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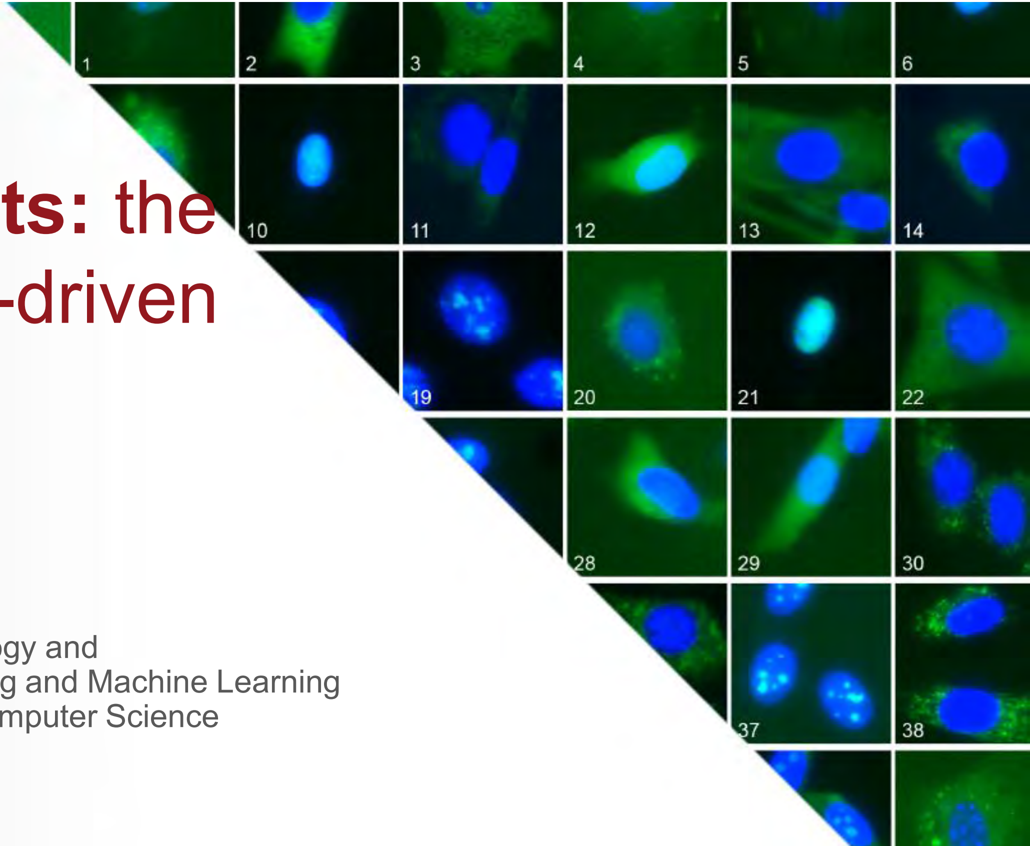

Self-driving instruments: the need for closed loop, AI-driven biomedical research

