The digital biomanufacturing revolution

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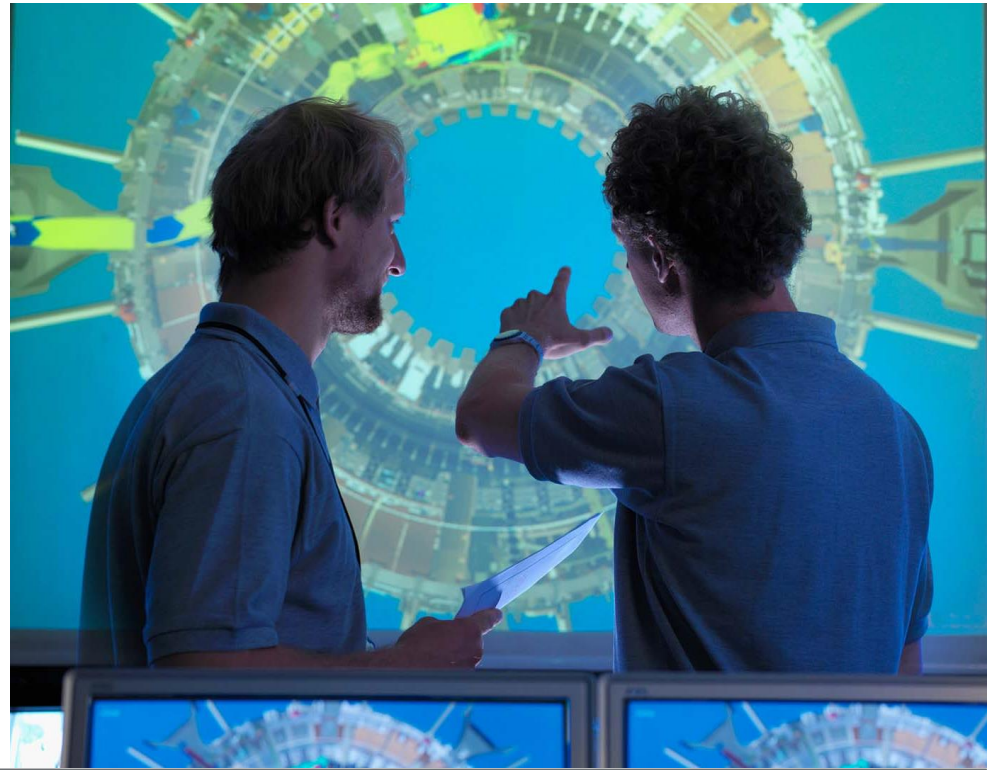
Agenda

Digital biomanufacturing

Bioprocess control trend

Monitoring developments

Conclusion



Digital biomanufacturing

Biomanufacturing current state

Blind to history: disregarding data lakes, past runs

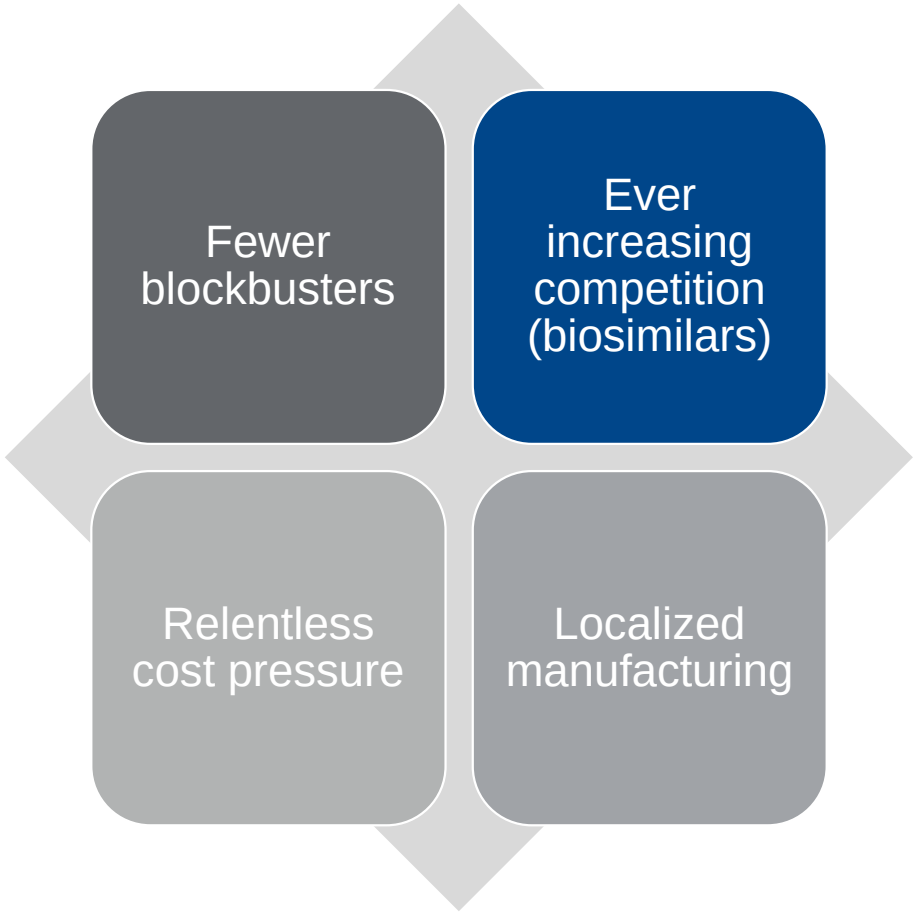
- Minimal and simple CPP
- Only essential KRI / KPI
- Instant performance blind
- Past-run result data blind
- Rudimentary PLC / MES
- Low / absent connectivity
- Many negative surprises
- Can’t see third party risks



LinkedIn Slideshare: Agomuoh Paul Kelechi Cyprus International University 2011

CPP- critical process parameter
KRI- key risk indicator
KPI- key performance indicator
PCL- programmable logic control
MES- manufacturing execution systems

Biopharmaceutical development and manufacturing is complex / competitive



Desired outcomes

- Higher plant utilization
- Higher productivity, titer/yield
- Higher efficiency across the plant
- Less variability, failures, and waste
- Multi-product, flexible manufacturing
- Higher manufacturing quality standards

Digital manufacturing

- Explosion in monitoring, analytics and new computing capability
- Artificial intelligence, automation and robotics are operating now
- From product development to materials supply to factory operations
- Connectivity between operations, design engineers, academic leaders
- Small-molecule drug manufacturers now exploit for continuous processes



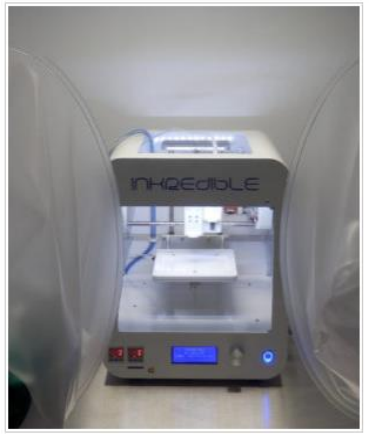
Courtesy David Gothard: http://www.davidgothard.com

Digital biomanufacturing (DB)

- Features similar to digital manufacturing
- Living components (i.e. cells) involved
- Adds different factors and systems
- Similar concepts in other terms
  - Biomanufacturing automation
  - Next Gen biomanufacturing
  - Smart technology
  - Industry 4.0

Digital Biomanufacturing Will Enable Tissue Bioprinting

The Cell Culture Dish





FOCUS ON... MANUFACTURING

The Era of Digital Biomanufacturing

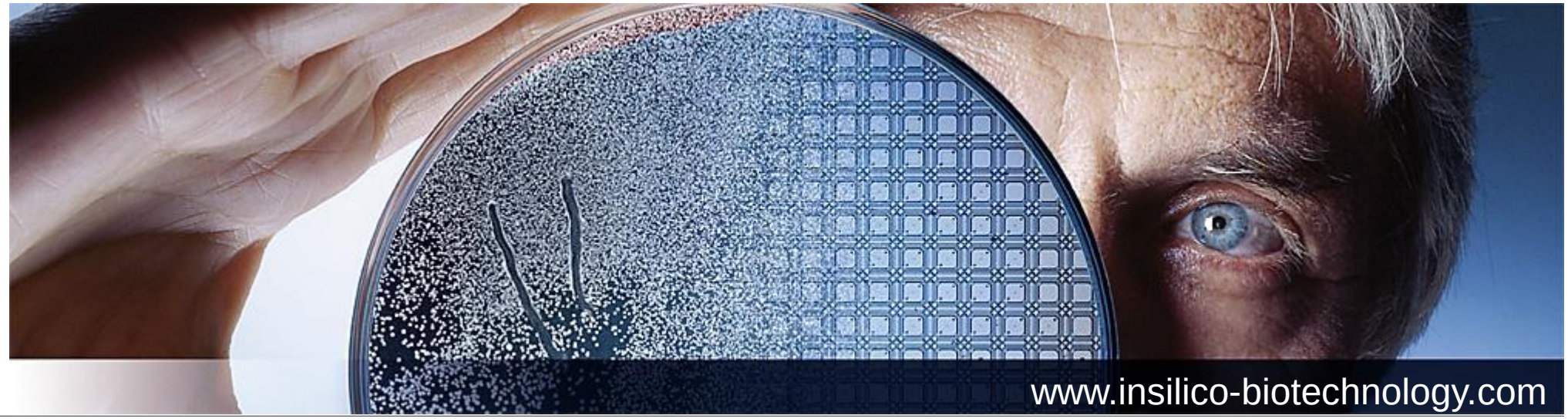
William Whitford

The digital revolution in manufacturing began with an explosion in monitoring, analytics, and new computing capabilities. Combined with such advances as artificial intelligence (AI), automation, and robotics, they are changing our concepts of manufacturing in general — from product development and factory operations to materials supply. This evolution also brings connectivity between product and process designers and leaders in manufacturing engineering. Digital manufacturing (DM) isn't a dream or a concept on some advanced developer's design table; it's occurring now and will

