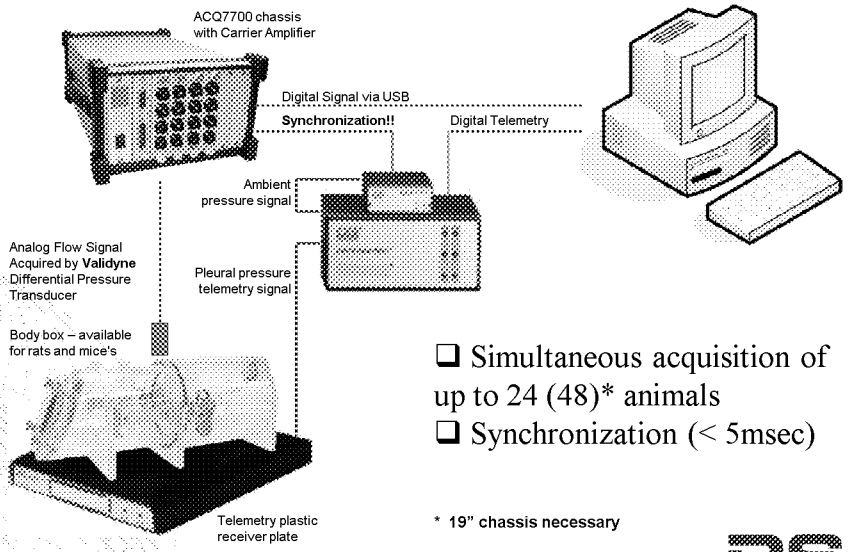
马甲式遥测 JET-RIP





DSI™

肺顺应性和气道阻力研究



- ❑ Simultaneous acquisition of up to 24 (48)* animals
- ❑ Synchronization (< 5msec)

* 19" chassis necessary

DSI™

中枢神经研究

SP Study: Changes in sleep, development of seizure, other unwanted side-effects

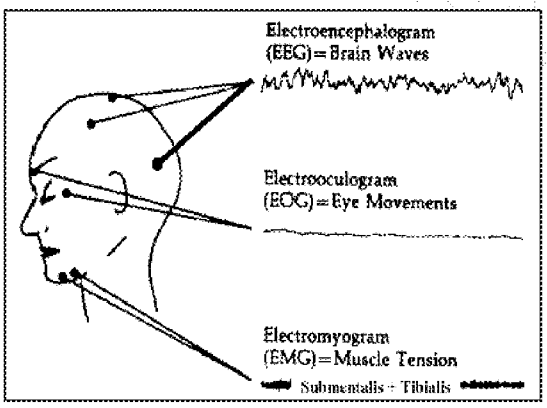
以睡眠研究为例

- 静息状态
  - 活动度减少Reduced mobility
  - 闭眼Closed eyes
  - 对外界刺激的反应变小Reduced response to external stimuli
  - 典型的睡眠姿势Characteristic sleep posture
  - 可逆昏迷状态
- Hypothesis: *Sleep serves to reverse &/or restore biochemical & physiological processes that are progressively degraded during wakefulness*

DSI™

怎样监测和评价睡眠?