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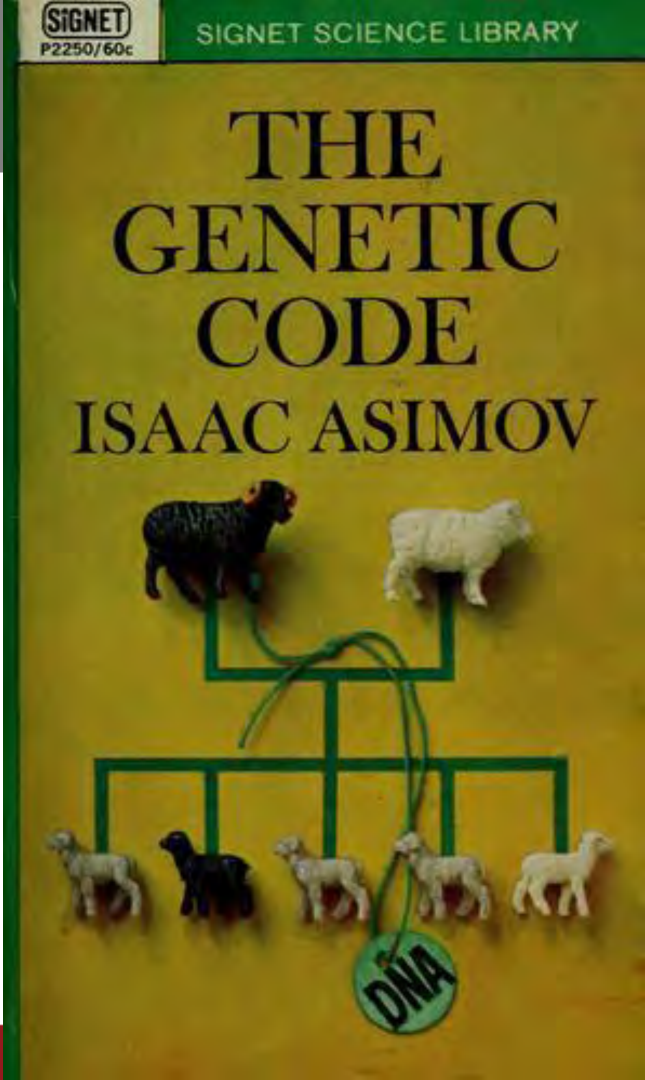
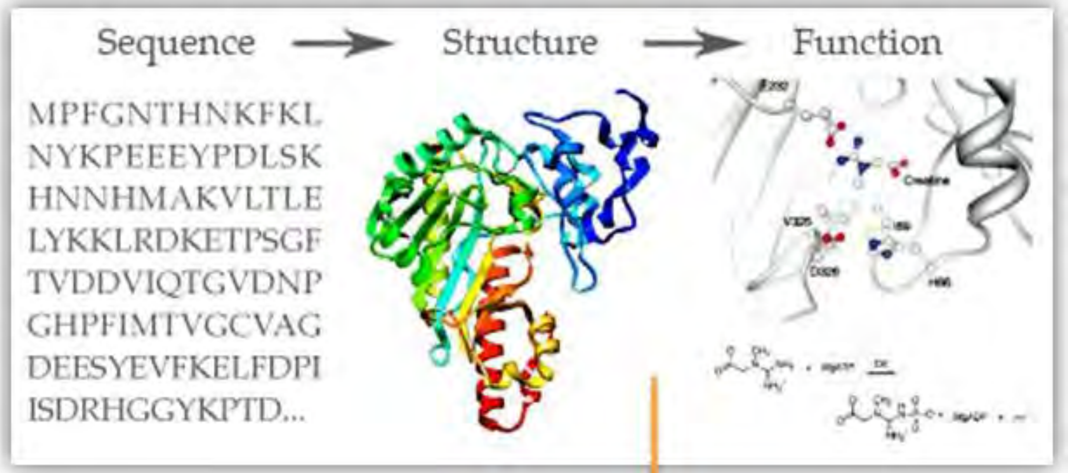
The glory days of reductionism

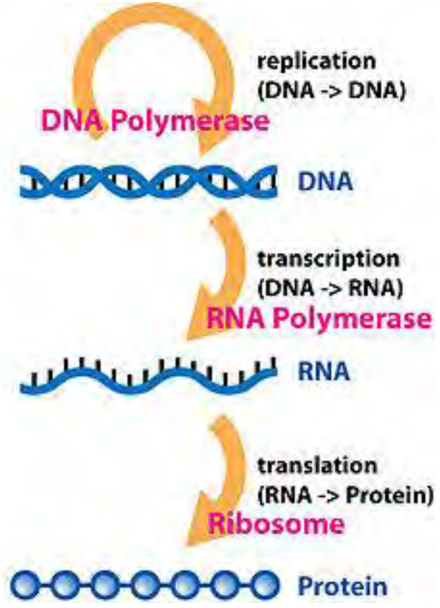
- *Drosophila* Genetics
- Watson-Crick DNA structure
- The Genetic Code
- Biochemistry of Metabolism
- Receptors, channels
- Organelle structure/function
- DNA recombination