Whitford W, BioProcess Int. 15(3) 2017:12–18
Courtesy www.bioprocessintl.com

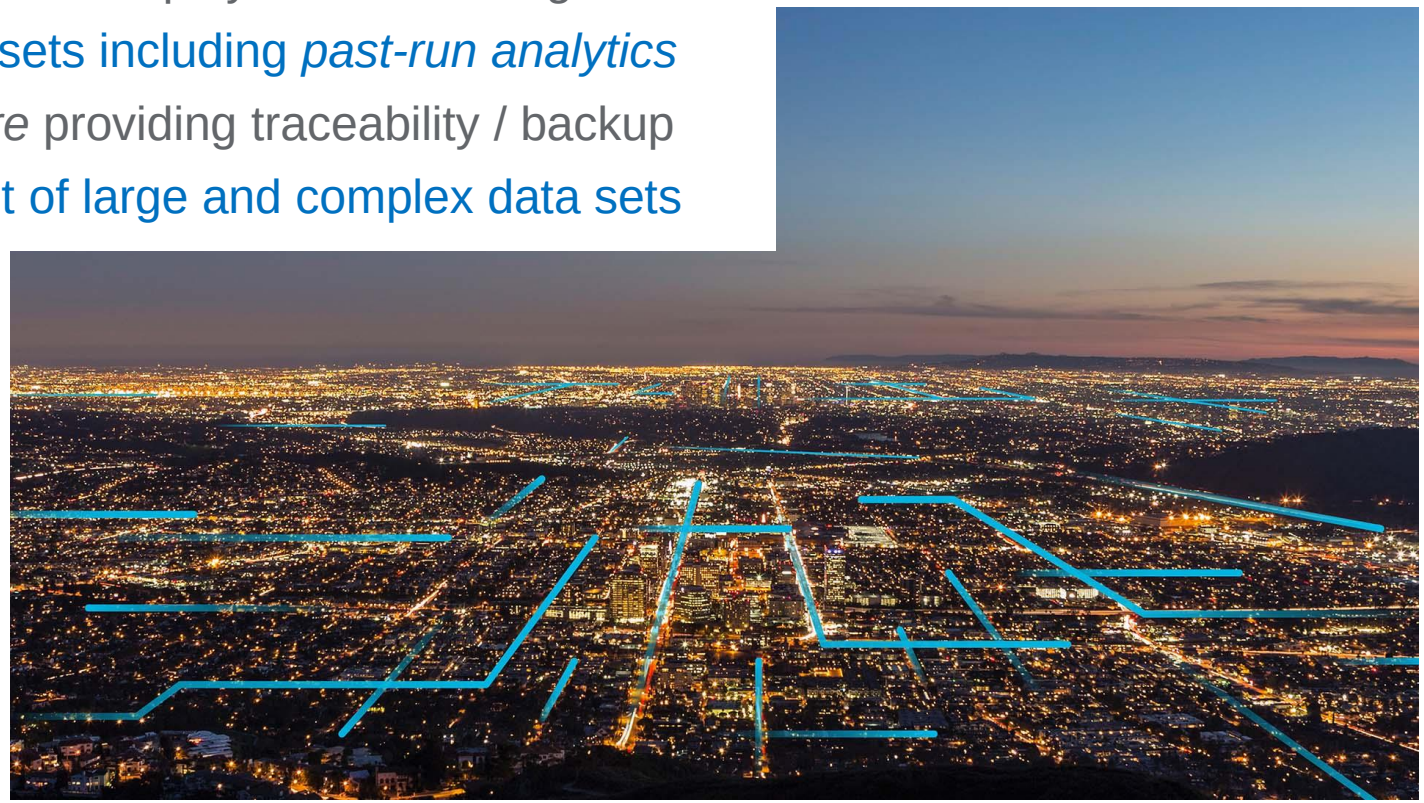
Digital biomanufacturing (DB) drivers

- For many years, *more and better data* in biomanufacturing
- Interest in *process flexibility*, real-time quality assessment
- Calls for *operations efficiency*, robustness and productivity
- New *bioprocess knowledge*, metabolomic and flux analysis



DB IT enablers A

- Powerful *processors,* data storage, interfacing and cloud hosting
- Advanced interfacing, process analytics and controls *algorithms*
- Adaptive fuzzy expert systems now employ *artificial intelligence*
- Control with built-in knowledge sets including *past-run analytics*
- *FDA-regulation suitable software* providing traceability / backup
- *Big Data:* effective management of large and complex data sets



DB- digital biomanufacturing
IT- information technology

DB IT enablers B

- *Industrial internet of things* (IIoT); object linking/embedding (OLE)
- *Analytical QbD* (AQbD) or QbD as applied to analytical methods
- *OPC server* / clients link organization's manufacturing hardware
- *OLAP* (online analytical processing) data discovery, calculations
- Beyond simply Hadoop*, data/source-agnostic platforms* growing
- *Metadata catalogs* enable selection of relevant and worthy data

Hadoop is an open-source software for storage and processing of big data

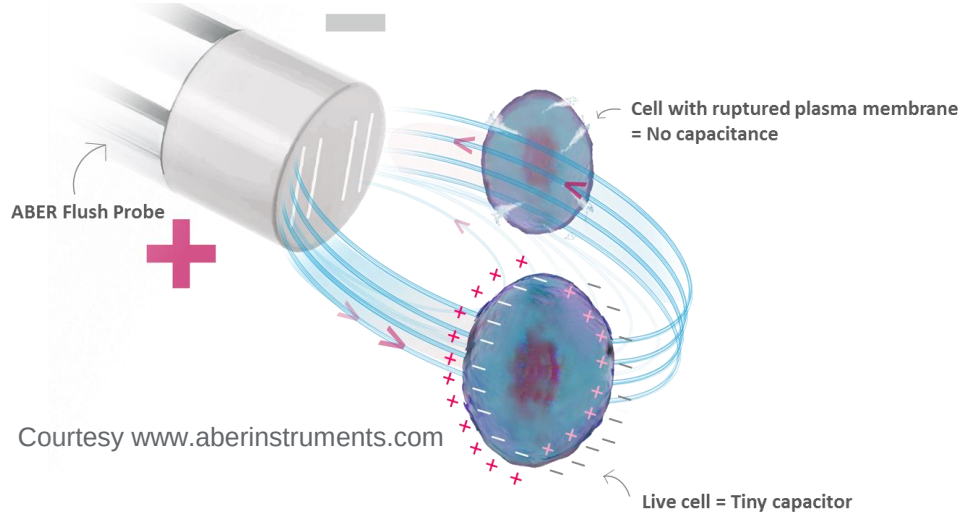


Features of The BioAnalyst™ www.biointelligence.com

DB- digital biomanufacturing
IT- information technology

DB biotech enablers

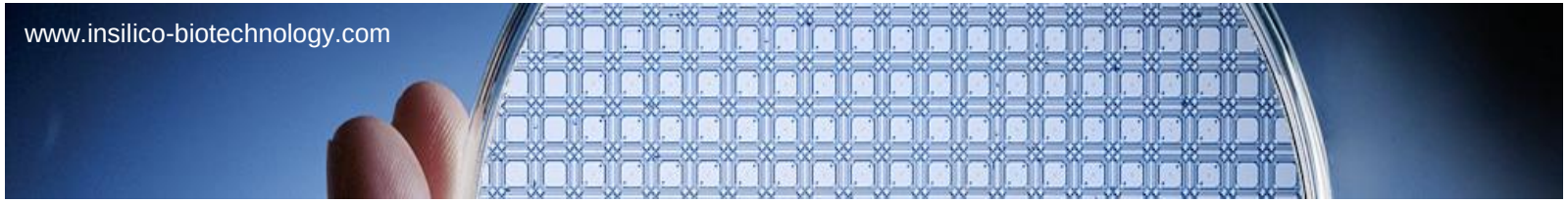
- Advanced process engineering, analytics equipment*, at-line assay*
- New in-line (SU) probes and automated *at-line (cell-free) sampling*
- Rapid at-line 2D fluorescence; *near / mid-IR;* Raman spectroscopy
- Near-real time concentration measurements using *CFCA methods*
- *At-line surface plasmon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



SU- single use
CFCA- Calibration-free concentration analysis
DB- digital biomanufacturing

