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Manipulation and challenges for robotics in the scientific laboratory

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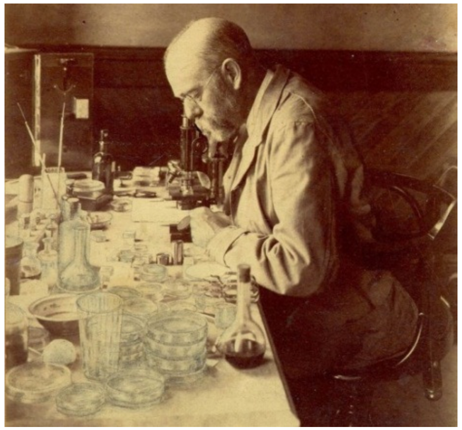
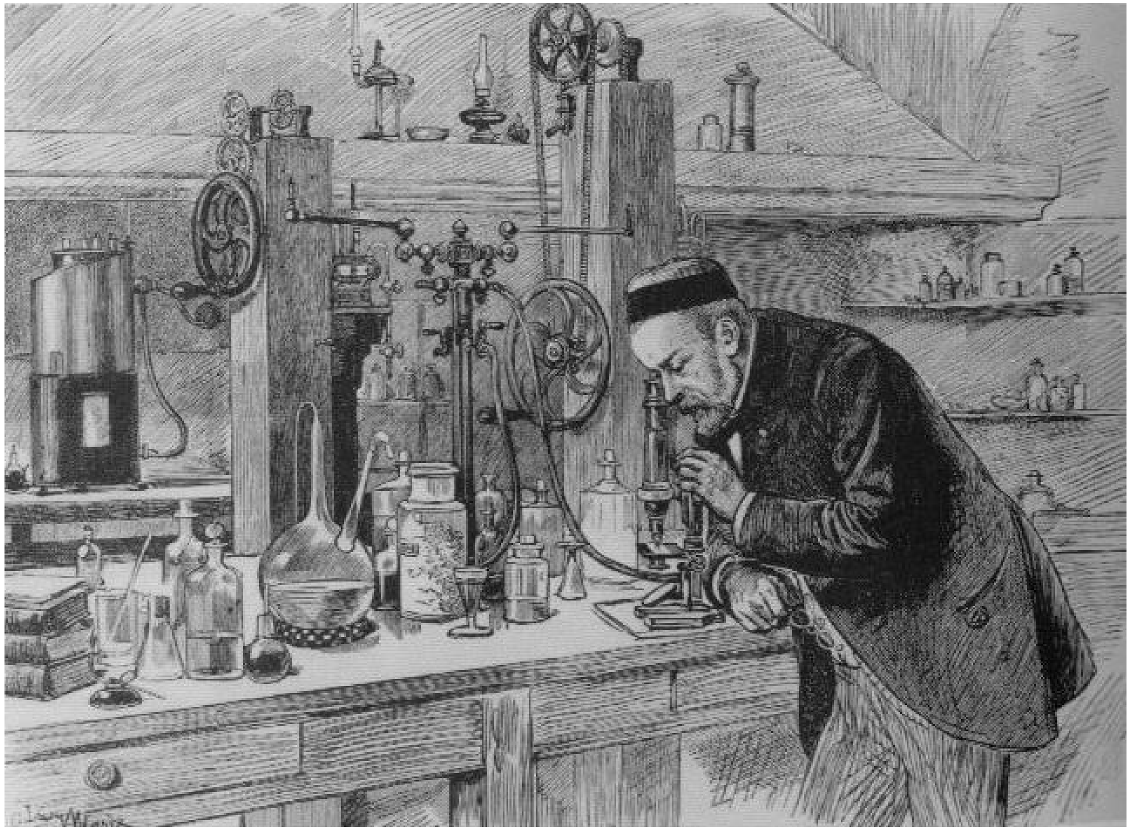
Manipulation in the scientific laboratory

- What is laboratory robotics and why is it important
- Types of sample and their behaviour
  - What we now do well
  - What we still do badly
- Invitation to further dialogue