Biological laws and principles

- The Central Dogmas
  - DNA >> RNA >> protein
  - Sequence >> Structure >> Function





By the 1970’s, exceptions begin to rule

- Horizontal gene transfer
- Transposons
- Reverse transcriptase
- Introns and alternative splicing
- Prions
- Disordered proteins
- Chaperones
- RNA interference / Non-coding RNA
- Epigenetic modification

Biomedical research: What doesn't work

- Reductionism fails because cells, tissues, and organisms are **complex systems**
- Engineering simplified biological systems to study in order to learn rules fails because **there are no rules**
- Systems biology approaches that do a block of experiments, build a predictive model and try to validate it fail because **you can't prove an empirical model**

Why we need AI-driven biomedical research

- We need to accept
  - biological complexity
  - absence of rules
  - inability to measure everything
- Which means
  - human understanding is not possible
  - we can only build predictive, empirical models
  - we can’t expect to be able to prove, interpret or explain them
  - need continuous AI-driven experimentation to *improve* models not test them
  - hypotheses are useless but specific predictions can be
  - humans can’t be relied upon to decide what experiments to do

Solution?

- Use ***active*** machine learning/iterative design of experiments
- Choose experiments not to ***prove*** model but to ***improve*** model

- **Illustration:**
  Drug Discovery

NATURE CHEMICAL BIOLOGY | VOL 7 | JUNE 2011

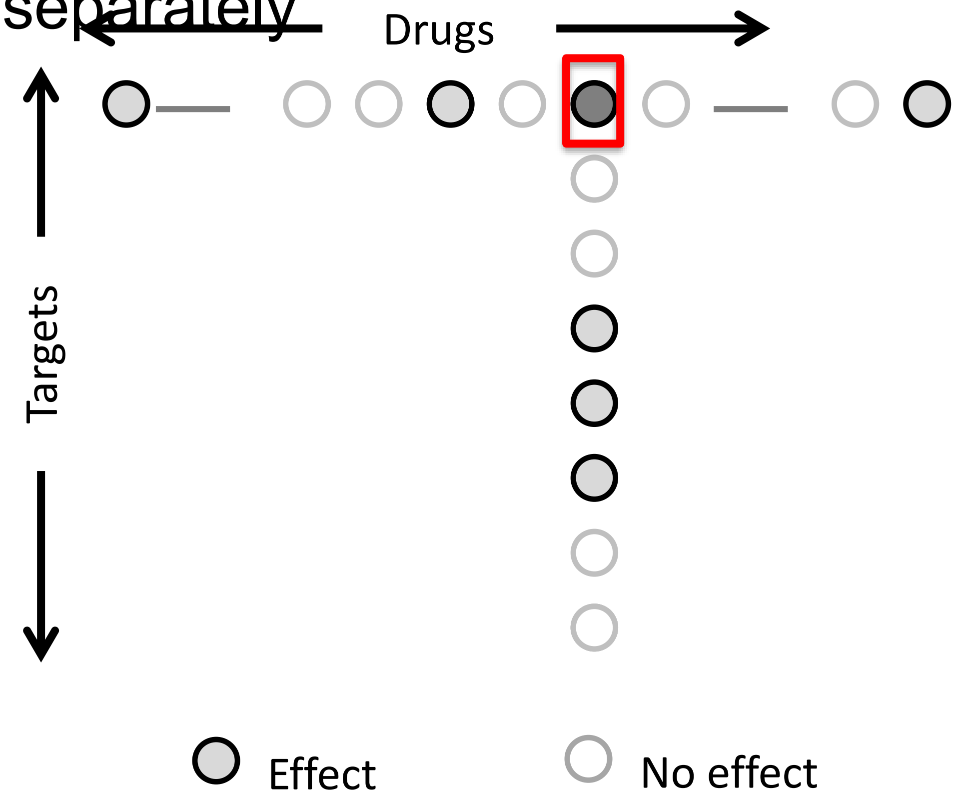
commentary

An active role for machine learning in drug development

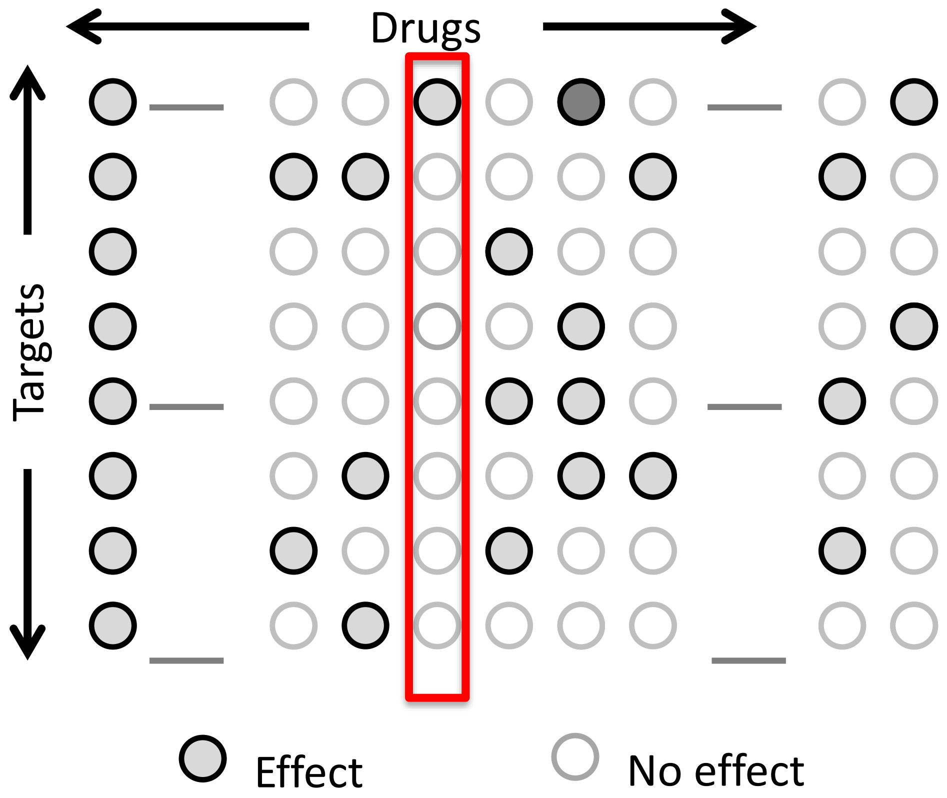
Robert F Murphy

Because of the complexity of biological systems, cutting-edge machine-learning methods will be critical for future drug development. In particular, machine-vision methods to extract detailed information from imaging assays and active-learning methods to guide experimentation will be required to overcome the dimensionality problem in drug development.

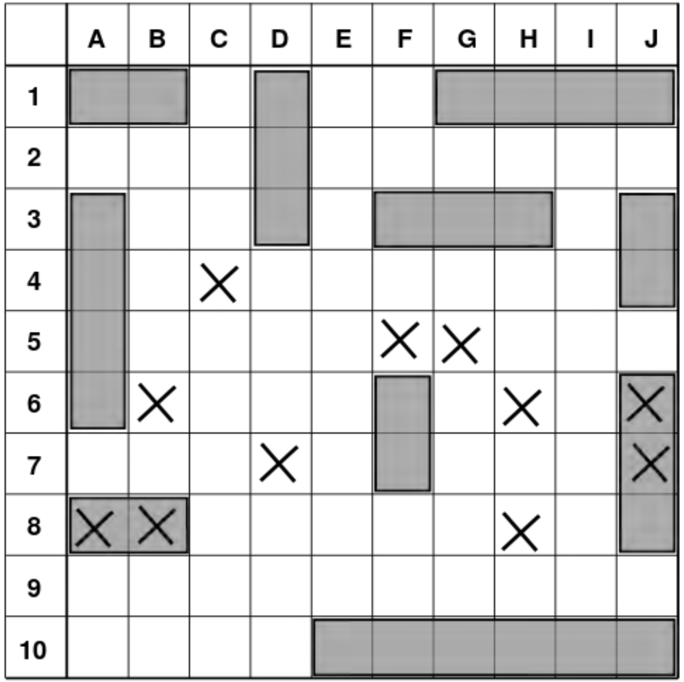
Typical drug development: consider each target separately



