A Vision of Advanced Manufacturing

Richard D. Braatz

Outline

- Some Definitions
- A Vision of Advanced Manufacturing
- A Sketch of What Needs to be Done
- A Biomanufacturing-on-Demand Platform
- Closing

What is Advanced Manufacturing?

- “The use of innovative technology to improve products or processes” (wikipedia)
- “A high rate of technology adoption and ability to use that technology to remain competitive and add value” (CTI Reviews)
- “Manufacturing that entails rapid transfer of science and technology into manufacturing products and processes” (White House 2014)

What is Smart Manufacturing?

- Industry 4.0?
- The cloud?
- Cyber-physical systems?
- Industry Internet of Things?
- Smarter than what industry is currently doing?

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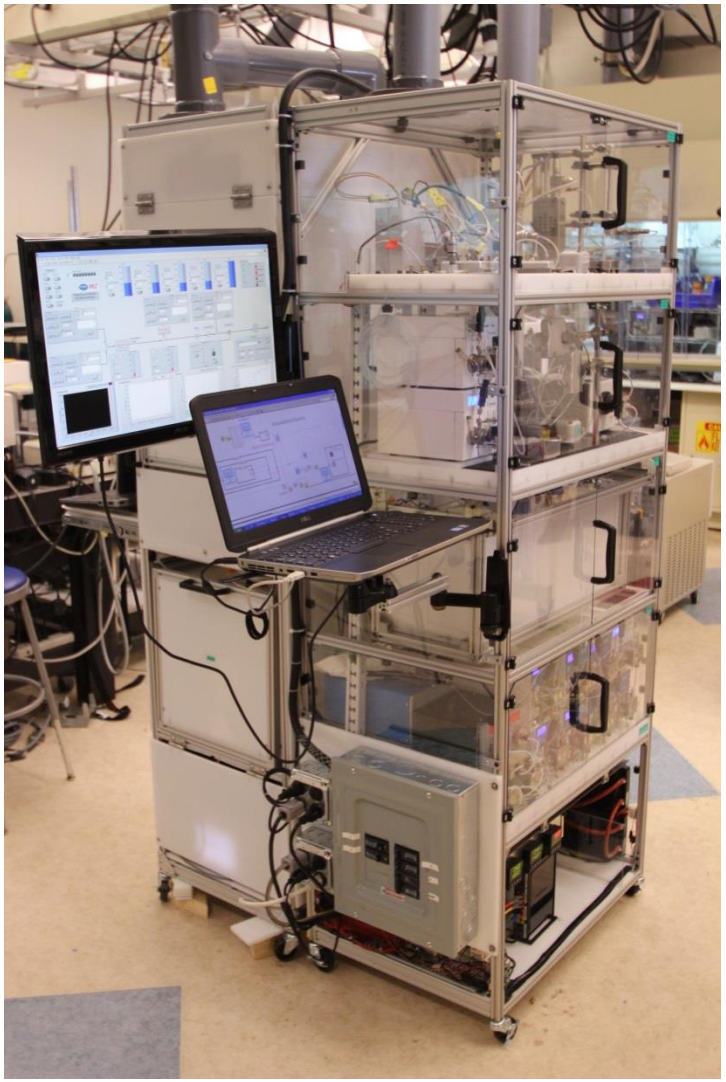
Automated System for Knowledge-based Continuous Organic Synthesis*

- A fully automated chemical synthesizer that produces, purifies, characterizes, and scales a wide range of organic molecules
- Includes
  - knowledge-based computational tools for reaction pathway & PFD prediction
  - process automation and control
  - interconnected fluidic modules for continuous synthesis, in-line characterization, purification, and formulation
- Speed the pace of chemical innovation and provide an accessible chemical synthesis platform for non-specialists

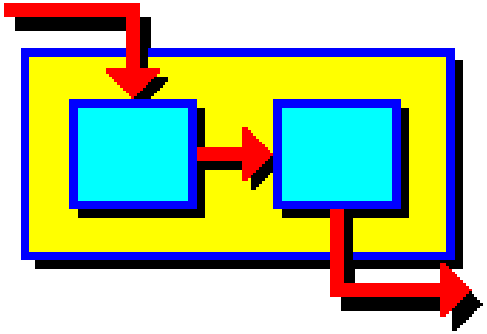


* http://www.darpa.mil/program/make-it

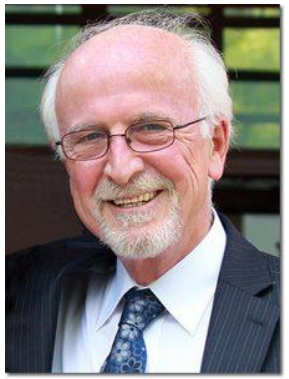
Science, 352(6281):61-67, April 1, 2016

Relationship to MODEL.LA*

1. A computer-aided phenomena-based modeling laboratory that supports synthesis, modeling, and analysis activities in chemical engineering ✓