DB features A

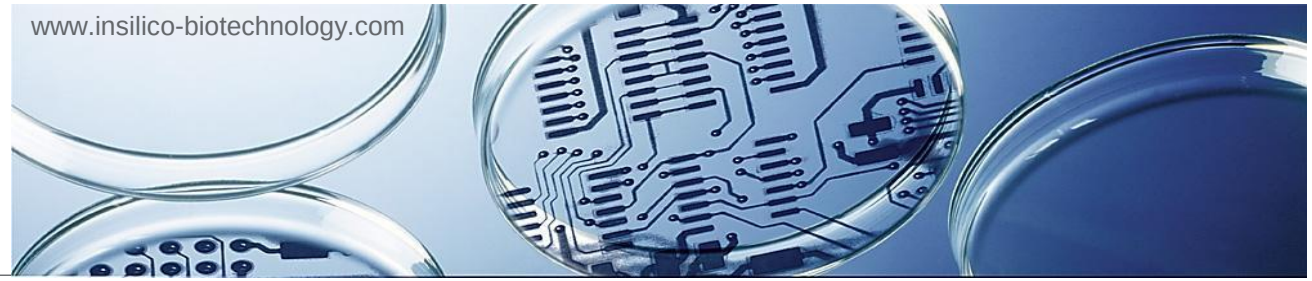
- *Heightens productivity* and robustness of processes and facilities
- *Supports diverse initiatives,* e.g, asset performance management
- Development of previously *unimaginable products and processes*
- Resident source: *continuous optimization* of process performance
- Deep processing of *dozens of measured parameters* in real-time
- Provides analysis *beyond simply current operations* performance
- Includes data from *both current and previous operational* periods



DB- digital biomanufacturing

DB features B

- Promises *deep analysis / predictions* for advanced process control
- Enables highly *adaptable processes*, supporting updates / revisions
- Assists in development / control of *process intensification* initiatives
- Accesses many *divergent sources of information* and control loops
- Disparate sources / advanced analytics produce *actionable insights*
- Establishes *machine learning:* online adaptive response to changes
- Supports *real-time prediction, analysis* and control of CQA and CPP
- Quality control tests / *parametric release* on the manufacturing floor
- Real-time *flexible quality assurance* development within operations



CPP- critical process parameter
CQA- critical quality attribute
DB- digital biomanufacturing

DB features C

- Enabling advanced *computer aided design; manufacture; verification*
- Comprehensive, *real-time interface*: human / machine sourced data
- *Updates model* of normal function based on current actions / results
- *More than DCS / SCADA*: predicts and improves with real-time data
- Advances *ERP systems; Lean PPD;* inputs security of supply (SoS)
- Including current business continuity management systems *(BCMS)*
- Major revision and *change-amenable:* provides future-proof process'
- Supports initiatives as *personalized medicine/companion diagnostics*
- A process network for *projecting product quality and batch profitability*



DCS- distributed control systems
SCADA- supervisory control and data acquisition
ERP- enterprise resource planning
PPD- lean product and process development
SoS- security of supply
DB- digital biomanufacturing

DB performance goals A

- Comprehensive *integrated adaptive control* from RM suppliers to patients
- *Modular, mobile, collaborative* and paperless manufacturing environment
- *"Plug-n-play" instrumentation* at all levels from unit operation to inter-plant
- *Zero down-time for deviation* or upgrade: continuous equipment evolution
- In-, on-line, real-time *orthogonal process monitoring* and adaptive control
- Real-time, continual, MDE-based, *process verification and quality release*

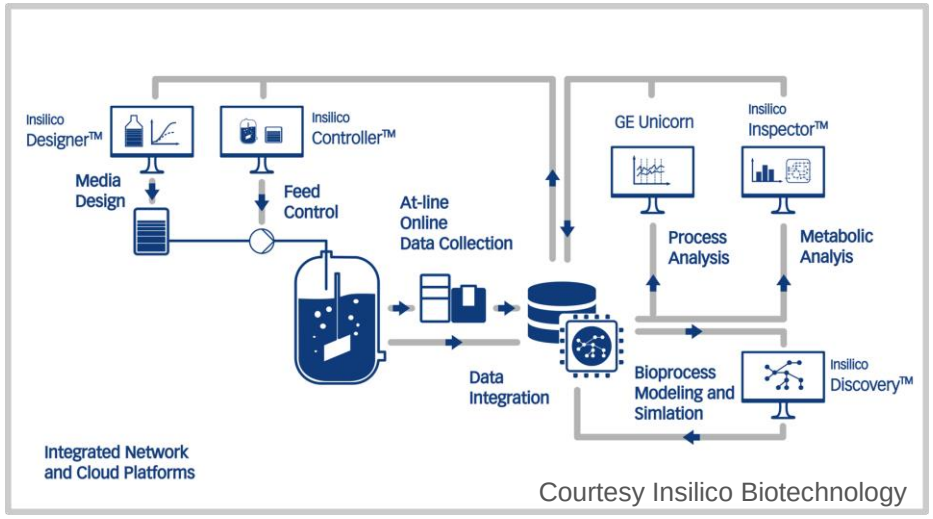


Sensor Chip CM5, GE Healthcare

RM- raw material
MDE- model-driven engineering
DB- digital biomanufacturing

DB performance goals B

- Self-aware, *continuously adaptive* “autonomous” plant with remote experts
- Both *process and business simulation* for models, tests and improvements
- Verified information and immediately available *real-time secure knowledge*
- *Enterprise adaptive analytics* and machine learning in a virtual value chain
- *Business continuity* / incident controls, for incident management / reporting
- *Process automations:* from process development to product manufacturing



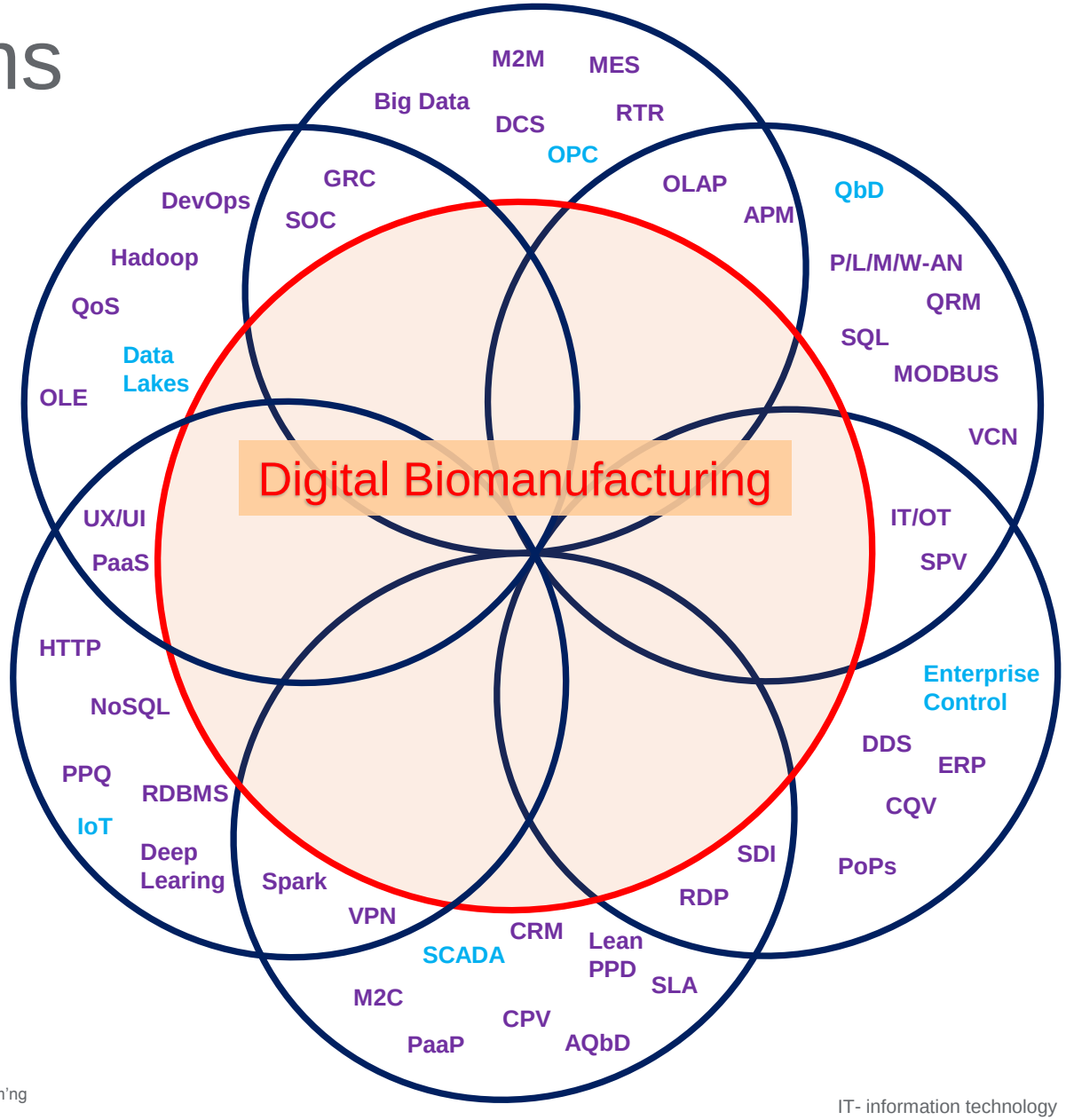
Courtesy Insilico Biotechnology
www.insilico-biotechnology.com

IT and quality acronyms



PaaS	Programmable Logic Controller
PLC	programmable logic controller
PoPs	Partitioned Optical Passive Stars
PPD	Pixels per Degree
PPQ	Policed Priority Queuing
QbD	Quality by Design
QoS	Quality of service
QRM	Quality Resource Management
RDBMS	Relational D-base Mgm't System
RDP	Remote Desktop Protocol
RTR	Real Time Release
SCADA	Sup Control and Data Acquisition
SDI	Serial Digital Interface
SLA	service-level agreement
SoC	system on chip
SPV	Segmented Path Vector
SQL	Structured Query Language
UX/UI	user interface / User experience
VCN	Virtual network computing
Spark	Cluster computing engine
Deep Learing	Machine learning algorithms
Data Lakes	Large repository of data
Hadoop	Distributed processing of large data