Where we'd like to be: measure all drugs for all targets



Playing Battleship with Drugs and Cells

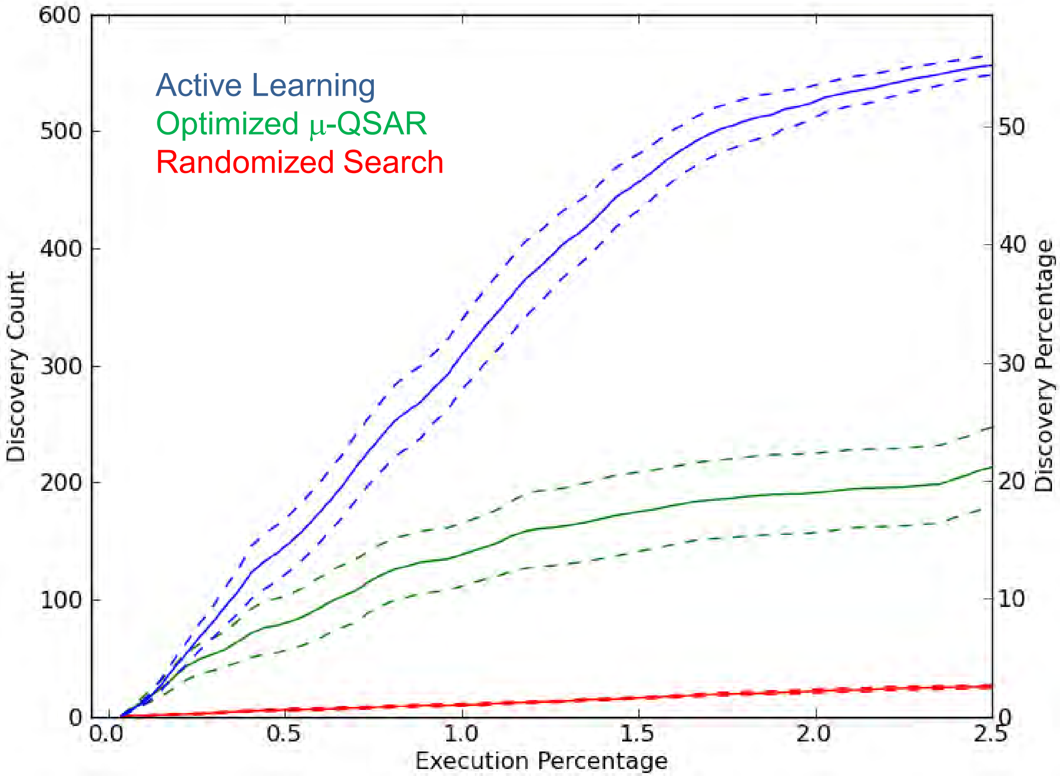


Retrospective Test: Use data from PubChem

- Assays: 177
- Unique Protein Targets: 133
- Compounds: 20,000
- Experiments: ~1,000,000 (30% coverage)
- Use features to measure similarity between drugs and between targets
- Compare discovery rate across different methods

With only **2.5%** of the matrix covered, we can identify **57%** of the active compounds using active learning