2. MODEL.LA enables process models to be constructed in terms of interacting physical and chemical phenomena written in an English-like syntax, not as sequences of hard-wired unit operation models or as sets of mathematical equations



3. Based on the assumed phenomena and structure, the complete set of model equations is derived from first principles ✓

replace #2 with automatic PFD construction

* G. Stephanopoulos, G. Henning, and H. Leone, "MODEL.LA, A Modeling Language for Process Engineering .1. The Formal Framework," *Comput. Chem. Eng.*, *14*, 813-846 (1990), web.mit.edu/modella

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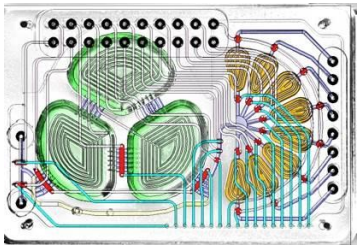
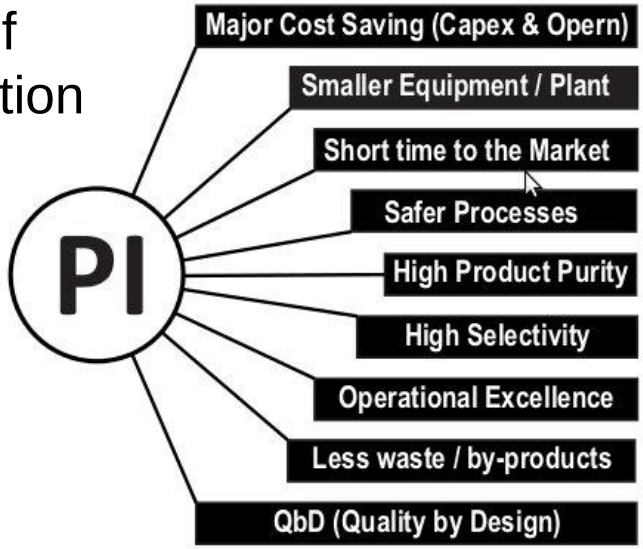
A Sketch of What Needs to be Done

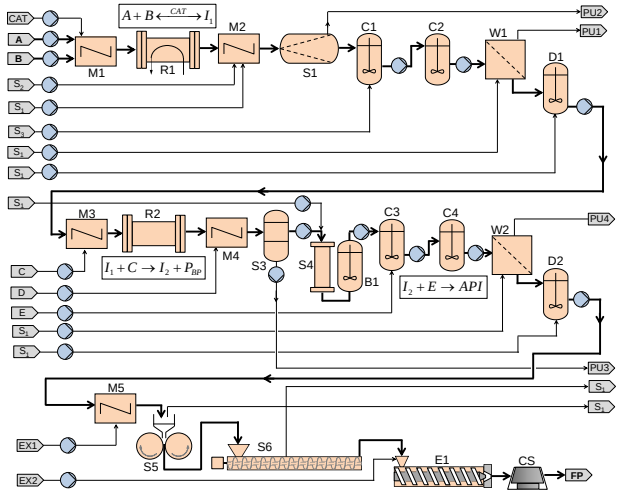
- Greatly increased understanding & optimization of each unit operation, exploiting process intensification
- Automated high-throughput microscale technology for fast continuous process R&D



- Plug-and-play modules with integrated control & monitoring to facilitate deployment

- Dynamic models for unit operations for automated plant-wide simulation & control design
- Autonomous model-based control technologies for optimizing operations including startup, changeover, and shutdown