APM	Asset Performance Management
AQbD	Analytical Quality by Design
CQA	Critical Quality Attribute
CRM	Customer Relations Management
DCS	Distributed Control System
DDS	Data Distribution Service
DevOps	Software / IT DEVelopment OPS
ERP	Enterprise Resource Management
GRC	Governance, Risk, and Compliance
HTTP	Hypertext Transfer Protocol
IoT	Hadoop
IT/OT	Data Lakes
M2C	Deep Learning
M2M	Enterprise Control
MES	Manufacturing Execution System
MODBUS	Modicon communication protocol
NoSQL	database for data storage / retrieval
OLAP	Online Analytical Processing
OLE	Object Linking and Embedding
OPC	OLE for Process Control
OMG	Object Management Group
P/L/M/W-AN	Personal - Wide Area Network
PaaP	Parallel Archit'res, Algor'ms and Progm'ng



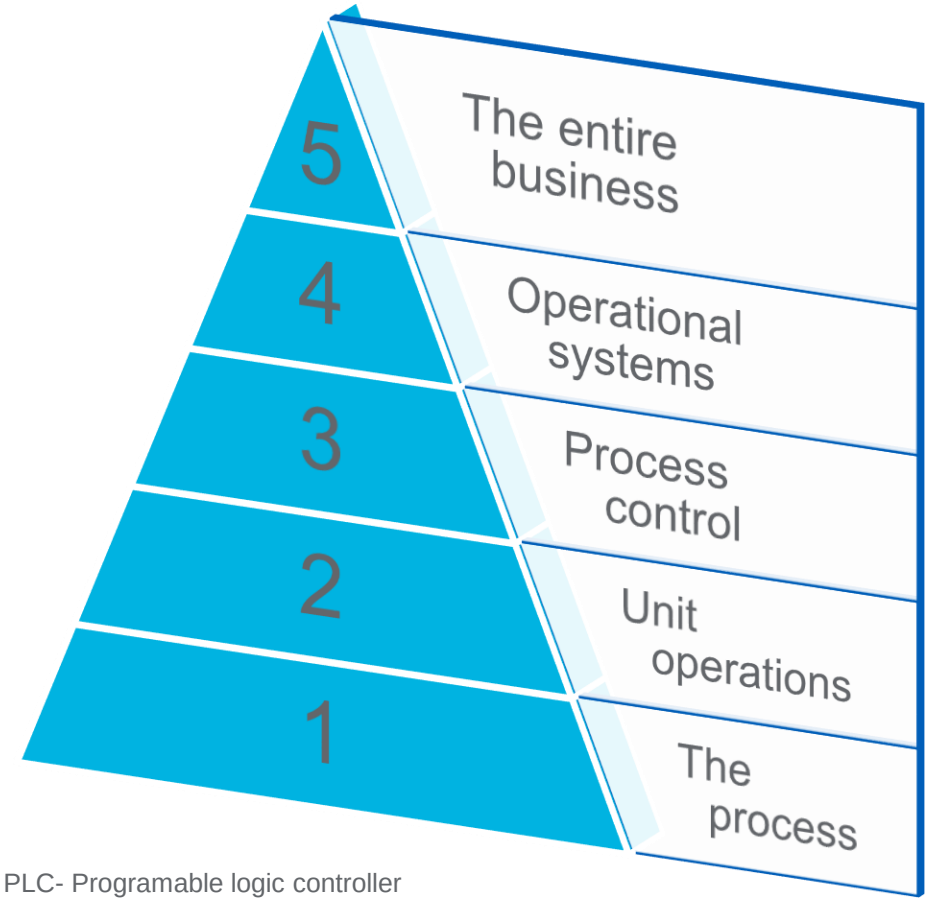
IT- information technology

Bioprocess control

Levels of biomanufacturing control

We are generally at level 3 now

1. The manufacturing process
   What's actually happening on the bioproduction floor
2. Sensing and altering unit operational processes
   Sensors, analyzers, and actuators
3. Supervising, monitoring, and controlling operations
   From simple devices to PLC to SCADA
4. Managing operational work flows
   Operations and laboratory management, plant performance management
5. Managing the entire business
   DB enabled ERP systems looking at all business activities
   Materials, scheduling, material use, manufacturing, shipping, and sales



PLC- Programable logic controller
SCADA- supervisory control and data acquisition
DB- digital biomanufacturing
ERP- enterprise resource planning

Cell therapy control improving

Example: Biosafe Sepax / Coolmix

- Central processor
- Optical line sensors
- Controlled stopcocks
- Line pressure sensors
- RS-232 and PS2 porting
- Integral security systems
- Fully integrated traceability
- Rotary pins driving stopcocks
- Controlled pneumatic axial drive
- Controlled electrical centrifugal drive
- CCD real-time volume measurement
- Application-specific software protocols
- Automated cryobag mixing and cooling



http://www.gereports.com/22109-2/

CCD- charge-coupled device

Biomanufacturing getting better control

Example: GE Healthcare ÄKTA™ systems

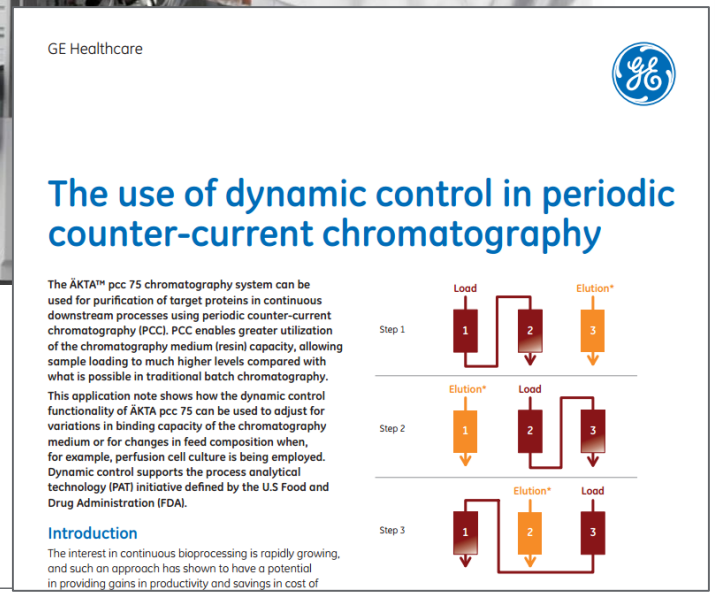
Heightened quality / economy demands

- Growing markets, aging populations
- Biosimilars, regional commitments

Continuous biomanufacturing

- Perfusion bioreactor culture upstream
- Periodic counter-current chromatography





GE Healthcare

The use of dynamic control in periodic counter-current chromatography

The ÄKTA™ pcc 75 chromatography system can be used for purification of target proteins in continuous downstream processes using periodic counter-current chromatography (PCC). PCC enables greater utilization of the chromatography medium (resin) capacity, allowing sample loading to much higher levels compared with what is possible in traditional batch chromatography.

This application note shows how the dynamic control functionality of ÄKTA pcc 75 can be used to adjust for variations in binding capacity of the chromatography medium or for changes in feed composition when, for example, perfusion cell culture is being employed. Dynamic control supports the process analytical technology (PAT) initiative defined by the U.S Food and Drug Administration (FDA).

Introduction

The interest in continuous bioprocessing is rapidly growing, and such an approach has shown to have a potential in providing gains in productivity and savings in cost of

In silico models promise process gains

Software appearing for at-line bioprocess diagnosis

- Identify predictive metabolic indicators of process performance
- Observe/manipulate statistical measures of cell-state values
- Cell metabolism based phase-wise analysis/comparison
- Receive an objective basis for a process evaluation
- Provide automated process performance ranking
- Product, by-product and biomass yields
- Citric acid cycle yield requirements
- Specific productivity assessment
- Time-resolved KPP assessment
- Inspector Controller™ in queue