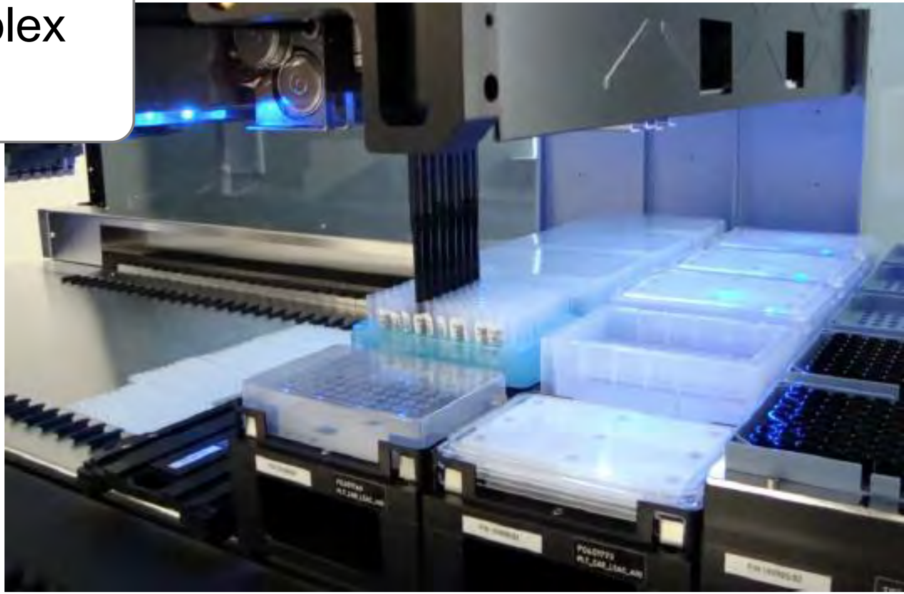
Kangas, Naik, Murphy, BMC Bioinformatics 2014



First *Prospective* Use of Active Learning for Complex System

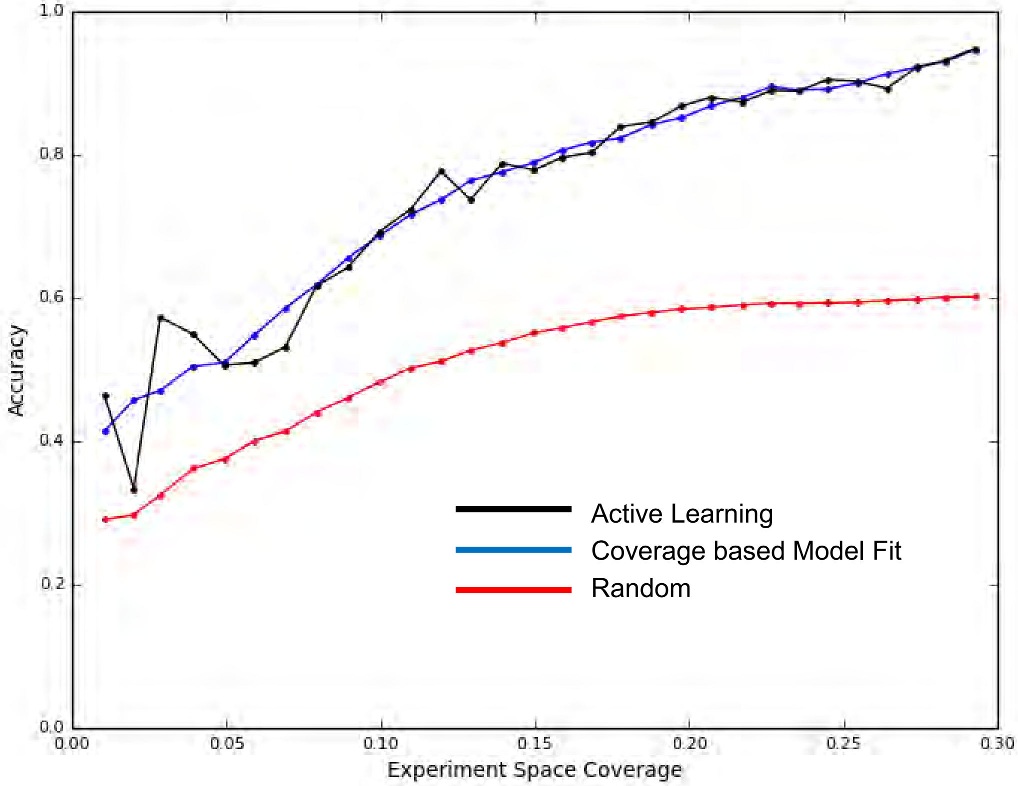
Use **laboratory automation** to execute experiments chosen by **AI** to model complex phenotypes

