The new age of digital biomanufacturing

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The new age of digital biomanufacturing

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Introduction

Advances in bioprocess monitoring and analytics, as well as in bioinformatics and computational biology, are changing the way we look at the bioproduction process. Heightened computing power and connectivity, automation, and robotics are enabling this revolution. New in-line probes and automated at-line sampling feed high-throughput analytics which are producing data-lakes to be processed. Powerful computing hardware, flexible and connected data storage capacities, and advanced interfacing and control algorithms determine a quantum leap in manufacturing capability. Adaptive fuzzy expert systems now employ artificial intelligence to provide a continuous optimization of process performance using previously developed metabolic models and data from current processes as well as historic data. Digital biomanufacturing is demonstrating its power in improving process development and operational performance, as well as quality systems and regulatory compliance.

Background

Drivers of the digital biomanufacturing revolution (Fig 1)

- Increase and better data appearing in biomanufacuring
- Recently harnessed data lakes gain new and deeper insights
- Calls for operations efficiency, robustness, and productivity
- New bioprocess knowledge, metabolomic and flux analysis

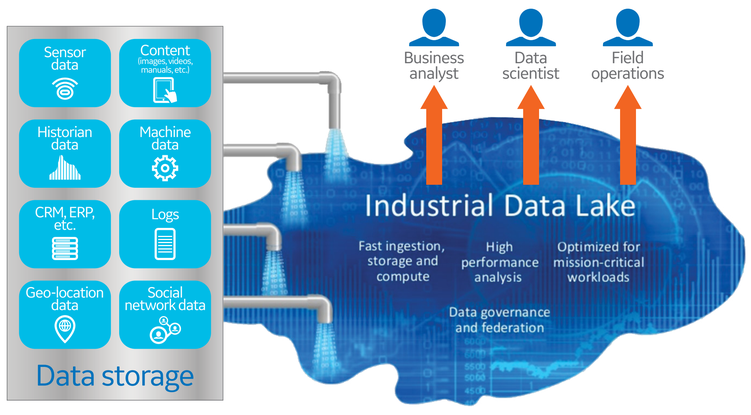


Fig 1.

Table 1

Information technology enablers of digital biomanufacturing
Advanced interfacing, process analytics, and control algorithms
Big Data: effective management of large and complex data sets
Adaptive fuzzy expert system now employ artificial intelligence
Flexible and affordable data storage and cloud hosting
Laboratory information management systems (LIMS)
Industrial internet of things (IIoT) and cloud computing
FDA-regulated suitable software providing traceability/backup
Analytical QbD (AQbD) or QbD as applied to analytical methods

Table 2

Biotechnology enablers of digital biomanufacturing
Advanced process engineering, analytics equipment, at-line assay
New in-line (SU) probes and automated at-line (cell-free) sampling
Rapid at-line 2D fluorescence; near/mid-IR; Raman spectroscopy
Near-real time concentration measurements using CFCA methods
At-line surface plasmon resonance specificity, kinetics, and affinity
Intriguing microfluidic platform-based at-line cell-condition analytics

Materials

Insilico Cells™ are mechanistic network models of prokaryotic and eukaryotic host organisms. Insilico Discovery™ is used for network reconstruction, calibration, and simulation. Insilico Designer™ enables in-silico medium optimization. Insilico Inspector™ provides in-depth process performance analysis and comparison by intracellular flux analysis. Insilico Controller™ (in development) enables automated process control. GE's Predix™ platform is an industrial Internet platform supporting both GE and non-GE assets. GE's UNICORN™ system control software supports systems from single PD operations to multiple units in regulated manufacturing.

Results

Intelligent software applications support process development and control (Fig 2)

- Databases using data collected online, at-line, and offline from bioprocesses operating worldwide
- Process data are used to generate metabolic network models that represent a specific host cell line in a bioprocess
- Model-based computational simulations improve process understanding and reduce experimental efforts for media design, clone selection, and metabolic engineering
- Automated data import and processing allow for a streamlined and standardized metabolic process analysis
- Identification of critical metabolic parameters is used for proactive steering of production processes

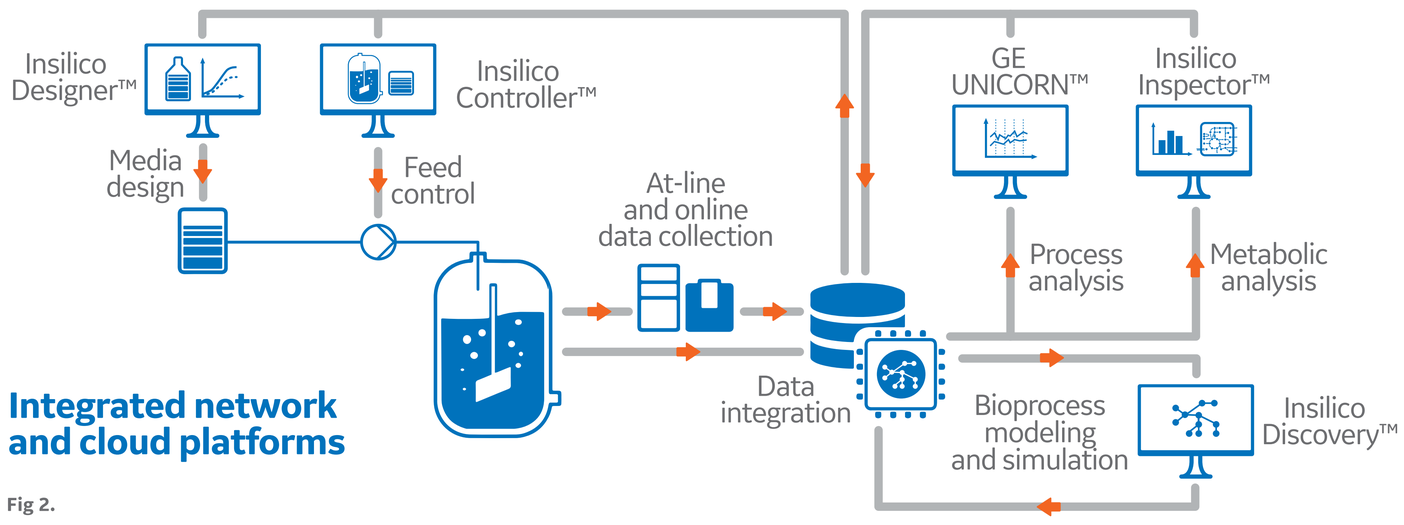


Fig 2.