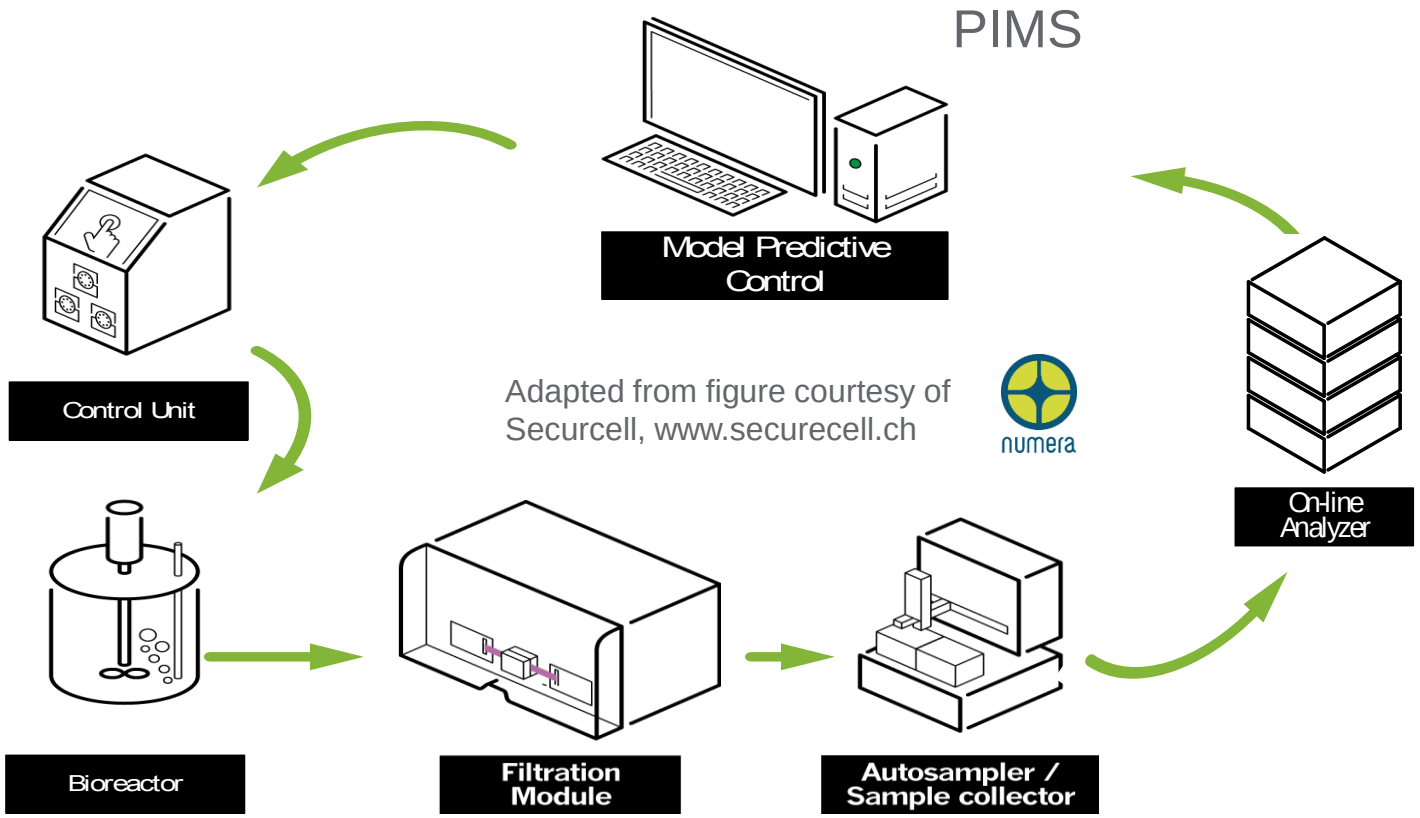
Courtesy Insilico Biotechnology
http://www.insilico-biotechnology.com

Model predictive control improving

Increasing versatility from such systems as Securecell Numera

Low volume/ high frequent sampling

- Supports multiplexed analysis
- Number of analytics growing
- Often in real, near–real time
- Speed/ simplicity increasing
- Driving greater PIMS power



PIMS- production information management system

Improving monitoring and control systems

Intelligent real-time bioprocess data acquisition, analysis and control

SCADA Equipment

- Emerson Delta V
- DASGIP DASware
- Broadley-James BioNet
- Sartorius BioPAT® MFCS
- New Brunswick BioCommand

Information / process management

- GE Healthcare: UNICORN™ 7
- Biointellengence: BioAnalyst™
- Insilico Biotechnology: Inspector™
- Securcell: Lucullus

Bioreactor sampling / distribution

- bbi-biotech: bioPROBE
- Flownamics: Seg-Flow
- Capsugel Bend: MAST
- Securecell: Numera



UNICORN™ 7 www.proteins.gelifesciences.com



The BioAnalyst™ www.biointelligence.com



Insilico Inspector™ http://www.insilico-biotechnology.com

SCADA- supervisory control and data acquisition

Monitoring developments

Integrated and at-line monitoring

Many approaches being developed

- Integrated / automated
  - Membrane-based analytics
  - UV-based concentrations
  - IR backscatter/trans Raman
  - MALLS light-scattering
  - Bioburden / endotoxin
  - pH / conductivity
  - color / clarity / appearance
- At-line near real-time
  - X-D MS/MS
  - Rapid UHLC
  - Myco/viral q/digital PCR

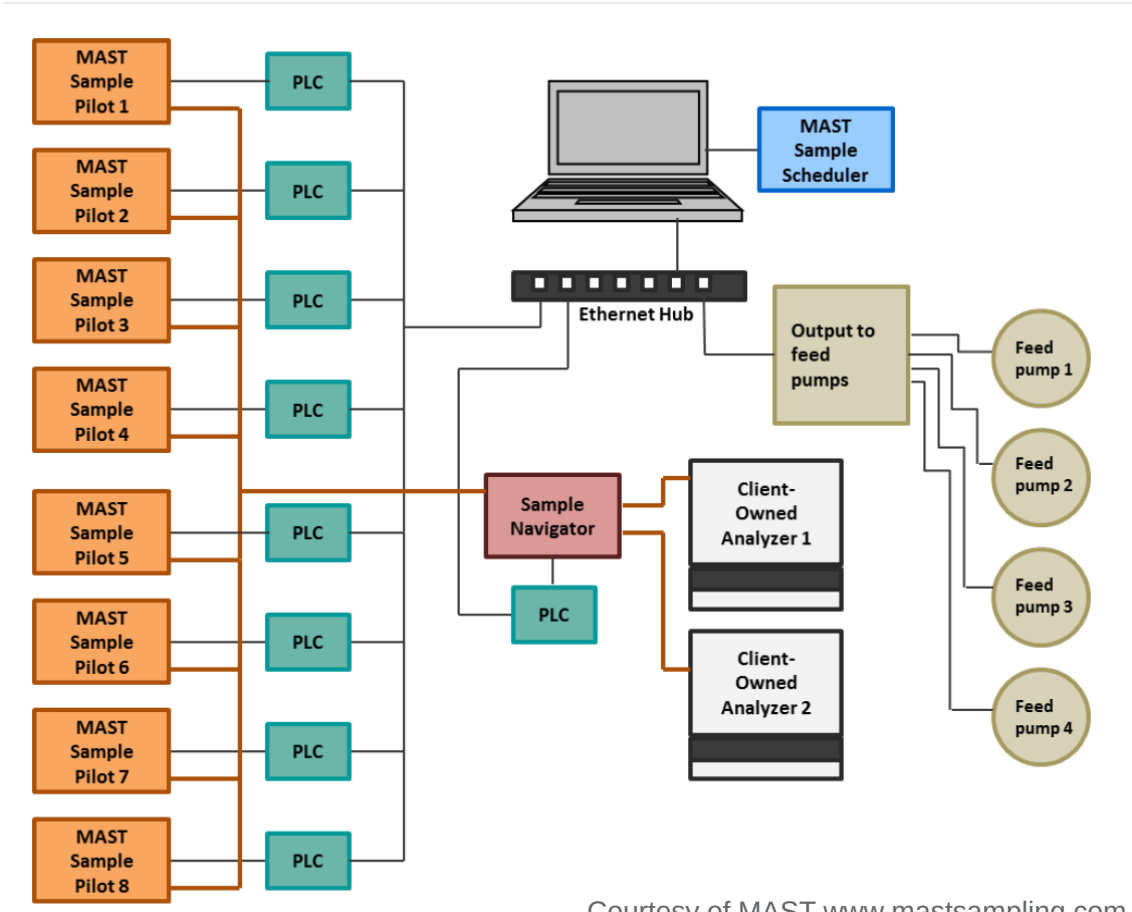


UV- ultraviolet
MALLS- multiangle laser light scattering
pH- negative logarithm of hydrogen ions
X-D- electron induced, (high-E) collision dissociation
MS/MS- tandem mass spectrometry
UHLC- ultra-high performance liquid chromatography
Myco- mycoplasma
qPCR- quantitative polymerase chain reaction
Digital PCR- high sensitivity polymerase chain reaction

Monitoring solutions

E.g., automated at-line sampling

- On-line manifolds ready for in-line sensors
- Hands-off, contamination-free sampling
- Central multiple-analyzer data storage
- Increased sampling reproducibility
- Automated sample scheduling
- Automated at-line analytics
- Heightened data reliability
- Increased sampling rate
- Reduction of activities
- Multiplexed analysis



Courtesy of MAST www.mastsampling.com

Biodetection probes

Direct and surrogate measurements

Transducers

- Resonant
- Optical
- Thermal
- Ion-Sensitive
- Conductimetric
- Amperometric
- Potentiometric

Receptor types

- Bioaffinity
- Biocatalytic

Probe types

- DNA/RNA-based
- Antibody-based
- Antigen-based
- Ligand-based

Immobilization

- Adsorption
- Direct cross-linking
- Encapsulation or confining
- Covalent Binding

MAST SP200 Sample Pilot on a SU bioreactor



Image compliments of Capsugel, www.capsugel.com

Analytics solutions

At-line automation and HT sampling

- Agilent® Infinity 1200 Series HPLC
- Beckmann Vi-CELL® XR Cell Analyzer
- Cedex Bio HT
- Cedex HiRes Cell Analyzer
- GE Healthcare IN Cell Analyzer 6000
- GE Healthcare Biacore 8000
- Mettler-Toledo Balances
- Nova® BioProfile Flex
- Siemans RapidPoint
- Waters Acquity UPLC
- YSI Biochemistry Analyzers