Try to learn the effects of 96 drugs upon 96 GFP-tagged proteins: have to learn phenotypes on the fly



After doing 28% of possible experiments, model is 92% accurate and 40% more accurate than would have been obtained by random choice of experiments

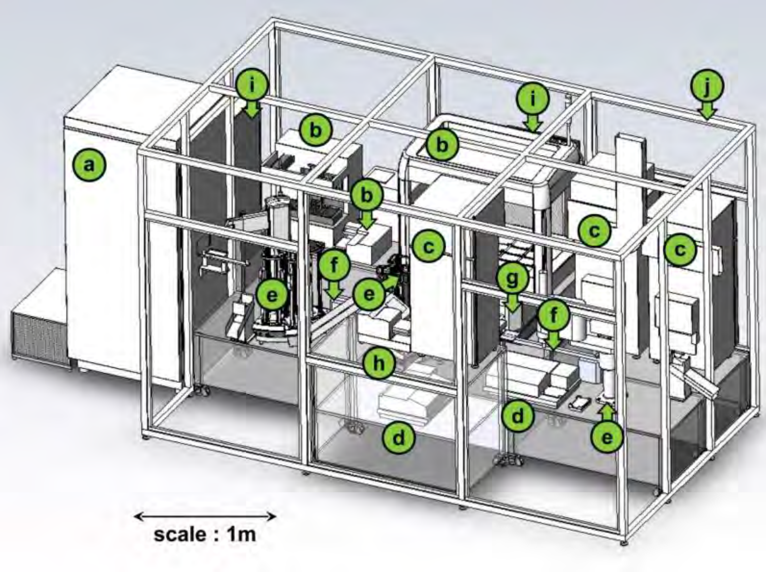
Naik, Kangas, Sullivan, Murphy, eLife 2016



