STANDARDS TO ADVANCE LIFE SCIENCE EXPERIMENTATION

Standardizing laboratory instrument communication and data exchange formats: Laying the foundation for the industrial revolution of life science experimentation.

Oliver Peter
Leader, HTS & Compound Management Group
Actelion Pharmaceuticals Ltd

oliver.peter@actelion.com
1. Why standardize?
   • *Standardization has been key to fundamental innovation throughout history.*

2. Why automate labs?
   • *The experimental life sciences have not undergone fundamental revolution.*

3. Standardize lab automation!
   • *A call to implement the emerging global standards, SiLA and AnIML.*

4. Imagine the lab of the future...
   • Examples of innovations that standardization will enable.
WHY STANDARDIZE?

Standardization has been key to fundamental innovation throughout history.
A COMMON MISCONCEPTION:

Standardization stifles creativity!
IN FACT:

Standardization facilitates innovation!
The Tower of Bable
Pieter Brueghel the Elder, ca. 1563
STANDARDIZATION AND MODULARIZATION

THE KEY TO THE EMERGENCE OF HIGHER ORDER COMPLEXITY
STANDARDIZATION AND MODULARIZATION

EXAMPLE: THE EVOLUTION OF LIFE

[Diagram with images of molecular structures and a timeline progressing from a chemical compound through microbial cells to a mammal and a plant]
STANDARDIZATION AND MODULARIZATION

EXAMPLE:
THE INDUSTRIAL REVOLUTION
STANDARDIZATION AND MODULARIZATION

EXAMPLE:
THE ICT REVOLUTION

NACA High Speed Flight Station "Computer Room"
STANDARDIZATION AND MODULARIZATION

EMERGENCE OF A NEW CULTURAL AND ECONOMIC “ECOSYSTEM”
STANDARDIZATION AND MODULARIZATION

THE TECHNICAL BASIS OF THE ICT REVOLUTION:

- **Standardization:**
  - chip specific instructions → standard instruction sets
  - machine specific code → device indep. programming languages
  - vendor-specific interfaces → universal interfaces

- **Modularization:**
  - machine level programming → applications on top of an operating system
  - low-level programming → structured, object oriented programming
  - purpose-built calc. engines → universal computers
  - individual computers → computer networks
STANDARDIZATION AND MODULARIZATION

Standardization facilitates innovation!
WHY AUTOMATE LABS?

The experimental life sciences have not undergone fundamental revolution.
WHY LAB AUTOMATION?

A MISCONCEPTION FROM PAST EXPERIENCE:

Automation ↔ Quantity

“Designing HTS assays to accommodate modern large-scale robotic screening often involves compromises, such as using non-natural substrates or artificial reaction conditions, and defining imperfect hit selection criteria, which inadvertently fail to identify interesting inhibitors.”

Payne et al. (GSK), Nat Rev Drug Disc 6, 29, 2007
WHY LAB AUTOMATION?

IN FACT, TODAY:

Automation ↔ Quantity

Automation ↔ Quality!
WHY LAB AUTOMATION?

REPRODUCIBILITY OF PEER-REVIEWED PUBLISHED RESULTS - EMBARRASSING FINDINGS:

- Amgen found that 47 of 53 “landmark” oncology publications could not be reproduced.

- Bayer found that 43 of 67 oncology & cardiovascular projects were based on contradictory results from academic publications.

- John Ioannidis and colleagues found that of 432 publications purporting sex differences in hypertension, multiple sclerosis, or lung cancer, only one data set was reproducible.

From Elizabeth Iorns, Science Exchange Inc.: http://blog.scienceexchange.com/2012/04/the-need-for-reproducibility-in-academic-research/

WHY LAB AUTOMATION?

SOME REASONS FOR NON-REPRODUCIBLE RESULTS:

- Experimenter bias
  - samples are not randomized, experimentors are not blinded
  - semi-quantitative, subjective analysis ("0/+/+++/")
- Uncontrollable parameters
  - procedures rely on experienced individuals: implicit param’s
  - humans focus on few presumably relevant parameters
- Unclear procedures
  - ambiguous descriptions, implicit assumptions
  - inconsistent instructions, incomplete referencing
- Impenetrable audit trail
  - unstructured records
  - retracing experiments fully is practically impossible

WHY LAB AUTOMATION?

IMPROVING REPRODUCIBILITY - TECHNICAL SOLUTIONS:

- Experimenter bias
  - randomized samples, blinded experimenter
  - sensors and computational signal analysis
- Uncontrollable parameters
  - modularized and automated procedures
  - consistently enforced quality controls
- Unclear procedures
  - standardized, structured language
  - syntax checking
- Impenetrable audit trail
  - LIMS/ELN
  - structured experimental records

more lab automation, also in academia

more reproducible scientific findings
IMPROVING REPRODUCIBILITY - ORGANIZATIONAL SOLUTIONS:

In 2012, open-access Public Library of Science (PLOS) and private venture Science Exchange launch the Reproducibility Initiative to assist researchers in validating their findings by repeating experiments through independent laboratories.