In the 19th Century



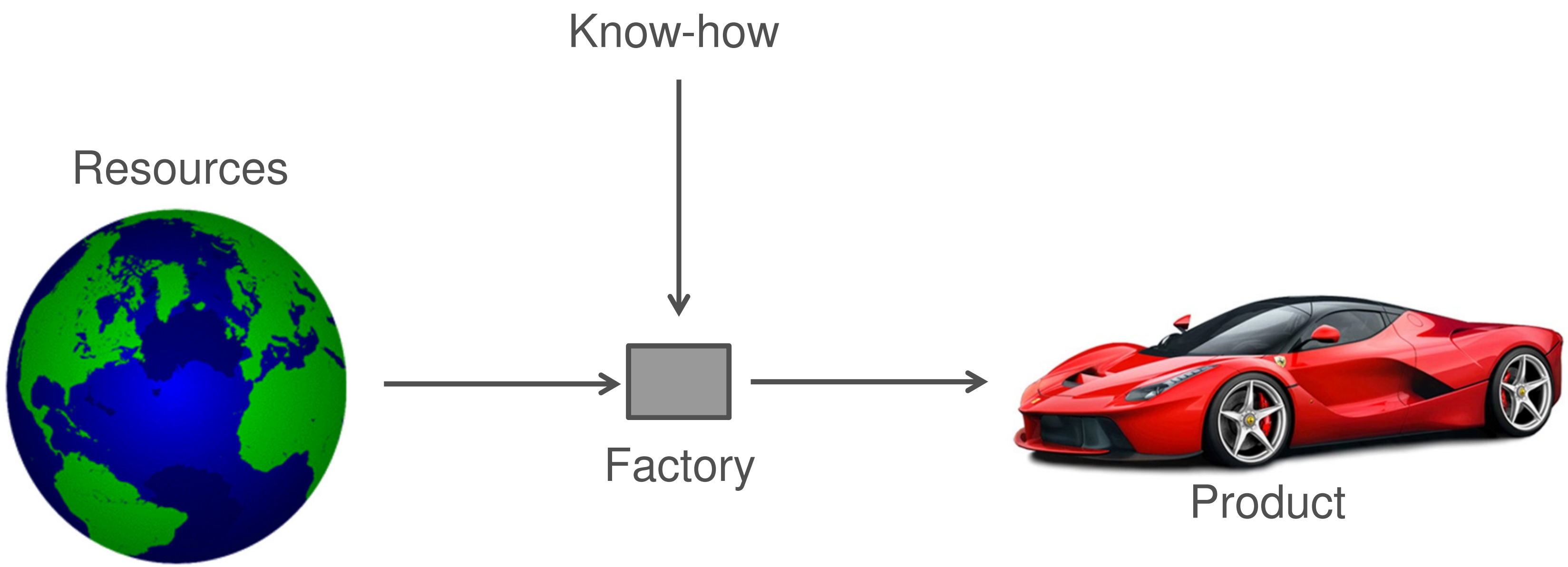


In the 21st Century

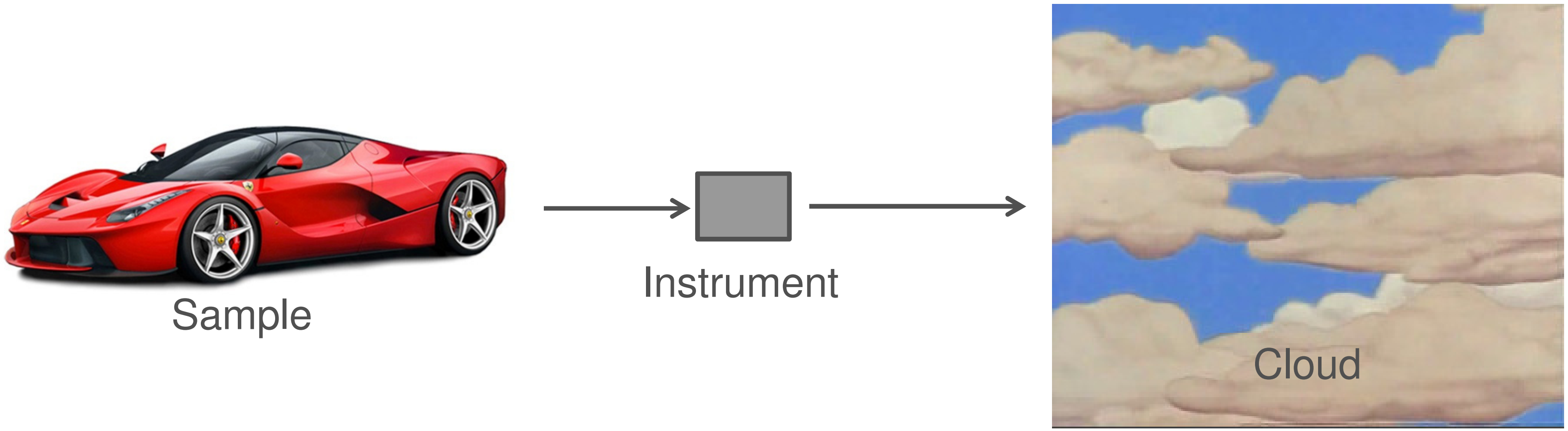
Measurement & sample handling

Complement to manufacture
From sample to information

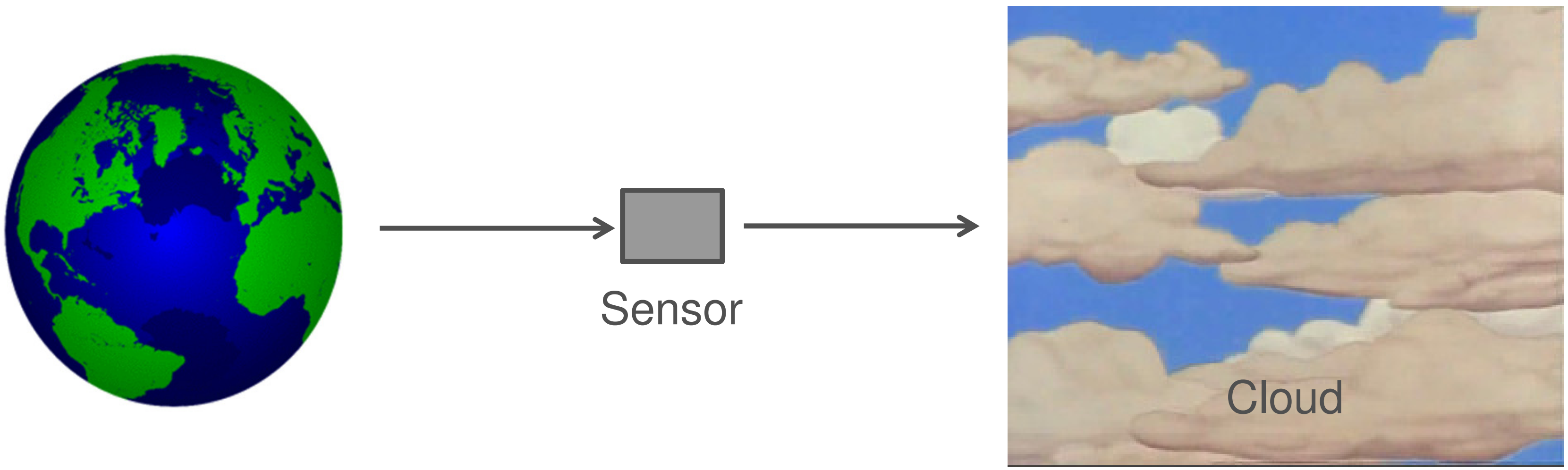
Manufacturing: turning know-how into products