GE Healthcare Biacore 8K system

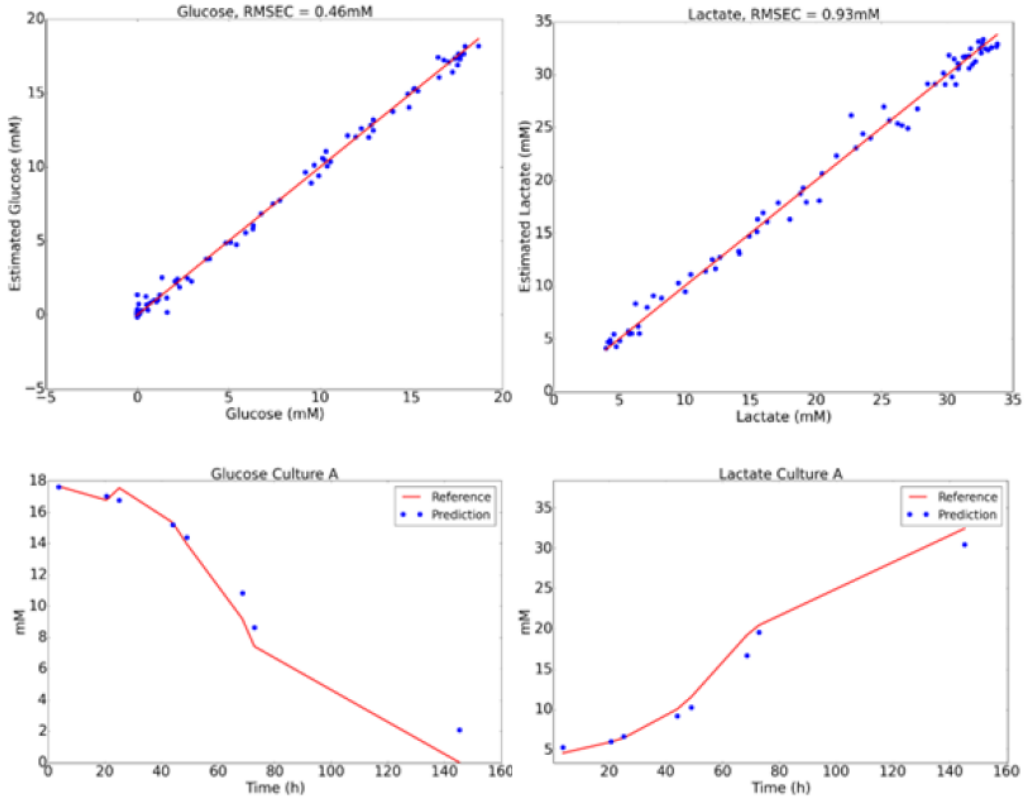
SU- single-use
HT- High throughput

In-line Raman analysis

Example: ProCellics™ Bioprocess in-line Raman Analyzer

- In-line, real-time sensing inside the bioreactor
- Main metabolites and nutrient concentrations
- Total / viable cell concentration measurement
- 12mm probe/ analyzer, IP65/ GMP compliant
- Spectra sorting and preprocessing submodule
- Connectivity through, e.g., OPC-UA® protocol
- Interface with available chemometric software e.g., SIMCA-OnLine (UMETRICS™ powered)
- Bioprocess - adaptable calibration procedure
- Working on supporting perfusion steady-state

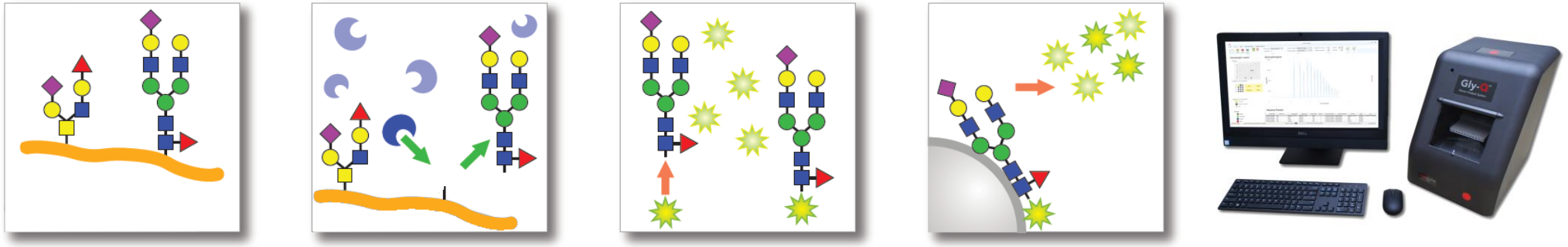
Example analytes



Near real-time glycan analysis

Example: ProZyme Gly-Q System

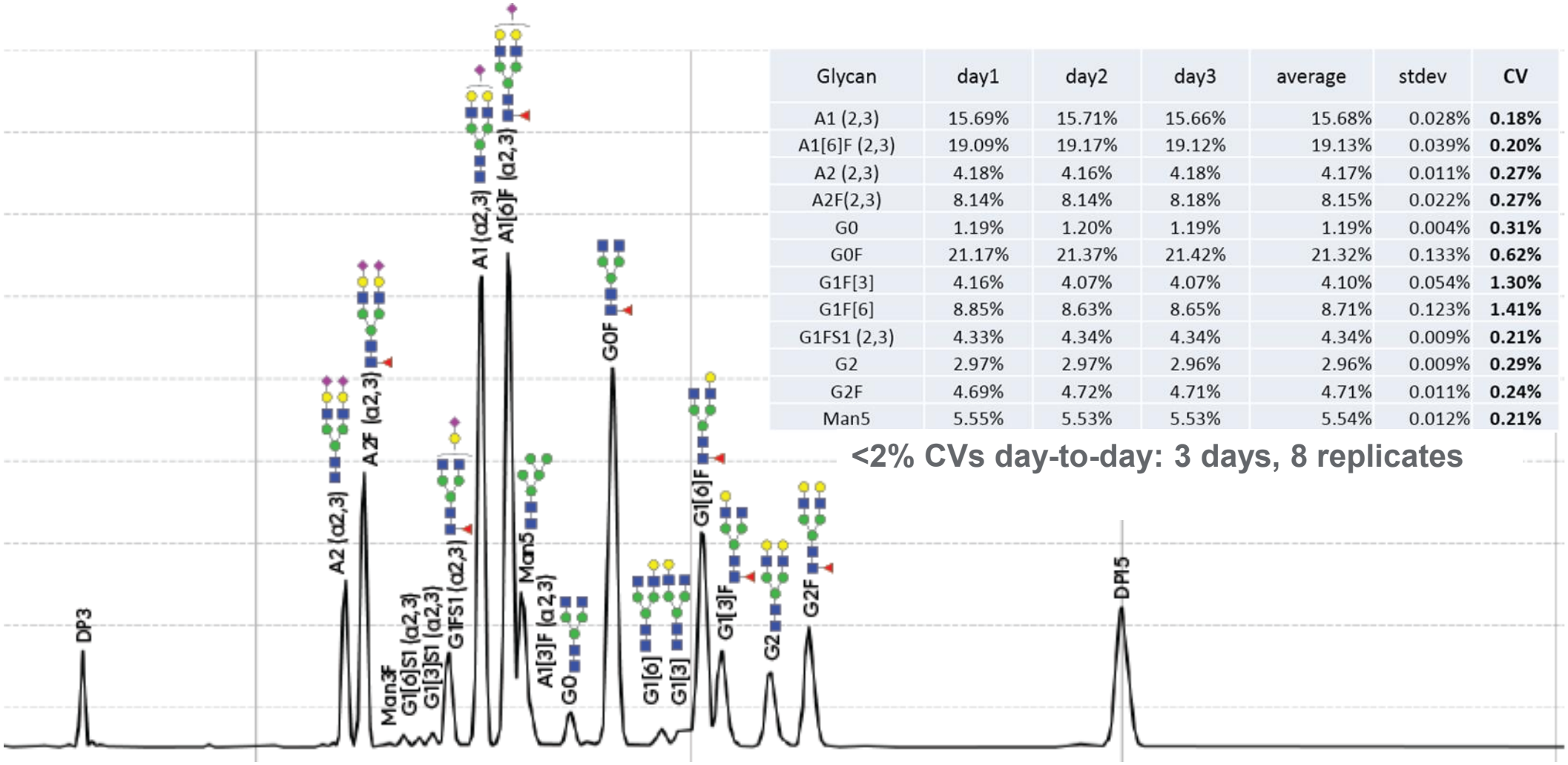
- Novel in-solution enzymatic deglycosylation
- Rapid labeling, easy cleanup, new standards kit
- CGE instrumentation and management software
- Sample development and primary analysis in 30 min.