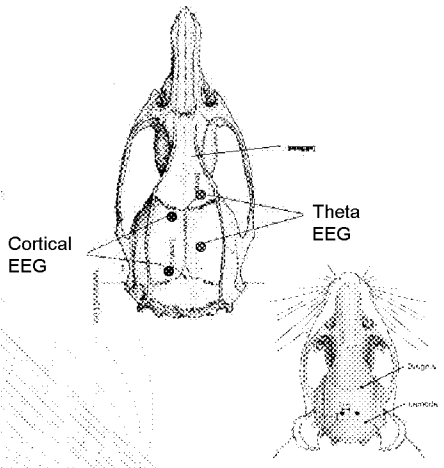
- EEG
- EMG
- EOG



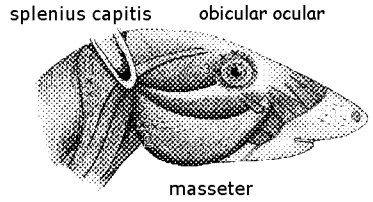
DSI™

EEG 和 EMG

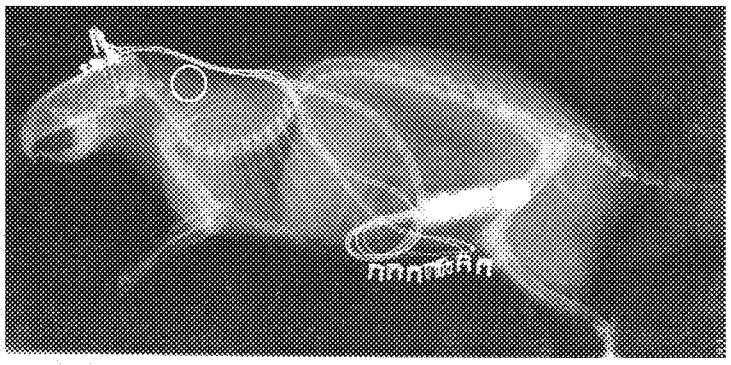
EEG locations



EMG Locations



DSI™



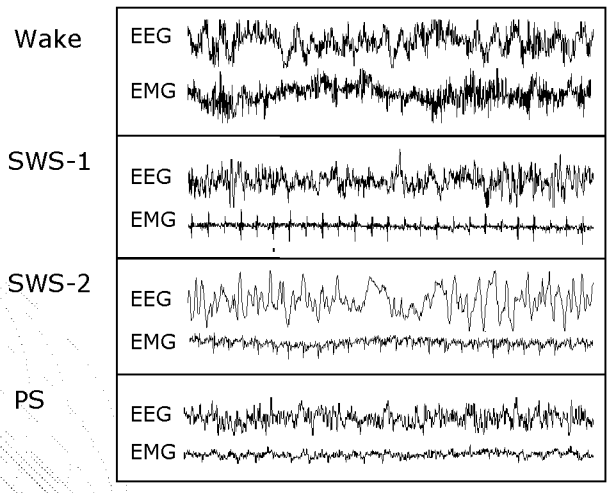
DSI™

如何对信号进行分析?

- EEG
  - 频率
  - 幅度
- EMG – 肌肉运动收缩情况
- EOG – 眼动
- 活动度

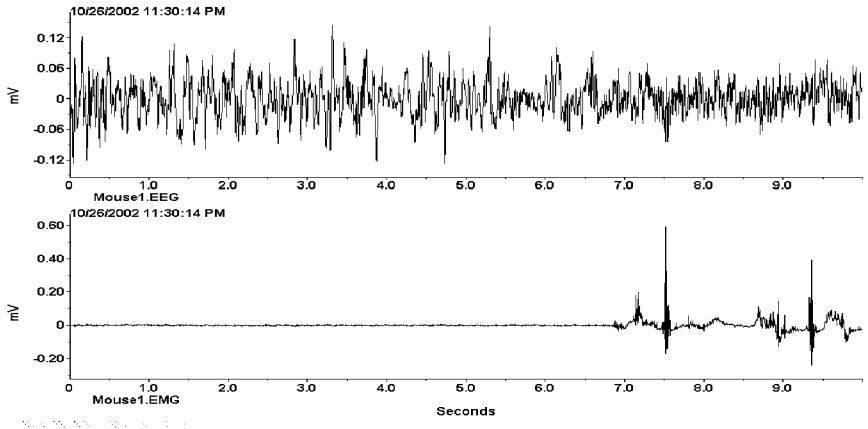
DSI™

信号波形



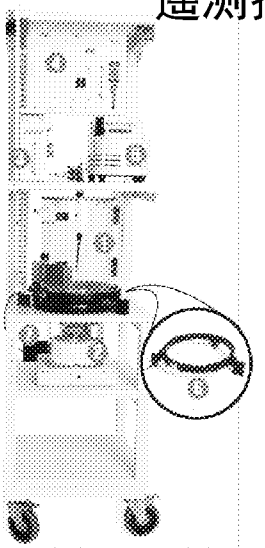
DSI™

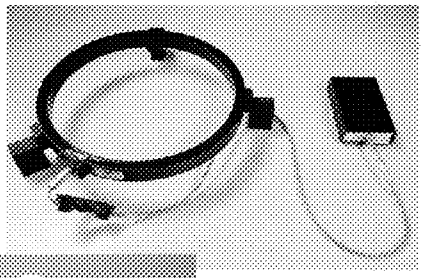
小鼠EEG睡眠数据

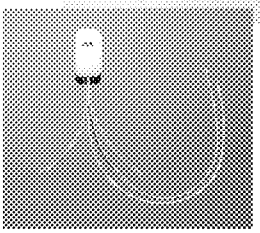


DSI™

遥测技术与代谢实验结合



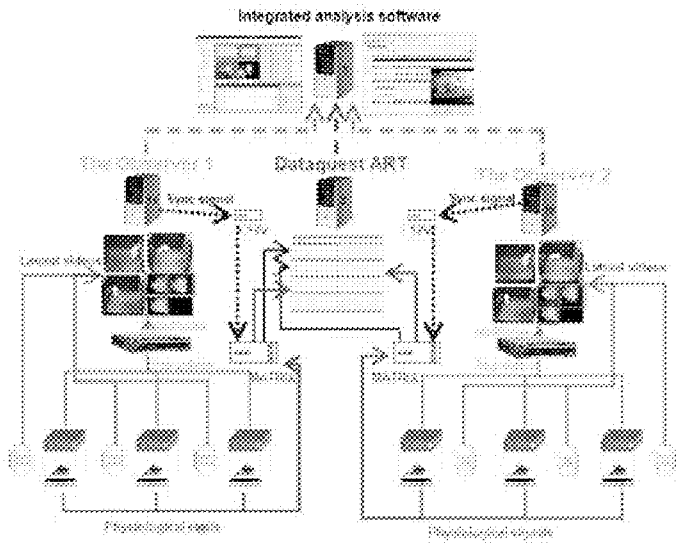




Combine PK and PD parameter

DSI™

遥测技术与行为学实验结合



DSI™

谢 谢!

Shining Su
Country Manager, AP
DSI (Data Sciences International)
Room 618, Cailun Rd 780, Zhangjiang Hi-Tech Park
Shanghai, China
021-50793177
ssu@datasci.com