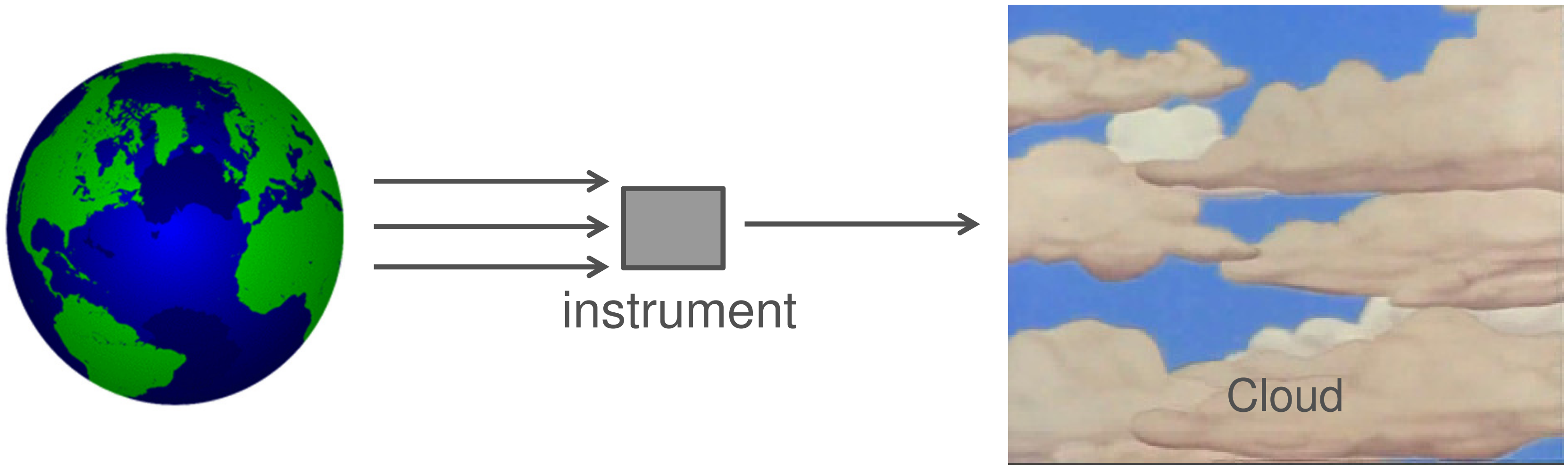
Analytical laboratory: material into information