Maybe there is an emerging business case for large-scale contract reproduction of experiments - and for remote experimentation in general.
OBSTACLES TO AUTOMATION IN THE LAB

Available automation from most scientists’ perspective:

- “not flexible enough”
- “too complicated”
- “too expensive”
- “too large”
- “not for me”

And they are right!

The root cause is a lack of standards:

→ no universal technical ecosystem
→ slow technical evolution
→ no fundamental innovation
STANDARIZE LAB AUTOMATION!

A call to implement emerging global standards:

- SiLA for instrument integration
- AnIML for data exchange
STANDARDIZATION IN LAB AUTOMATION

THE MULTIWELL PLATE STANDARD

Gyula Takátsy
(1914-1980)
Wikipedia
STANDARDIZATION IN LAB AUTOMATION

THE MULTIWELL PLATE STANDARD
STANDARDIZATION IN LAB AUTOMATION

THE MULTIWELL PLATE STANDARD: ENABLES MODULARIZATION
STANDARDIZATION IN LAB AUTOMATION

THE MULTIWELL PLATE STANDARD: ENABLES WORKFLOWS
STANDARDIZATION IN LAB AUTOMATION

NO PLATE STACK FORMAT:
WORKFLOWS DISRUPTED
STANDARDIZATION IN LAB AUTOMATION

ROBOTIC INTEGRATION: PHYSICALLY POSSIBLE
STANDARDIZATION IN LAB AUTOMATION

ROBOTIC INTEGRATION: DEVICE INTERFACE REQUIRED
STANDARDIZATION IN LAB AUTOMATION

ROBOTIC INTEGRATION:
DEVICE INTERFACE REQUIRED
STANDARDIZATION IN LAB AUTOMATION

THE SILA STANDARD FOR DEVICE INTEGRATION

Device Interface Standard
- Ethernet based interface standard for device control and data exchange

Common Command Library
- Device Class based command sets for main device functions

Labware Specification Standard
- Standard parameter set for specification of labware properties

Data Interface Standards
- Data Capture
- LIMS
- Remote Service & Monitoring
- Enterprise IT
STANDARDIZATION IN LAB AUTOMATION

THE SILA STANDARD FOR DEVICE INTEGRATION
STANDARDIZATION IN LAB AUTOMATION

THE SILA STANDARD FOR DEVICE INTEGRATION

- Laboratory Information Management System (LIMS A)
- Process Management System (PMS) / Scheduler
  - Thermo
  - UK Robotics
  - OpenSource

- Dell
- Panasonic
- Mediamarkt
- Wi-Fi

- Tecan
- BioTek
- Agilent

- BioTek
- BMG
- Thermo

- UK Robotics
- OpenSource
- Mediamarkt
- Wi-Fi
STANDARDIZATION IN LAB AUTOMATION

www.sila-standard.org
IMAGINE THE LAB OF THE FUTURE!

Inspirational examples of innovations that standardization will enable
LAB OF THE FUTURE

INSPIRATIONAL EXAMPLES

▸ Simplicity:
  1. Ad-hoc automation
  2. Distributed systems

▸ Complexity:
  3. Iterative experimentation
  4. Automated tissue culture

Simpler, cheaper, more flexible systems, for more scientists

Partially autonomous experimentation systems
SIMPLICITY

AD HOC AUTOMATION

From standalone devices...
SIMPLICITY

AD HOC AUTOMATION

... to an ad hoc system

SiLA
SIMPLICITY

AD HOC AUTOMATION

... to an *ad hoc* system
SIMPLICITY

DISTRIBUTED SYSTEMS

From a dedicated system...
SIMPLICITY

DISTRIBUTED SYSTEMS

... to distributed systems
SIMPLICITY

DISTRIBUTED SYSTEMS

... to distributed systems
SIMPLICITY

DISTRIBUTED SYSTEMS

blend into existing labs!
MISSING INNOVATION

SELF TEACHING LAB AUTOMATION

- casual users cannot be bothered with robot teaching
- *ad hoc* systems will not be mechanically rigid
- distributed systems share space with humans
MISSING INNOVATION

FREE-RANGE LABWARE TRANSPORTERS

- floor-based autonomous robots
- bench-based carrier vehicles
- quadrucopter plate carriers
ITERATIVE EXPERIMENTATION:
DRUG LEAD OPTIMIZATION
ITERATIVE EXPERIMENTATION:
DRUG LEAD OPTIMIZATION

“Automated Lead Optimization of MMP-12 Inhibitors Using a Genetic Algorithm”
S. D. Pickett et al., ACS Med Chem Letters 2010 (doi: 10.1021/ml100191f)

SynCar: An Approach to Automated Synthesis
Angelika Weber et al, Sanofi-Aventis,
ITERATIVE EXPERIMENTATION: YEAST MOLECULAR GENETICS

Towards Robot Scientists for autonomous scientific discovery

Andrew Sparkes¹, Wayne Aubrey¹, Emma Byrne¹, Amanda Clare¹, Muhammed N Khan¹, Maria Liakata¹, Magdalena Markham², Jem Rowland³, Larisa N Soldatova¹, Kenneth E Whelan¹, Michael Young³ and Ross D King¹

University of Manchester

“The Automation of Science”
RD King et al., Science 324, 85-89 (2009)
COMPLEXITY

REQUIREMENT SHIFT

from *multiplexing* ...