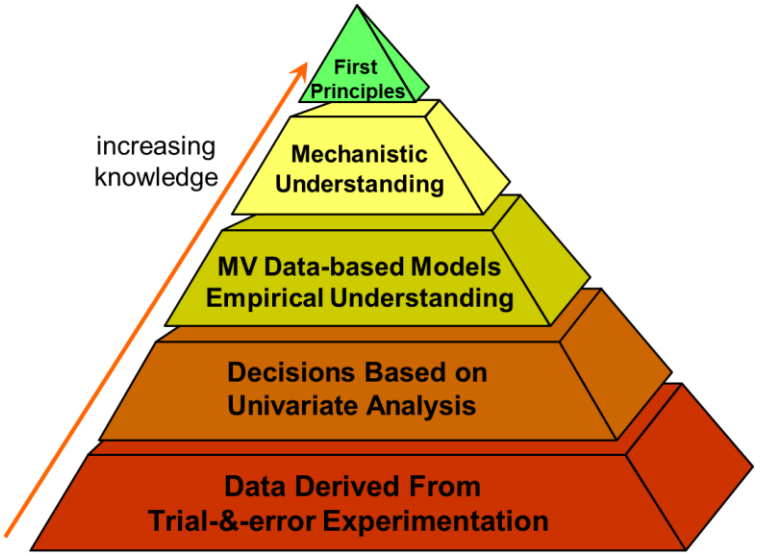


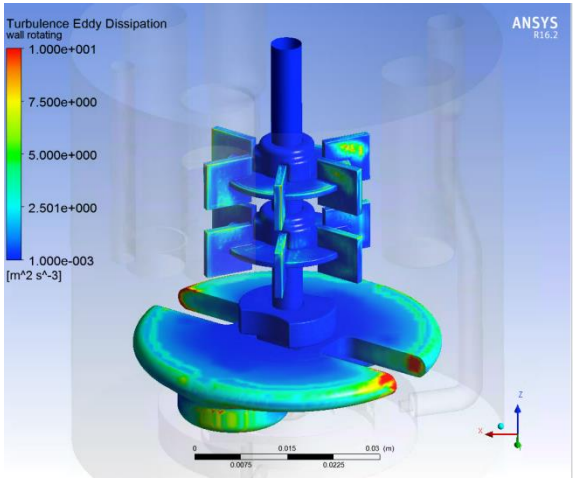


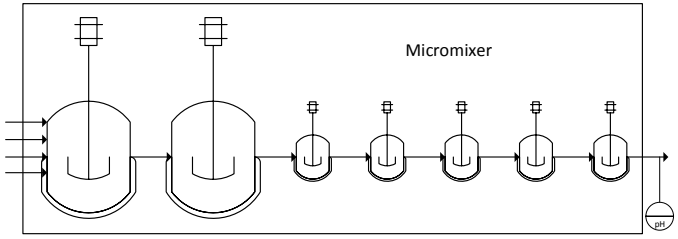
pi-inc.co, www.pharyx.com/technology.html, *Angew. Chem. Int. Ed.*, 52(47):12359-12363, 2013

Design of Control Systems Based on “Virtual Plant”

- Constructed from first-principles models wherever possible, grey-box models where necessary
- Highest complexity models used for the invention and optimization of process designs and development
- Lower complexity plant-wide model runs in parallel with process operations, for process control and quality and equipment condition monitoring
- Goal is “right first time”

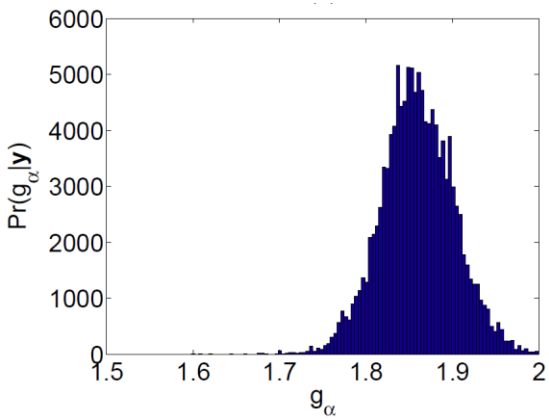






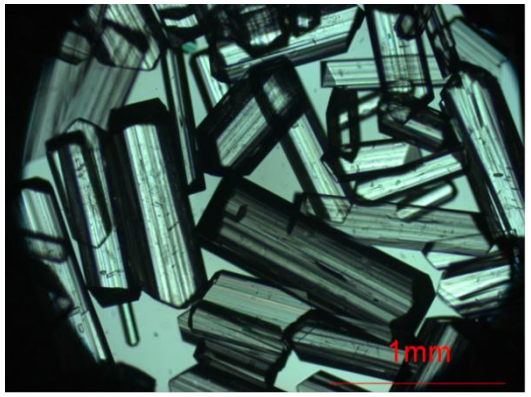
What is Available and What is Needed in Advanced Manufacturing Control Technology

- The best commercial plant simulation software handles nonlinearities, time delays, unstable zero dynamics, constraints, mixed continuous-discrete operations, and some uncertainty analysis methods (e.g., S_i, Monte Carlo)



- More advanced uncertainty analysis tools can be wrapped around or integrated into such software
- Distributed states facilitated by moment analysis, transforms, characteristics, finite volume methods
- More research needed on automating tuning, reducing on-line computations, proving stability, and optimizing startup/changeover/shutdown

→ especially for <u>time-invariant probabilistic uncertainties</u>



Ind. Eng. Chem. Res., 53:5325-5336, 2014; *AIChE J.*, 54:1449-1458, 2008; *AIChE J.*, 54:3248-3259, 2008