Sample in the world

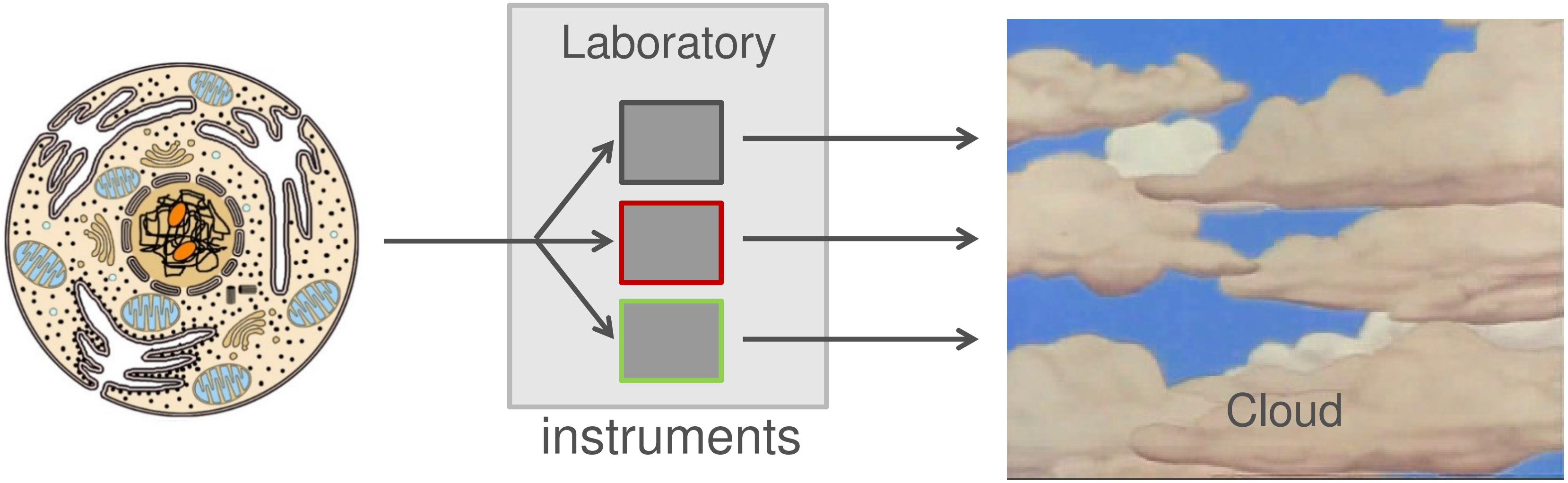


Turning material into information: multiple samples



Need for sample transport

Turning material into information: complex samples

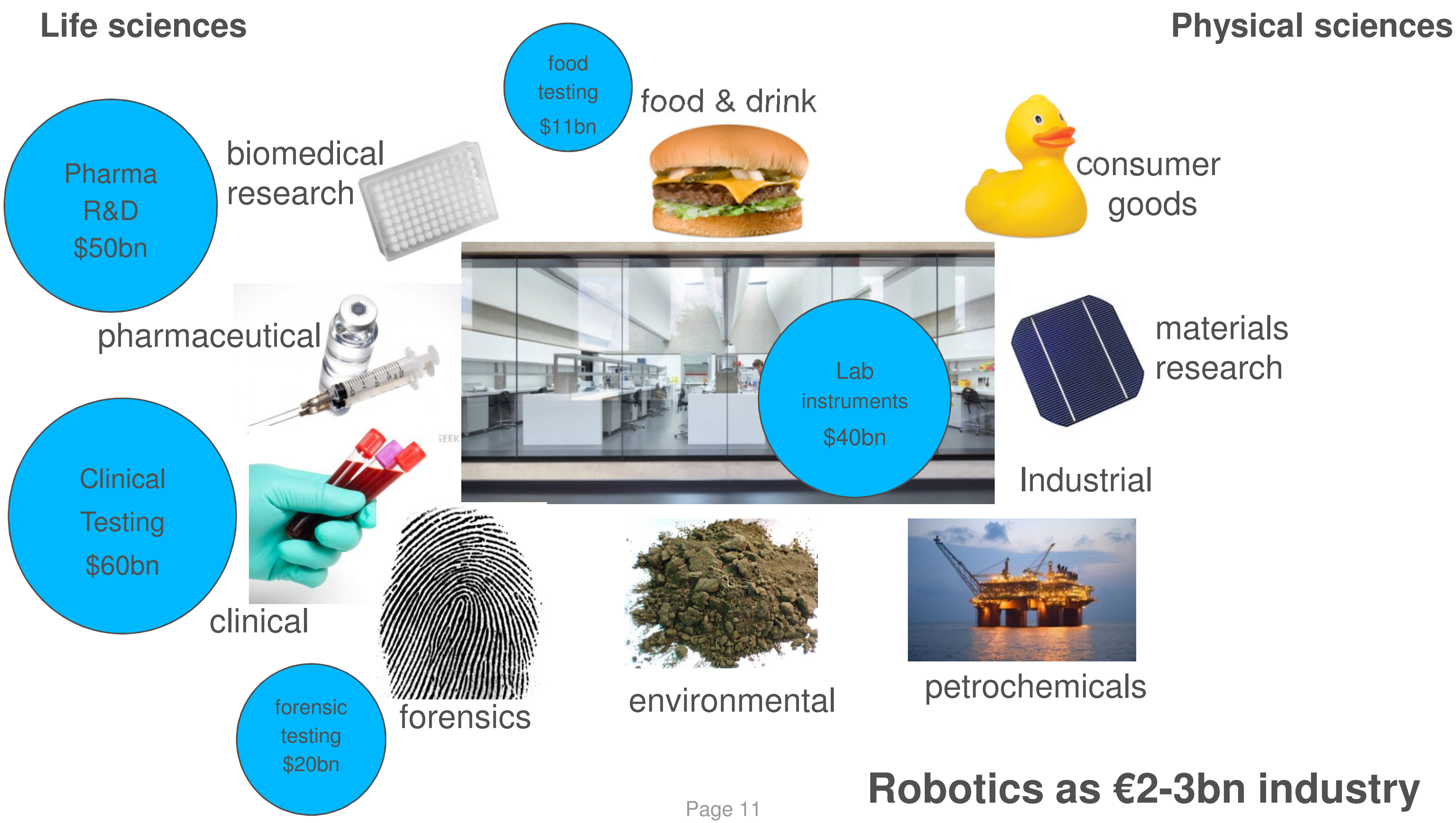


Typology of end-user laboratory

Life sciences **Physical sciences**

from well behaved to heterogenous; from solid into liquid form

Typology of end-user laboratory



Robotics as €2-3bn industry

The remote laboratory

Life sciences

Physical sciences

biomedical
research

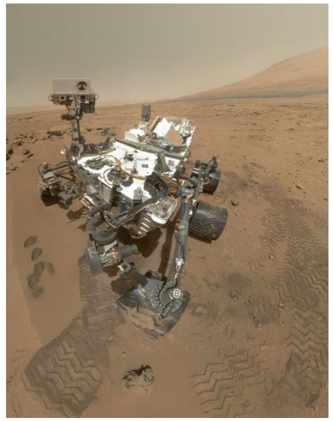
food & drink

museum

materials
research

clinical

space



forensics

environmental

mining

large, dangerous, toxic, legal, fragile, remote: robotic potential

Manipulation in the scientific laboratory

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Handling liquids: how hard can it be ?

Liquids: from viscous to mobile

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- Efficient
  - high precision (%CV no evaporation)
  - high reliability (no clogging)
  - high throughput (24/7)
  - small volume (ml-ul-nl)

- Safe
  - low carry-over
  - low aerosol generation
  - low contamination

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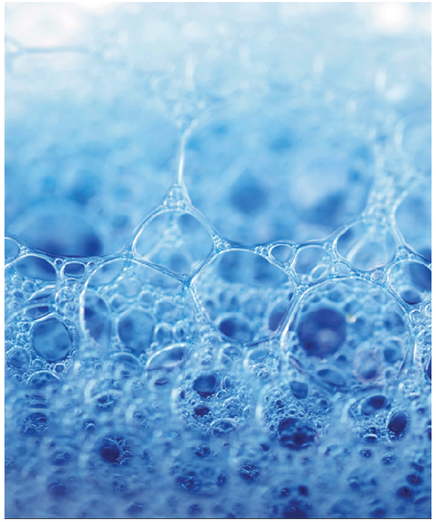
Liquids: mobile to viscous / emulsions & colloids

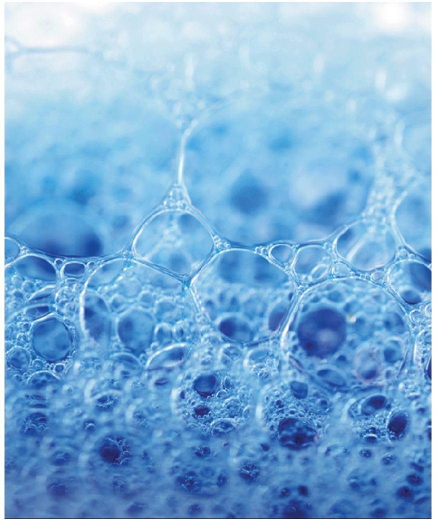


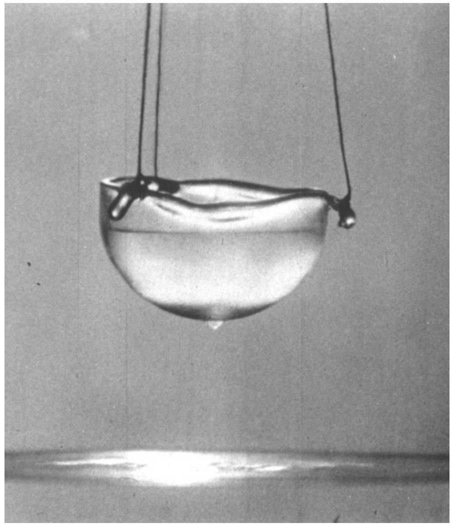
Handling samples

vs

Dealing with challenges

Liquids: mobile to viscous / emulsions & colloids





Liquids – successes and challenges

- Viscosity: from foams to creams
- Mobility: from methanol to live culture

- All with high precision, high reliability and high throughput

- Reduced evaporation
- Reduced clogging

- Economic: small volumes from 10ml to 100ul to 25nl
- Safe: low carry-over, aerosol generation & contamination
- Use of replaceable tips