- repetitive experiments
- batch operation
- predetermined scheduling

to *complexity!*

- interlacing, asynchronous experiments
- open-end, iterative experiment cycles
- event-driven process control
**COMPLEXITY**

**EXAMPLE: AUTOMATED PATIENT TISSUE CULTURE**

patient derived reconstructed tissue, *eg,* skin

patient

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**iPSCs:** induced pluripotent stem cells (adult derived stem cells)

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Standards for Experimental Life Sciences

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COMPLEXITY

EXAMPLE: AUTOMATED PATIENT TISSUE CULTURE

- healthy patients
- multiple donor cohorts
- asynchronous processing
- multiple stem-cell markers
- multiple differentiation markers
- multiple disease biomarker readouts
- multiple tissues
EXAMPLE: AUTOMATED PATIENT TISSUE CULTURE

T-cell isolation: magnetic bead kit

de-differentiation: viral transduction kit

colony isolation: cell cultivation, mechanical colony disintegration

colony selection: cell seeding, cell cultivation, IF staining kits, HCS, image analysis

colony expansion: cell cultivation, controlled freezing, low temp. storage

differentiation: cell thawing, cell cultivation, differentiation kits

differentiation check: IF staining kits, HCS, image analysis

tissue reconstruction: cell cultivation, tissue printing, automated histology, IF staining kits, image scanning, image analysis

HTS: tissue cultivation, compound management, biomarker readout kits, data analysis
MISSING INNOVATION

STANDARD EXPERIMENT DESCRIPTION LANGUAGE

In analogy with computer programming languages:

- device-independent description of experiments
- complexity encapsulated into re-usable modules
- allows checking for syntax and logical consistency
- program execution may be manual and/or automated
MISSING INNOVATION

STANDARD EXPERIMENT DESCRIPTION LANGUAGE

http://www.jbioleng.org/content/4/1/13

JOURNAL OF BIOLOGICAL ENGINEERING

METHODOLOGY

Open Access

Biocoder: A programming language for standardizing and automating biology protocols

Vaishnavi Anantharayanan1*, William Thies2*

Max Planck Institute for Molecular Cell Biology and Genetics, Dresden; Microsoft Research India, Bangalore

Figure 1 Overview of the BioCoder system.

Figure 3 BioCoder example: Example BioCoder code for plasmid DNA extraction (excerpt). Steps 7-13 are omitted for brevity.
MISSING INNOVATION

STANDARD EXPERIMENT DESCRIPTION LANGUAGE

Combining ontologies and workflows to design formal protocols for biological laboratories

Alessandro Maccagnan¹,², Mauro Riva³, Erika Feltrin¹, Barbara Simionati⁴, Tullio Vardanega⁵, Giorgio Valle¹ and Nicola Cannata⁶

CRIBI Biotechnology Centre, University of Padua
MISSING INNOVATION

STANDARD EXPERIMENT DESCRIPTION LANGUAGE

BIOINFORMATICS

The EXACT description of biomedical protocols
Larisa N. Soldatova*†, Wayne Aubrey†, Ross D. King and Amanda Clare
Department of Computer Science, Aberystwyth University, Penglais, Aberystwyth, SY23 3DB, Wales, UK

Fig. 2. (1) Protocol from Methods in Yeast Genetics. (2) Protocol represented using EXACT. (3) Text generated automatically from EXACT representation.
MISSING INNOVATION

LAB STANDARDIZATION INITIATIVES

**Aim:** Standardization of device communication and lab data exchange

**SiLA**
sila-standard.org

- users (some big pharma)
- integrators (smaller)
- vendors (most large ones)

**Aim:** Experimental data file standardization

**AnIML**
animl.sourceforge.net

- vendors (most for MS)
- users (some big pharma)

**Aim:** Managing analytical data throughout its lifecycle

**Allotrope Foundation**
www.allotrope.org

- most of US big pharma
STANDARDS WILL COME!

The more we ask for them, the sooner this will happen.
LAB STANDARDS WILL COME

SUPPORT THEM TO BENEFIT SOONER!

- Propagate the idea of open standards in the lab, and demand vendors to implement them.
- Ask your institution to become a member of the standardization initiatives.
- Join the standardization communities, and contribute to the development of standards.
THANK YOU.