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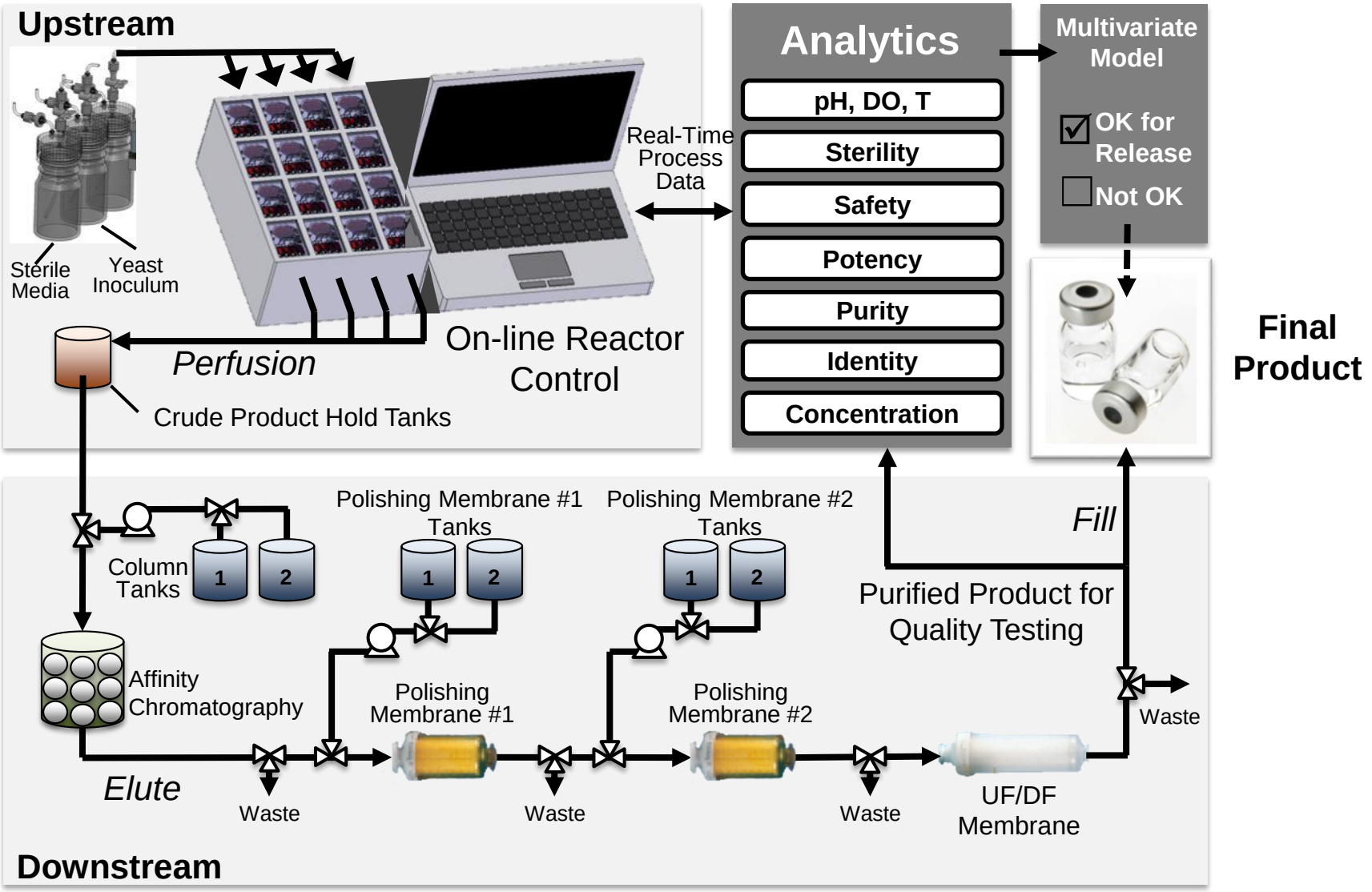
A Biomanufacturing-on-Demand Platform