Microtitre plates – role of standards, consumables

96 well

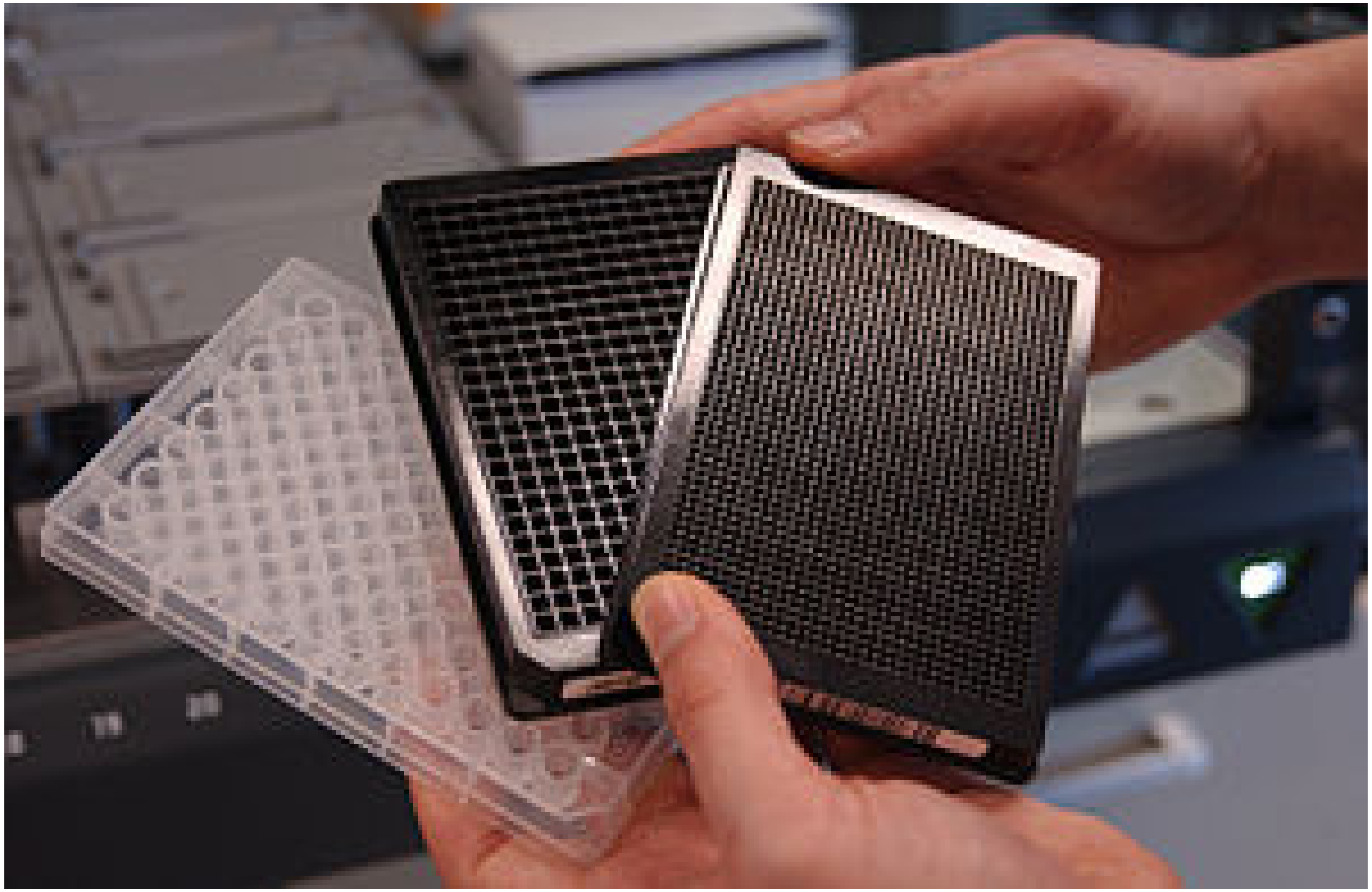
100-200ul

384 well

20-80ul

1536

to 8ul



1996 to 2003

Manual *versus* automated pipetting – the challenge

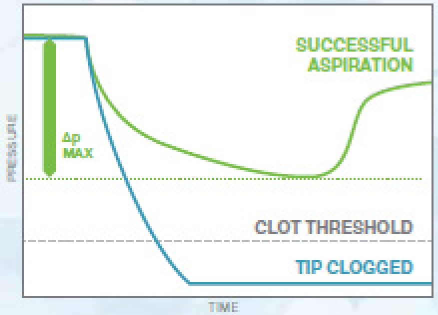
	Manual Detection Method	Control / Feedback loop	Automated Detection	Challenge
Temperature, pressure, humidity	Ignored, eyes monitor liquid uptake	None	Impacts physics of volume. Expectation of better accuracy & precision	Need to be modeled in SW to ensure accurate & precise pipetting
Visocity	Eyes detect aspirate/dispense rate	Adjust speed of thumb on plunger, humans adjust automatically	None	Have to know what type of liquid is being pipetted. Adjust parameters
Sample liquid level	Eyes, adjust till tip of pipette just in liquid	Lower pipette as liquid level falls	Need an electrical or visual method Avoid 'diving' due to contamination/surface drops	Conductive liquids and tips Non-opaque sample vessels
Dispensing volume	Eyes	See pipette tip is empty	Electrical or pressure None, use air gap to blow pipette tip empty	Depends upon viscocity
Speed of movement	Eyes	Arm/hand moves to required position	Need to know liquid to adjust accordingly	Acceleration, speed and deceleration of movement critical
Complete dispensing	Eyes	Watch to see if any liquid left in pipette	Use air gap to blow pipette tip empty	Speed of air gap, no aerosols generated, drop formation. Dependent upon dispense speed
Sample homogeneity, foam	Eyes	Mix sample or avoid particles, Tip through foam to liquid	Monitor electrical parameters or pressure changes	Tip blockage relatively easy,