Denature
3 min at 90°C
→
Deglycosylate
5 min at 50°C
→
Label
1 min at 50°C
→
Clean up
10-15 min at RT
→
Labeled N-Glycans
Analysis on Gly-Q
2 min/sample

CGE- Capillary gel electrophoresis

Enbrel N-Glycans in Gly-Q System



Glycan	day1	day2	day3	average	stdev	CV
A1 (2,3)	15.69%	15.71%	15.66%	15.68%	0.028%	**0.18%**
A1[6]F (2,3)	19.09%	19.17%	19.12%	19.13%	0.039%	**0.20%**
A2 (2,3)	4.18%	4.16%	4.18%	4.17%	0.011%	**0.27%**
A2F(2,3)	8.14%	8.14%	8.18%	8.15%	0.022%	**0.27%**
G0	1.19%	1.20%	1.19%	1.19%	0.004%	**0.31%**
G0F	21.17%	21.37%	21.42%	21.32%	0.133%	**0.62%**
G1F[3]	4.16%	4.07%	4.07%	4.10%	0.054%	**1.30%**
G1F[6]	8.85%	8.63%	8.65%	8.71%	0.123%	**1.41%**
G1FS1 (2,3)	4.33%	4.34%	4.34%	4.34%	0.009%	**0.21%**
G2	2.97%	2.97%	2.96%	2.96%	0.009%	**0.29%**
G2F	4.69%	4.72%	4.71%	4.71%	0.011%	**0.24%**
Man5	5.55%	5.53%	5.53%	5.54%	0.012%	**0.21%**

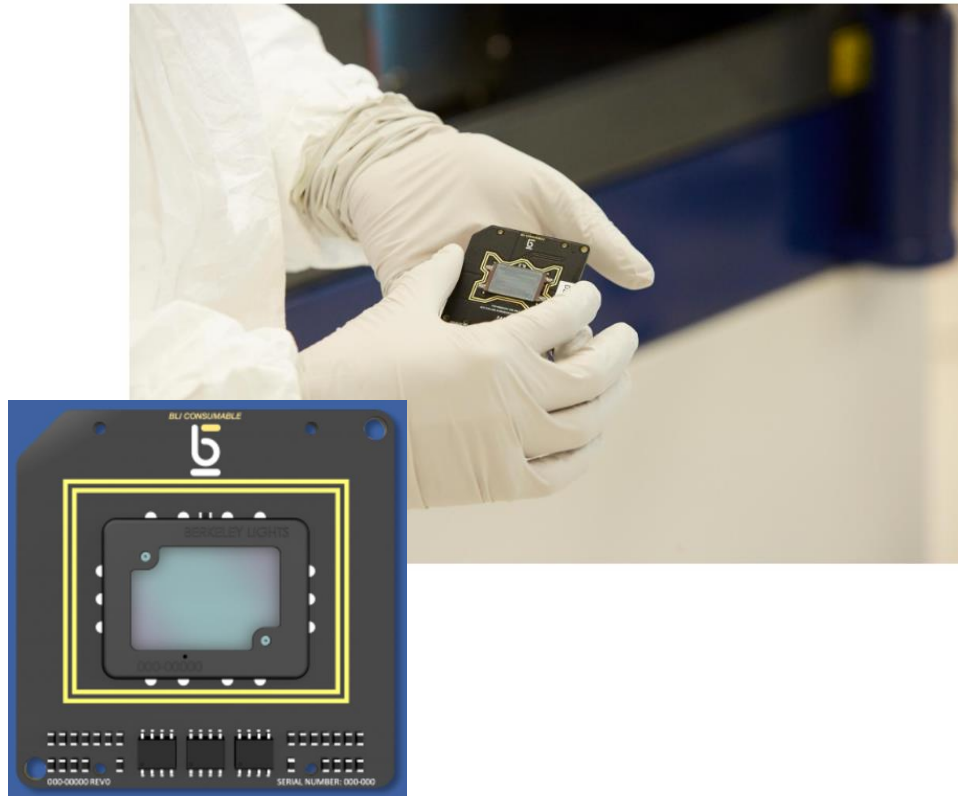
<2% CVs day-to-day: 3 days, 8 replicates

Discrete culture analysis

Example: Berkley Lights' OptoSelect™

- OptoElectro Positioning (OEP)
- Nanofluidic based chip analysis
- Dielectrophoretic force manipulation
- Assaying thousands of single cells in parallel
- Point analysis revealing modal cellular productivity

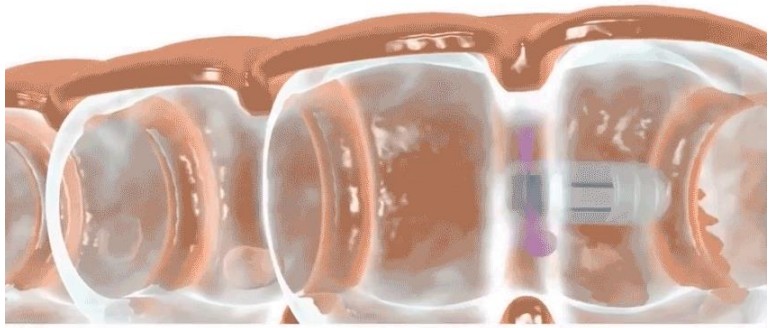
Courtesy Berkley lights www.berkeleylights.com



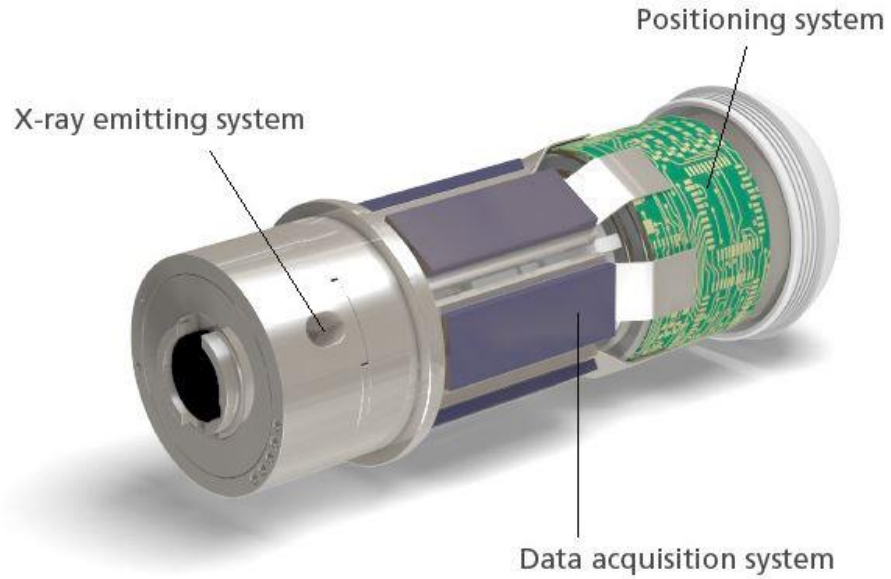
Advanced in-situ monitoring

Now in multi-center, prospective clinical trial

- Miniaturized capsule passes through bowel
- X-ray source, detectors and photon counting
- Positioning, data generation and transmission
- Microprocessor and RF signal communication



Check-Cap C-scan® www.check-cap.com

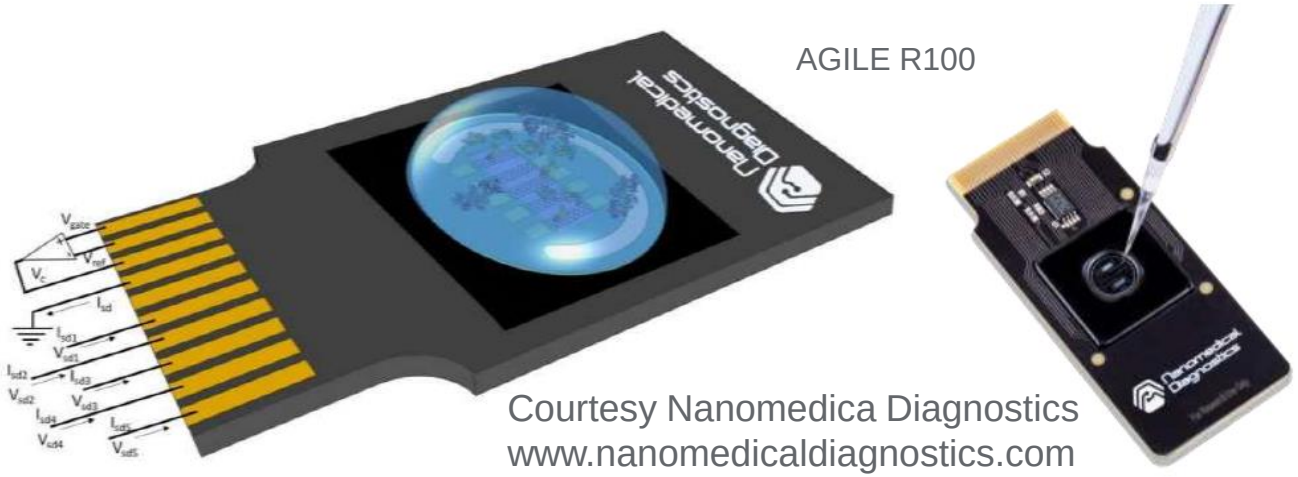


Now in multi-center, prospective clinical trial

Field Effect Biosensing (FEB)

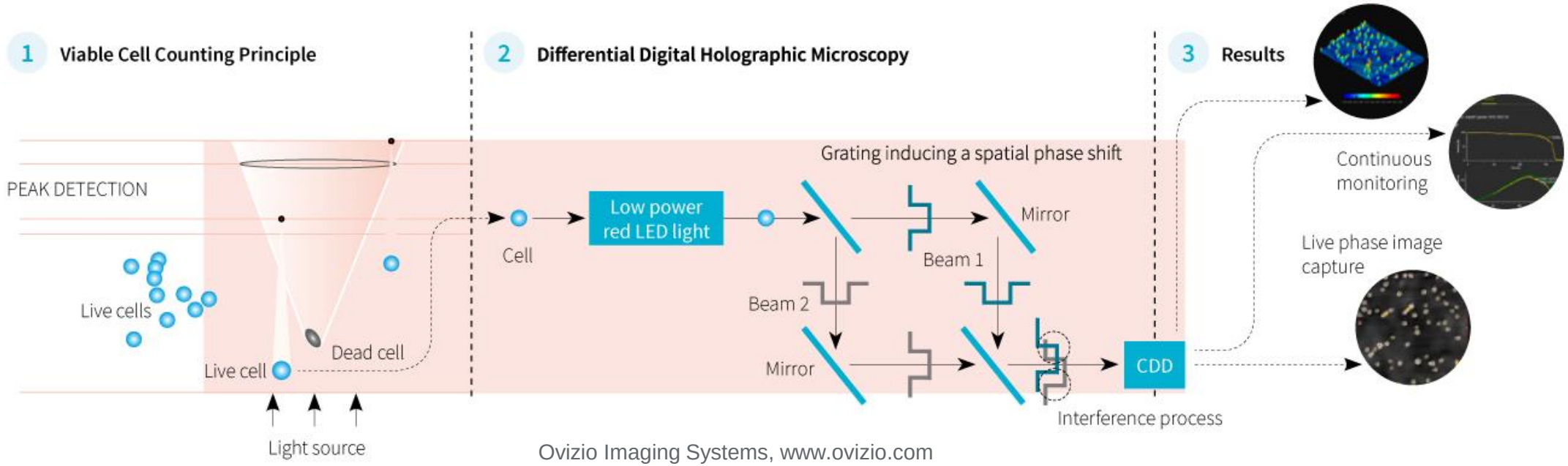
Automated sample monitoring on functionalized graphene-based chips