Using bioprocess data in process modeling and simulation (Fig 3)

- Data from a bioprocess are combined with omics data to generate and calibrate an in-silico model of cellular metabolism as a representation of a specific host cell line and bioreactor
- Insilico Discovery allows for visual network reconstruction, omics data integration, and bioprocess simulation for media development, feed optimization, or metabolic engineering.

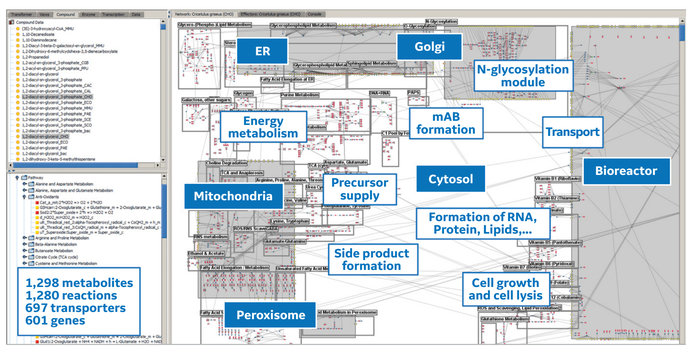


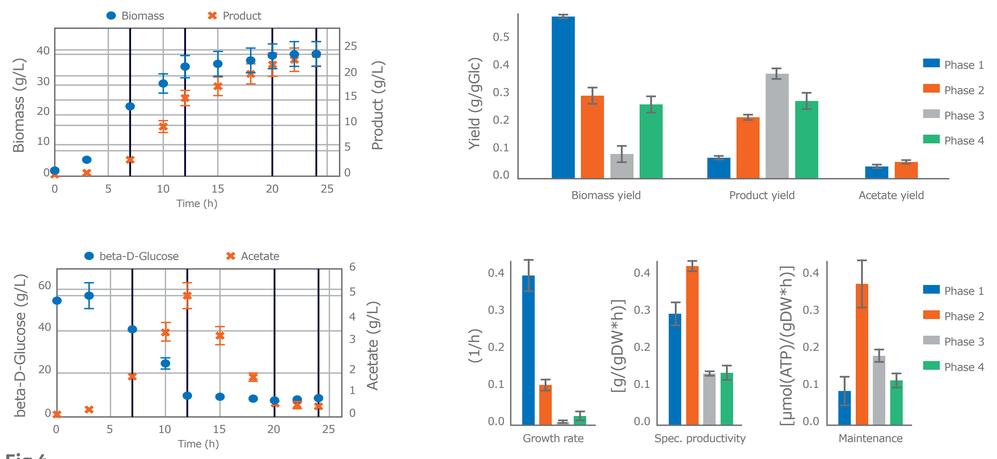
Fig 3.

Features of advanced operating systems, such as GE's Predix platform

- Software platforms for building and managing industrial internet applications
- Enables industry to optimize assets and operations with scalable architecture
- Machine intelligence and big data analytics from small machines to the cloud
- Development of apps that look at what is, then compare it to what should be
- Make current machines "brilliant" by optimizing both the process and assets

Deep metabolic analysis of cell culture bioprocesses by Insilico Inspector (Fig 4)

- Employing on- and at-line sourced comprehensive bioprocess data
- Metabolic fluxes are calculated and compared
- Process phases are identified and analyzed statistically. Bioprocesses can be automatically ranked by customized scores
- Metabolic indicators of process performance are identified and used in preemptive process control.



Name	E.coli Ferm. 11	
Product titer	24±1.4	g(Prod)/L
Biomass yield	0.35±0.018	g/gGlc
Product yield	0.23±0.016	g/gGlc
Acetate yield	0.0022±0.0019	g/gGlc

Phase	Start (h)	End (h)
Ph 1	0	7
Ph 2	7	12
Ph 3	12	20
Ph 4	20	24

Fig 4.

Features of advanced control, such as GE's UNICORN software

- Software that supports research, PD, and manufacturing
- Flexible "futureproofed" software grows as your needs do
- Keeps data secure, yet allows sharing of methods/results
- To plan, control, analyze columns, bioreactors, filtration
- Scalable, regulatory compliant, computer-type agnostic

Discussion and conclusions

Digital biomanufacturing is being driven by advances in bioprocess monitoring and analytics, computing hardware power and connectivity, as well as bioinformatics and computational biology. Gains in bioprocess design and dynamic control are moving from research to commercialized products. Forward-thinking suppliers are providing products and services enabling next-generation automated applications. But, the products available now are only the beginning of a revolution toward science-based increased plant-wide efficiency, quality, adaptability, and profitability. Process Performance Qualification (PPQ) and such lifecycle-based initiatives as Continuous Quality Verification (CQV) and Continued Process Verification (CPV) are greatly supported by improved control of short- and long-term variability, as well as more effective primary control strategies resulting from enhanced development approaches. Furthermore, business initiatives such as Enterprise Resource Planning (ERP) are advanced by the deep understandings provided by analysis of comprehensive historic manufacturing data.

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