Ian Shuttler (2015)

Pipetting and sensing

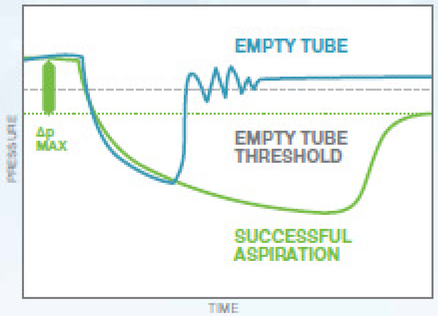
WHAT TYPES OF PIPETTING ERRORS ARE DETECTED BY QPM?

Below are some examples of how the pressure curves for various common pipetting errors will look relative to a successful aspiration.



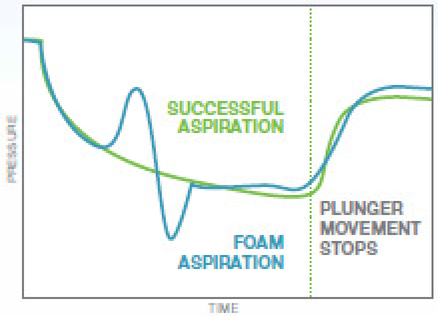
CLOGGED TIP DETECTION

If the tip clogs during aspiration the pressure will spike down. As the plunger moves, sample is not being aspirated to help equalize the pressure.



INSUFFICIENT LIQUID DETECTION

If there is insufficient liquid in the tube, the pressure curve will start down as normal but then will return to a pressure much higher than the expected level represented by Δp in the graph. The higher pressure is a result of having less liquid in the tip due to an incomplete aspiration.

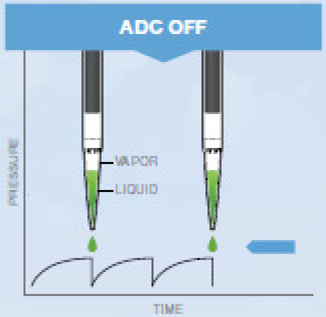


ASPIRATION OF FOAM

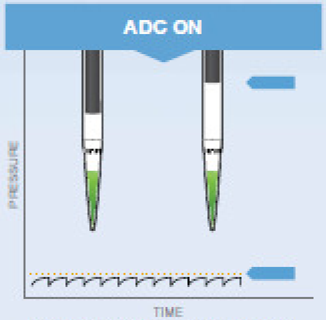
If ZEUS pipettes foam instead of liquid, the pressure sensor detects spikes during the aspiration. Based on the severity of the spikes, a threshold can be set for a failed aspiration.

PIPETTING VOLATILE LIQUIDS

Volatile liquids like acetone and methanol can be extremely difficult to pipette using air displacement. These liquids tend to vaporize in the tip which raises the air pressure resulting in liquid dripping from the tip. ZEUS is equipped with Anti-Droplet Control (ADC). When enabled the pressure is monitored in the tip. As the pressure rises the piston is retracted to equalize the pressure and prevent dripping. The illustrations show the pressure curve when ADC is on and off.



Pressure reaches a maximum; a droplet is lost and pressure drops.



Piston retracts when pressure threshold is reached so no droplet forms.

Hamilton Zeus (2015)

Solids – diversity and challenges

Machined part

- shiny
- articulated
- CAD model

Solids – diversity and challenges

Machined part

Filled flask

Powders

Pizza dough

Live animal

complex

multi-phase

uncooperative

anti-cooperative

EDITORIAL

nature neuroscience

Troublesome variability in mouse studies

We urge greater awareness of the potential genetic and environmental confounds involved in designing and interpreting studies with mice, and encourage the accurate reporting of the study's design.

All scientific disciplines grapple with the issues of standardization of methods and reproducibility of results. Standardizing seems especially difficult when dealing with genetically modified

(the heterogenized replicates), the authors found an increased rate of false positives in the standardized replicates. Würbel and colleagues suggested that environmental standardization may actually increase the

NATURE | NEWS

Male researchers stress out rodents

Rats and mice show increased stress levels when handled by men rather than women, potentially skewing study results.

Alla Katsnelson

28 April 2014

Print

Olfactory exposure to males, including men, causes stress and related analgesia in rodents

Robert E Sorge[1,2,8], Loren J Martin[1,8], Kelsey A Isbester[1], Susana G Sotocinal[1], Sarah Rosen[1], Alexander H Tuttle[1], Jeffrey S Wieskopf[1], Erinn L Acland[1], Anastassia Dokova[1], Basil Kadoura[1], Philip Leger[1], Josiane C S Mapplebeck[1], Martina McPhail[3], Ada Delaney[4], Gustaf Wigerblad[4], Alan P Schumann[3], Tammie Quinn[3], Johannes Frasnelli[5,6], Camilla I Svensson[4], Wendy F Sternberg[3] & Jeffrey S Mogil[1,7]

We found that exposure of mice and rats to male but not female experimenters produces pain inhibition. Male-related stimuli induced a robust physiological stress response that results in stress-induced analgesia. This effect could be replicated with T-shirts worn by men, bedding material from gonadally intact and unfamiliar male mammals, and presentation of compounds secreted from the human axilla. Experimenter sex can thus affect apparent baseline responses in behavioral testing.

Rodents can discriminate human experimenters by smell, and their behavior can be affected by such perception[1,2], but it has not been shown that human presence can affect the results of laboratory experiments. Our laboratory personnel have reported anecdotally that pain behavior appears to be blunted while experimenters are present (for example, after administering pain-inducing algogens). The recent development of a highly sensitive and totally blinded pain measure, the mouse grimace scale[3], allowed us to evaluate this hypothesis.