Design ← Requirements ← Patient

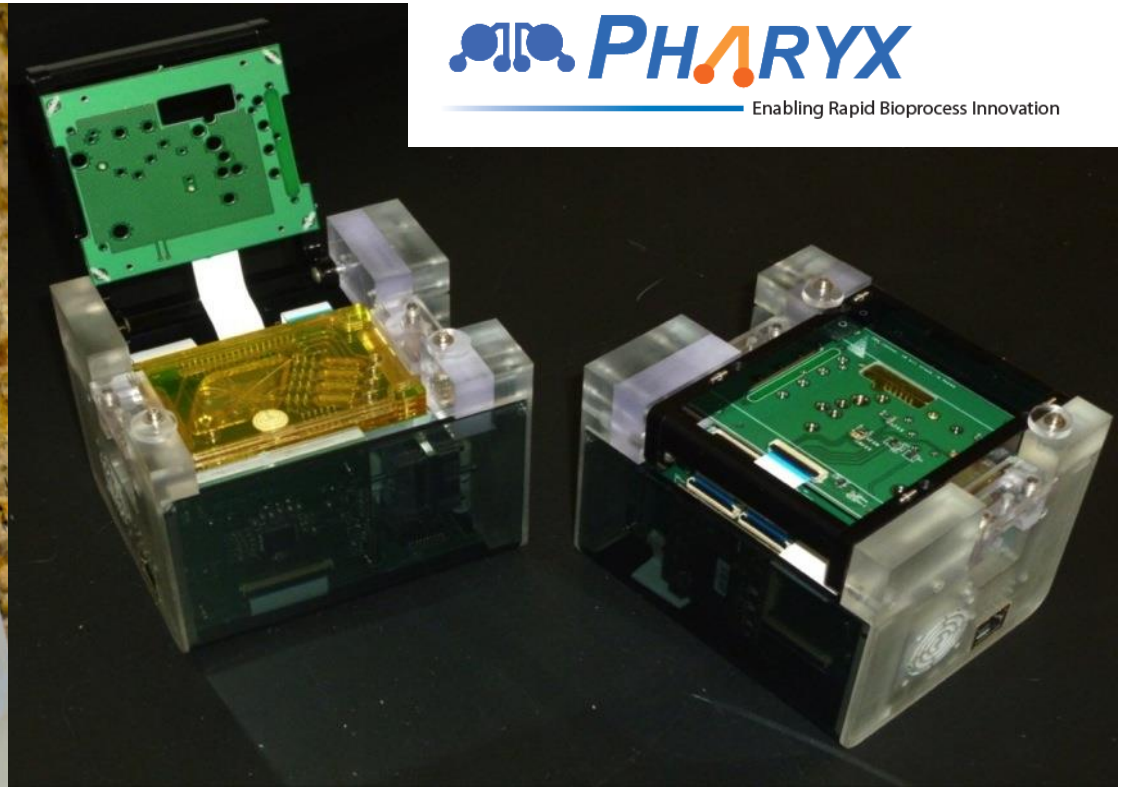
- Enable flexible methodologies for genetic engineering/modification of microbial strains to synthesize multiple and wide-ranging protein-based therapeutics
- Develop flexible & portable device platforms for manufacturing multiple biologics with high purity, efficacy, and potency, at the point-of-care, in short timeframes, when specific needs arise
- Include end-to-end manufacturing chain (including downstream processing) within a small-scale platform

Integrated and Scalable Cyto-Technology (InSCyT) Biomanufacturing Platform



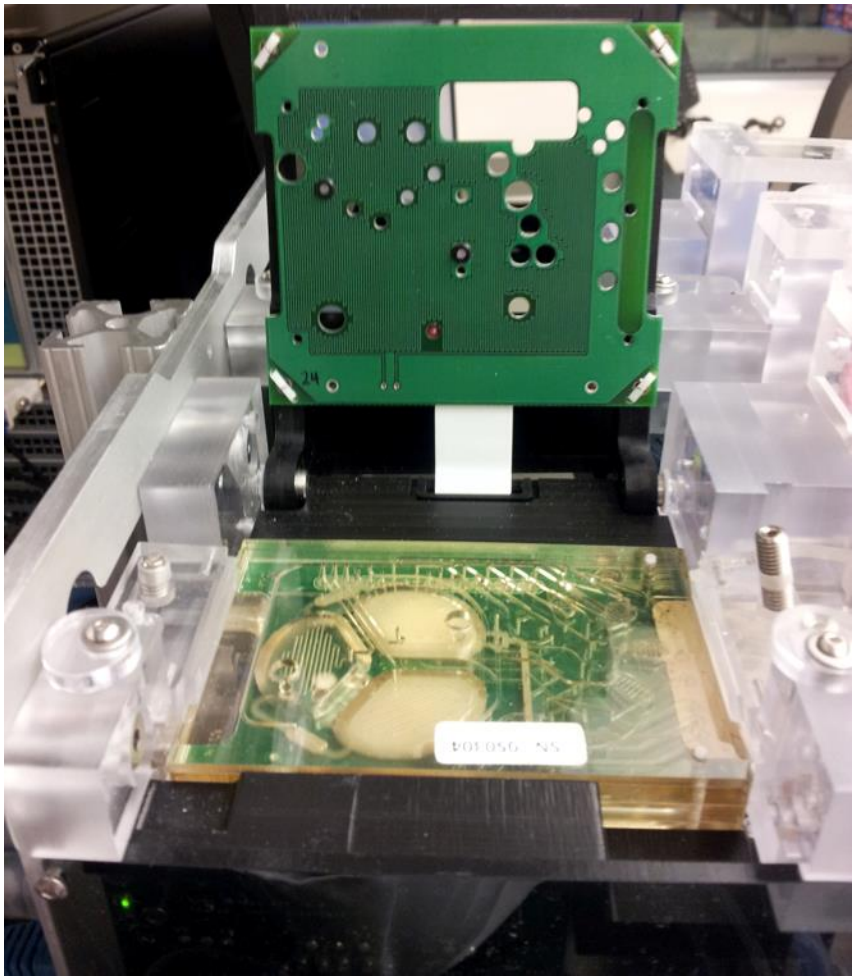
J.C. Love, Towards making biologic drugs on demand, 4th Int. Conf. on Accelerating Biopharmaceutical Development, January 25, 2015