- FEB technology based upon graphene
- Monitor discrete local changes in potential
- Selectivity / sensitivity by capture molecules
- Measures in even opaque, turbid suspensions
- Direct measurement shortens development time



DDHM technology

Differential digital holographic microscopy (DDHM)

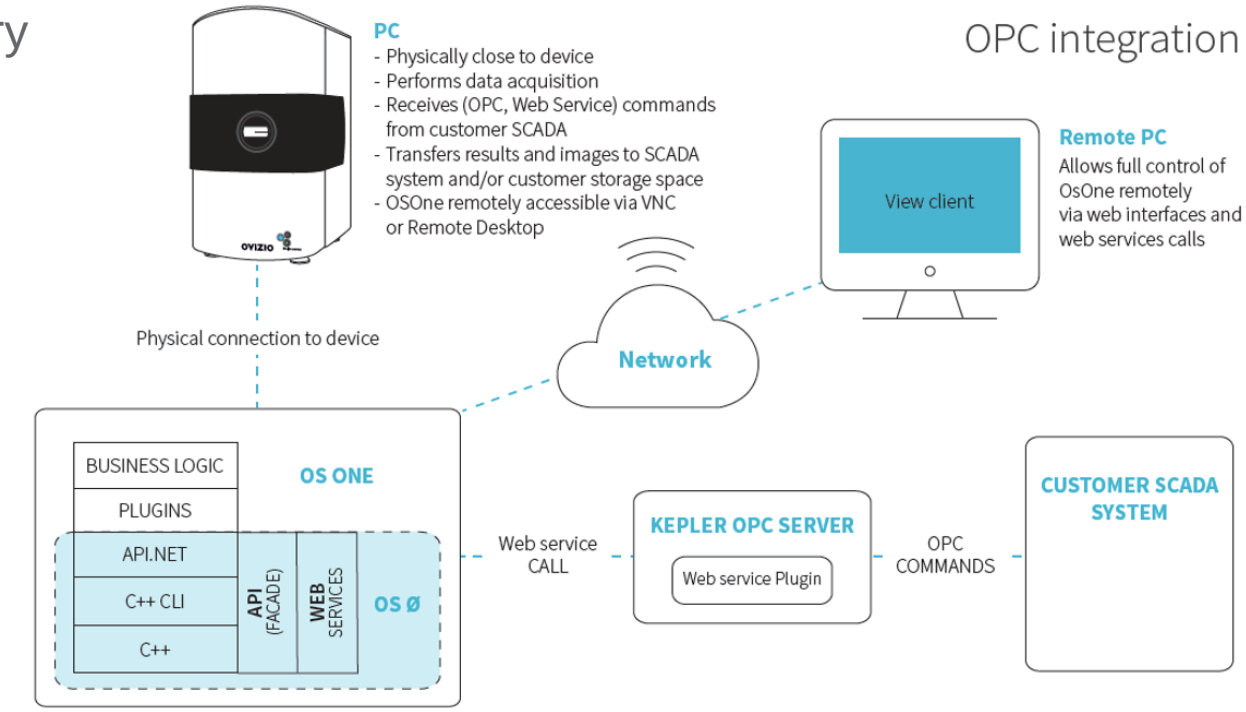


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Real-time, integrated cell physical KQI

- Automated quantitative cell monitoring
- Label-free, non-invasive measurement
- Works with any transparent recipient
- Unifies microscopy & flow cytometry
- In-line, real-time 3D imaging

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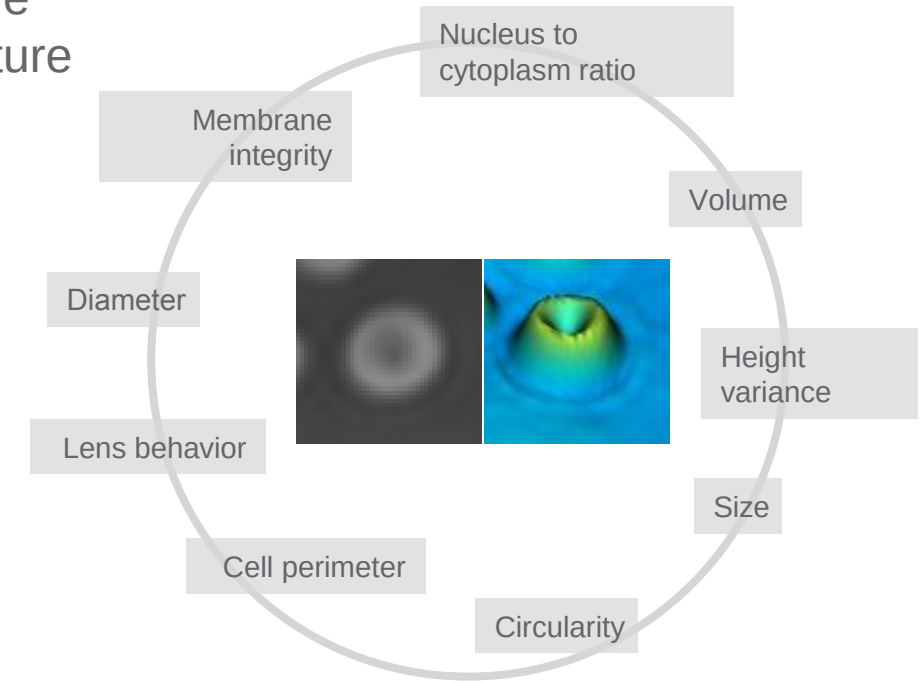
KQI-Key quality indicator
DDHM- differential digital holographic microscopy
OPC- open platform communication

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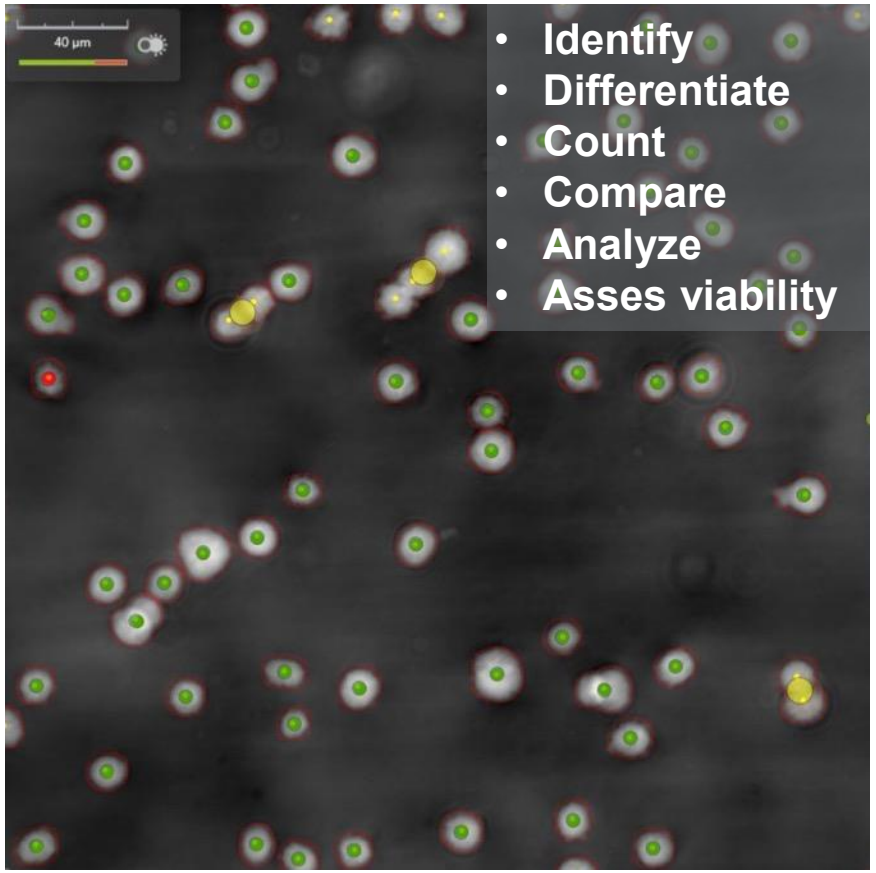
Machine learning in 74 measured parameters

Holographix Fingerprint for cells

Parameters
- Morphology
- Optical
- Phase texture
- Intensity texture



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Conclusion

Digital Biomanufacturing

- Fulfills many desired goals
- Is not a dream, but happening now
- Involves advanced bioprocess controls
- Is being fed by significant monitoring developments