Pain was produced by bilateral ankle injections of sterile zymosan A, an inflammatory agent (Online Methods). We placed experimentally naive mice into clear Plexiglas cubicles and recorded facial expressions of pain. We compared facial grimacing in mice tested in the presence of an experimenter (seated quietly at a distance of ~0.5 m) to that of mice tested in an empty room. Four different adult male experimenters produced robust

[1]Department of Psychology, McGill University, Montreal, Quebec, Canada. [2]Department of Psychology, Haverford College, Haverford, Pennsylvania, USA. [3]Department of Physiology ... Coeur Hospital, University of Montreal, Montreal, Quebec, Canada. [4]Centre de Recherche ... of Montreal, Montreal, Quebec, Canada. [7]Alan Edwards Centre for Research on Pain, McG... work. Correspondence should be addressed to J.S.M. (jeffrey.mogil@mcgill.ca).

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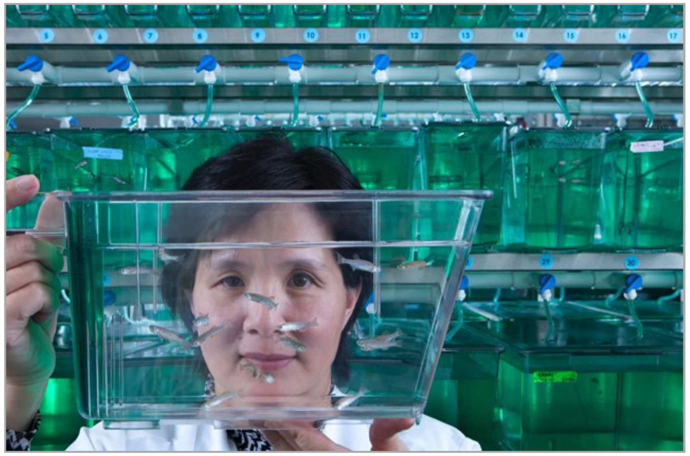
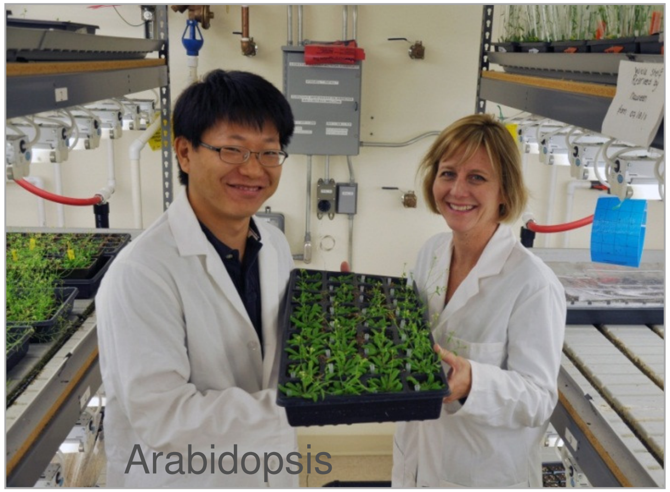
Bringing the field into the laboratory
of mustard and zebrafish



Danio rerio



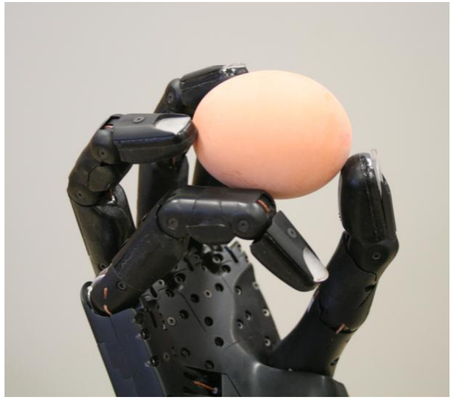
Arabidopsis

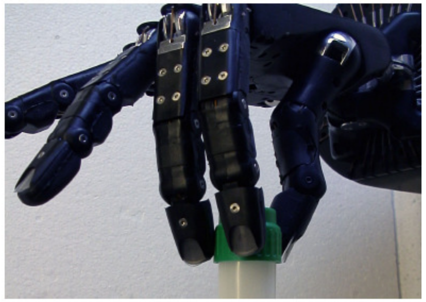
Advances in manipulation technology

- University of Bielefeld / Bayer (2004)