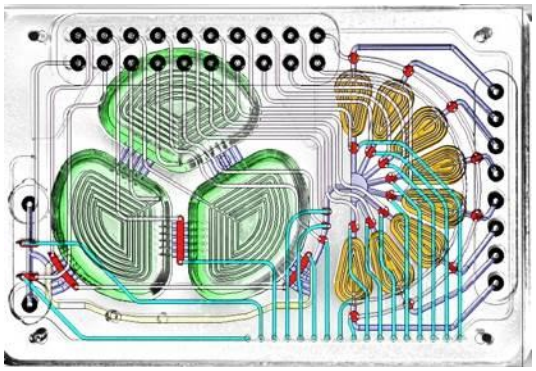
Upstream process development



PHARYX
Enabling Rapid Bioprocess Innovation

Microscale Controlled Cell Culture

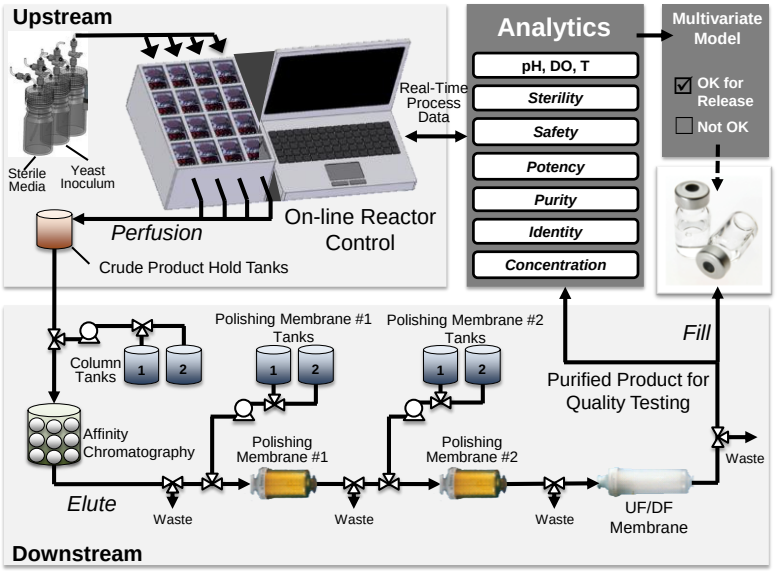




Plant-wide Control Approach

System Characteristics

- Multi-product manufacturing plant
- Continuous & discrete operations
- Dynamics, nonlinearities, distributions, uncertainties, constraints, disturbances
- No SS & must align with regulatory requirements (no off-spec product)



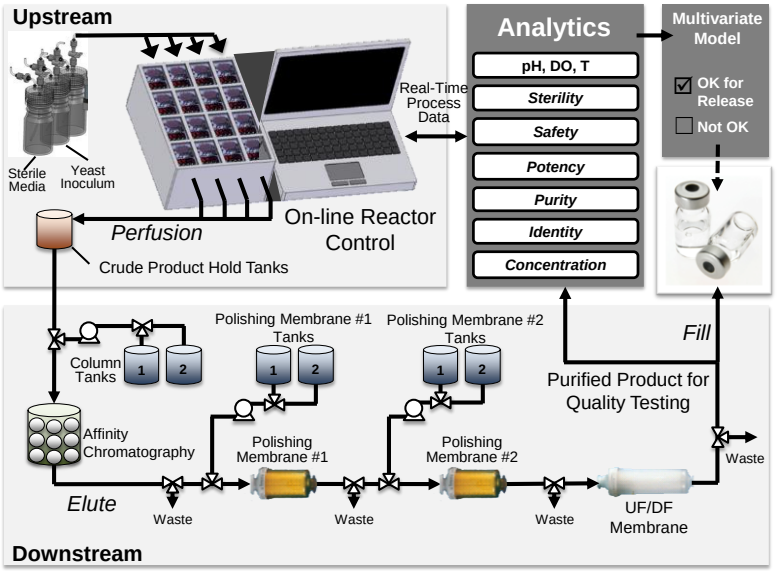
Approach adapted from the chemical industry

- Employ systematic & modular design of plantwide control strategies for large-scale manufacturing facilities (Stephanopoulos/Ng, JPC 2000)
- Employ algorithms that can handle nonlinearities, distributed states, unstable zero dynamics, time-invariant probabilistic uncertainties, constraints, time delays, and mixed continuous-discrete operations

A.E. Lu, J.A. Paulson, N.J. Mozdzierz, A. Stockdale, A.N. Ford Versypt, K.R. Love, J.C. Love, R.D. Braatz (2015). Control systems technology in the advanced manufacturing of biologic drugs. Proc. of the IEEE Conference on Control Applications, 1505-1515.

