The optimal level of automation in a research environment (with protein crystallization as an example)

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Automation in Pharmaceutical Industry,
Leiden, Oct 11, 2011
UNIVERSITIES ARE:
- innovative in novel disease biology
- not successful in out-licensing their know-how and IP to pharma

PHARMA IS:
- withdrawing in early phase drug discovery
- intensifying in-licensing efforts

Increasing Value and Commercialisation Potential
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THE INNOVATION GAP

Increasing Value and Commercialisation Potential

NETHERLANDS TRANSLATIONAL RESEARCH CENTER
**Drug Discovery**

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<th>CELL-BASED ASSAYS</th>
<th>PROTEIN CRYSTALLOGRAPHY</th>
<th>MEDICINAL CHEMISTRY</th>
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**Fee-for-services**

- Initiative for Life Sciences Park Oss
- Team with > 10 years of drug discovery expertise in pharma (Merck, Schering-Plough, Organon)
- Focus on protein kinases
• **Joost Uitdehaag**, *protein expression and X-ray crystallography*
  – 2002-2009 Biotech section of Organon / Schering-Plough
    • introduced protein crystallography as a technique internally
    • responsible for its automation
    • determined 100s of structures with my group
  – 2009-2011 Group leader in kinase assay design and screening
Protein crystallography can show how small molecules bind to their protein target.

In this way, more directed chemical changes can be made in optimization.
Quick overview of the experimental cycle

- Pure protein
- Crystallization
- Fishing in a loop
- Structure elucidation
- Data collection
- Mounting
Automation of protein crystallography

- 1960-2000: development of the technique in academia
- 1990-2000: adoption in the pharmaceutical industry
- 2000-2005: structural genomics initiatives

Call for automation

Rigaku automated crystallization system at PSI - La Jolla

Imaging and crystallization robots at Syrrx, San Diego (now Takeda)
Joint Center for Structural Genomics setup

- JCSG Pipeline: Integration of custom and commercial instrumentation into a HT structural genomics pipeline.
- Data capture to central DB parallels the experimental pipeline. Currently collecting 520 parameters from 32 stages.
- GUI and data flow back to the experimental pipeline.
- Feedback to the experimental pipeline: Target selection & management
- Expanding interaction with community: TOPSAN wiki, KB
How to choose the optimal level of automation?

- all-manual ‘traditional’ approach
  - low throughput / low investment

- ultra-automated structural genomics setup
  - high throughput / high investment

**common sense parameters**

- does it make experiments cheaper?
- does it make experiments faster?
- does it give access to new types of experiments?
Can Lean Methods be useful?

- Lean is a method to increase efficiency by minimizing waste.
- There are seven types of waste (in the original Toyota factory).
- Can they guide us in choosing automation? Does it improve.....
  or does it introduce...
  - transportation: does it prevent shipments of reagents?
  - inventory: does it reduce reagent diversity and stocks?
  - motion: does it bring facilities closer to scientists?
  - waiting: does it reduce waiting times in experiments?
  - over-processing: does it reduce experimental steps?
  - over-production: does it allow working with more appropriate volumes?
  - defects: does it reduce failed experiments?
  - continuous improvement: does it give access to new types...
Automation of crystallization

Scientists spend large amount of time setting up drops
- reduce volume of drops (save protein)
- decrease time in drop preparation
- allows more massive screening of conditions

96-well crystallization plate
96-well protein dispensers
pre-made crystallization screens

Cartesian honeybee  TTP Mosquito  Cartesian presys
In-house data collection

Outsourcing data collection is slow and expensive
- reduce time lost in sending x-tals away
- reduce costs of testing lots of crystals
- increase turnover time

Rigakuy 007HF diffractometer
Bruker microstar diffractometer
Automated crystal imaging

Evaluating crystal conditions at microscope is tedious work
- facilitate the evaluation of images on computer
- assure proper timeframes and archiving
- detect time-dependent crystal formation / using UV light

Formulatrix RockImager  Bruker Crystal Farm  Rigaku Minstrel

...unfortunately no automatic crystal detection
Conclusions

• Automation in protein crystallography can serve as a model for many areas in life sciences
• Types of waste suggested by the Lean method can assist in making the proper choices
• More automated is not always more efficient (the outputs from structural genomics efforts were initially quite disappointing)
• An organic growth scenario, in which bottlenecks are resolved in turn, works for protein crystallography
• In a medium throughput lab, dispensers and diffractometer access are the most essential investments to achieve state-of-the-art
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