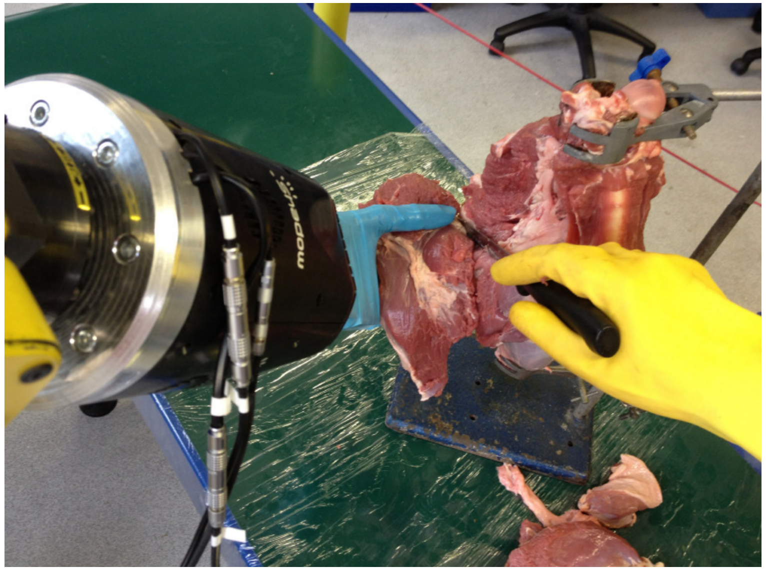
Advances in manipulation technology

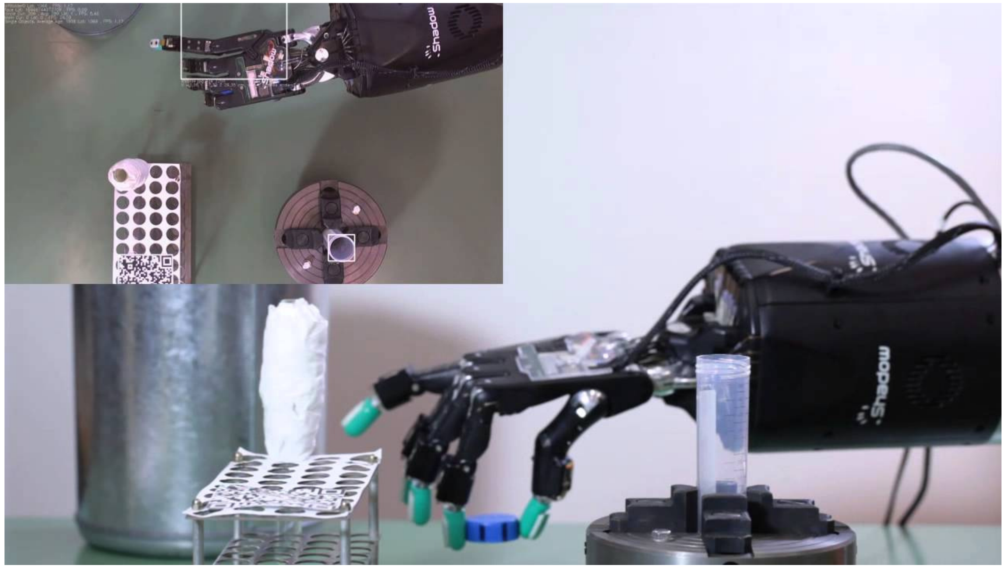
- Shadow robot hand / Health Protection Agency (2012)
- HYFLAM





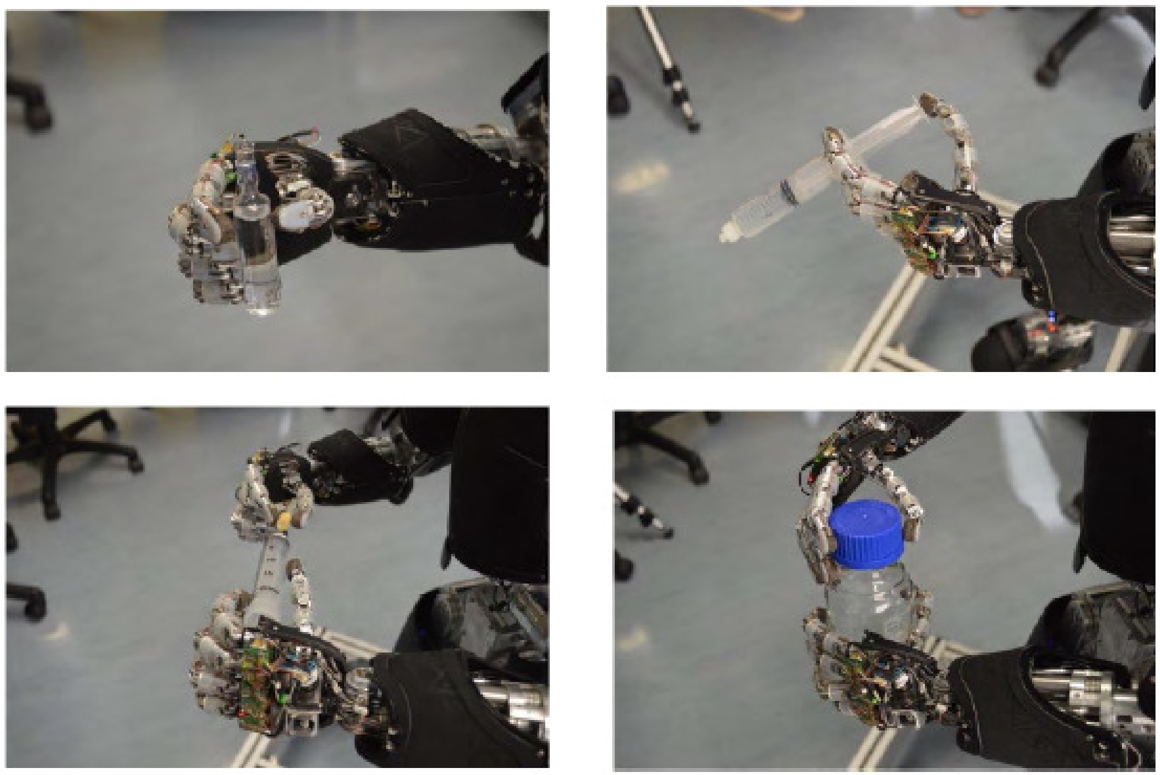
- DEXDEB





Advances in manipulation technology

- iCub2work: humanoid / GSK (2013)



Manipulation in the scientific laboratory

- What is laboratory robotics and why is it important
  - from sample to information

- Types of sample and their behaviour
  - What we do well: liquids

    Role of standards – plates and tips – as consumables
  - What we do badly: solids

- **Invitation to further dialogue**

For diagnostics and therapies

Demographics

- chronic rich world diseases
- aging population
  - Diabetes
  - Cancers
  - Cardio-Vascular Disease
  - Alzheimers

Emerging diseases

- globalisation
- more travel
- more infectious diseases
  - HIV SARS MERS (2012)
  - Ebola (2014-2015)
  - E coli O157 (2011)
  - Avian flu H5N1 (2009)
  - Chikungunya (2006)
  - Malaria (…)
  - Zika

new for 2016

Robot arm on an open bench

Manual process
tool use with
dual cameras

Andrews Alliance (2015)

Robotics capabilities across different fields

1 Configurability
2 Adaptability
3 Interaction Capability
4 Dependability
5 Motion Capability
6 Manipulation Ability
7 Perception Ability
8 Decisional Autonomy
9 Cognitive Abilities