Plant-wide Control Approach

- Build first-principles dynamic models for each unit operation (UO)
- Design control system for each UO to meet “local” material attributes
- Evaluate performance in simulations and propose design modifications as needed
- Implement and verify the control system for each UO
- Design and verify plantwide control system to ensure that the product quality specifications are met



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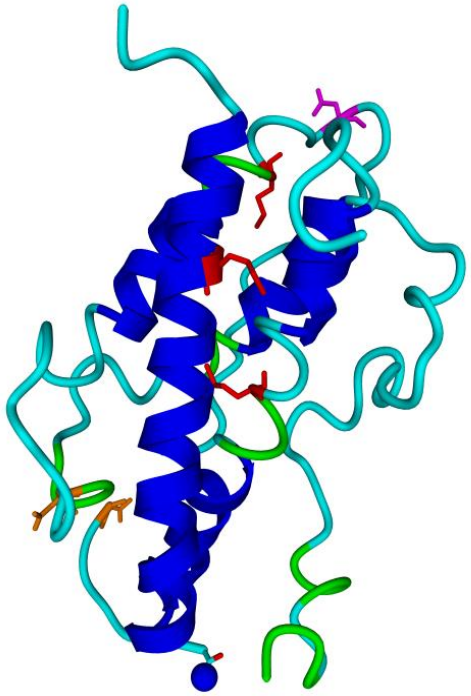
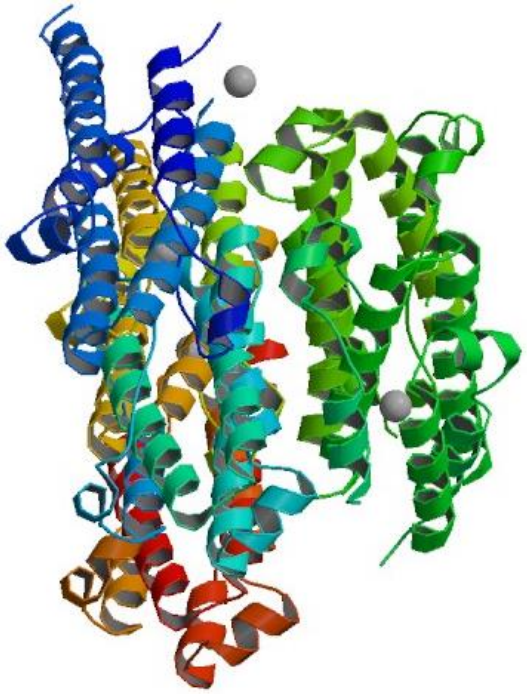
Biologic Drugs Produced