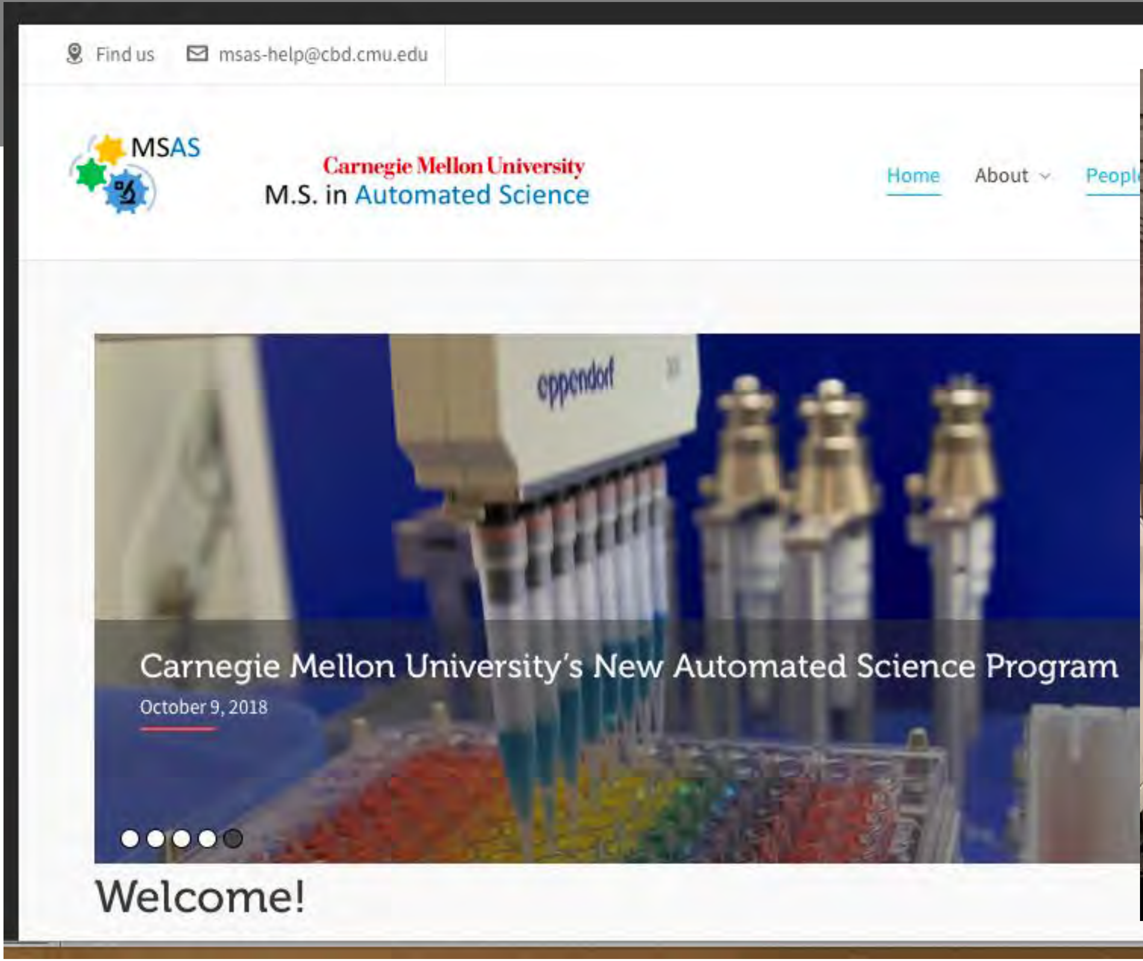
Automated Science

- The combination of *laboratory automation* plus *artificial intelligence* creates unique opportunities to expand research capabilities
- Analogous to self-driving cars: self-driving instruments

- Need better standards for laboratory automation
- Need trained experts



King et al, Science, 2009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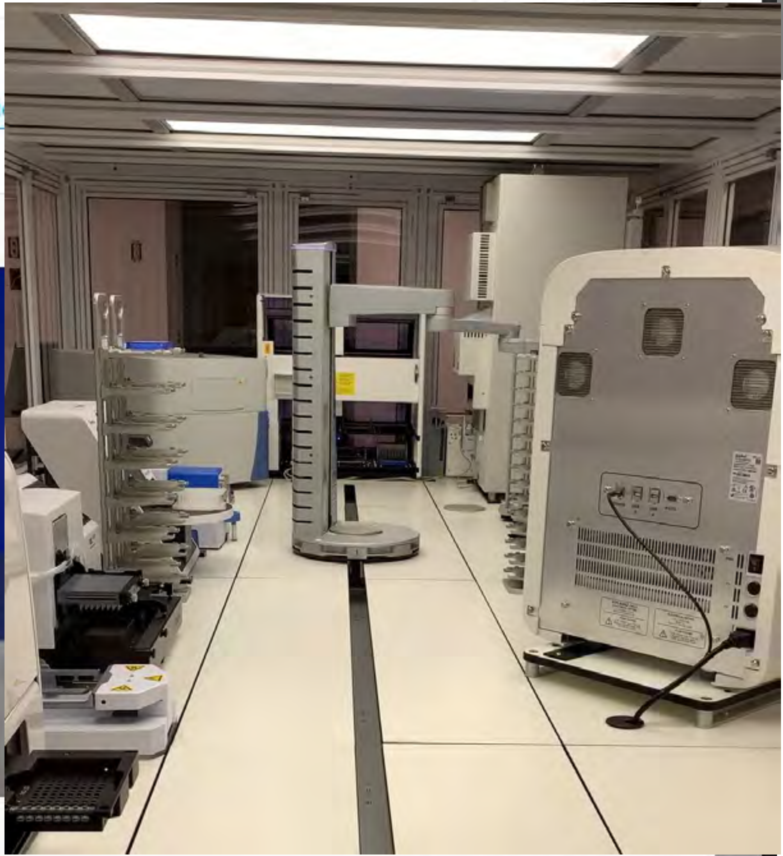

The future?

- **Autonomous** laboratory automation
- Real-time primary data sharing (and standardization)
- National research resources that execute particular types of automated experiments on request – enabling cost-sensitive, proactive learning
- Training of researchers to
  - **Choose** goals and define campaigns combining diverse technologies
  - **Invent** new measurement technologies
  - Develop and improve AI methods

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