Human growth hormone

Used for treatment of growth disorders



Interferon–α2b

Used for treatment of cancers and viral infections

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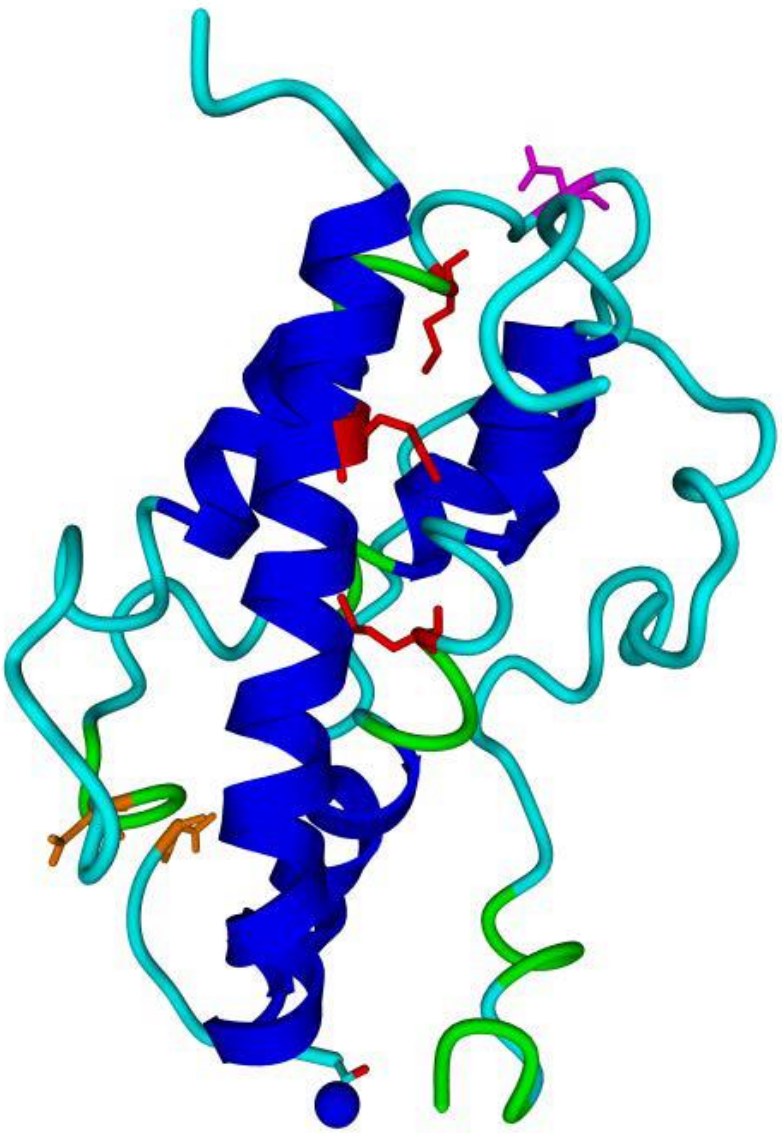
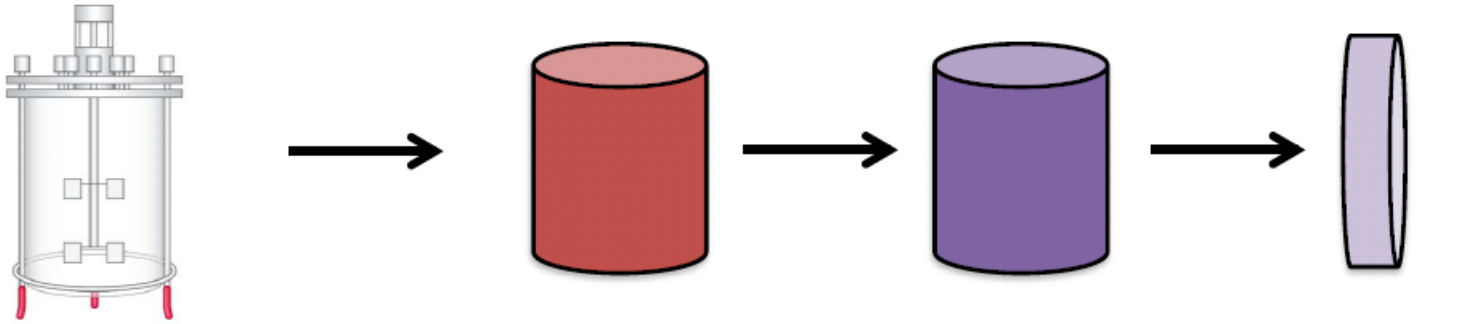
First Product: Human Growth Hormone (hGH)



- Indication: adult growth hormone deficiency
- Product purity > 95%
- Cleaved forms < a few %
- Aggregates < 1%
- HCP < 1000 ppm/dose
- DNA < 100 pg/dose

Cumulative Timeline for Integrated Production



Titer: ~100-150 µg/mL

	Outgrowth and Production	Affinity capture	Polish 1	Polish 2
Timing	40-44 h	**Load:** 3 h **Wash:** 0.17 h **Elute:** 0.17 h	0.17 h	0.12 h
Recovery				2+ mg (65-80% yield)

Single purified maximum adult dose of hGH achieved in ~ 48 h

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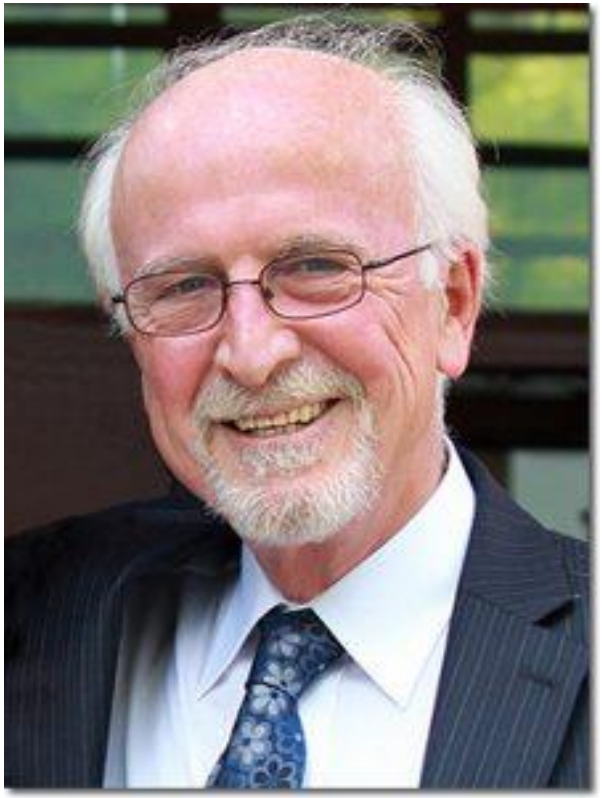

colleague, mentor, friend