BIOTECH AUTOMATION – THE PAST, PRESENT AND FUTURE

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Biotech Automation - The Past, Present and Future.

Automation in Biotech

- History (PLC's and DCS's)
- Advances in Automation (past 20 years)

The Current Forces Shaping Biotech

Disposables in Biotech

Continuous Process

The Future of Automation

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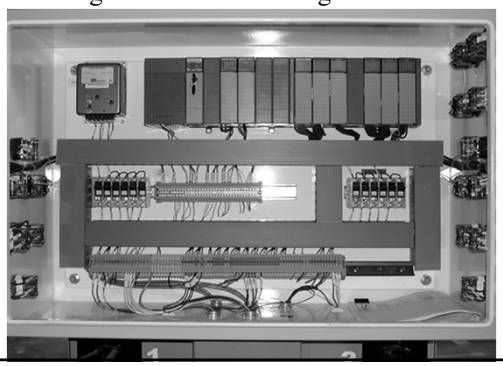
Programmable Logic Controllers (PLC)

- - 1969 - Auto Industry – Dick Morley
- - High Speed, rugged, programmable
- - Relay replacement
- - Discrete inputs and outputs (I/O)
- - Analog inputs and outputs
- - Programmed in ladder logic



Distributed Control Systems (DCS)

- 1975 – Honeywell TDC 2000 based on IBM 1800 (Mainframe Computer)
- Proprietary system using I/O and minicomputers (VAX, IBM, Data General)
- Oil refineries, chemical plants, power industry
- 1990's used PC's rather than minicomputers (Hybrids)

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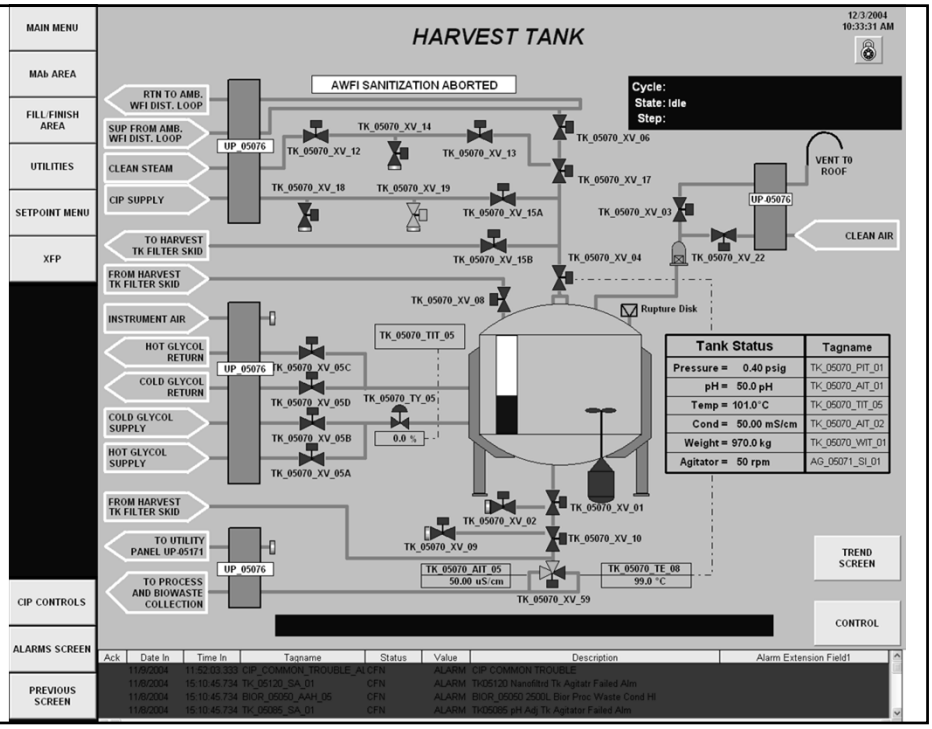
PC based Operator Interfaces

- *PC – 1981 IBM*
- *Late 80's – Window to the PLC*
- *Replaced pilot lights, pushbuttons and selector switches*
- *1990's DCS systems – Hybrid*



PLC to PC Communications

Problem – individual device drivers required for every PLC to PC interface. Each PC vendor would require approximately 200 software drivers.

PLC Vendors

- Allen Bradley
- GE
- Modicon
- Siemens

SCADA Vendors

(Supervisory, Control and Data Acquisition)

- RS View
- iFIX
- WinCC
- Wonderware
- Genesis

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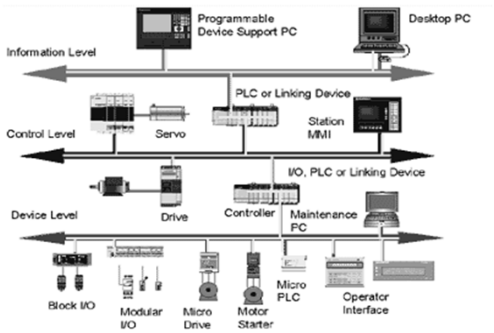
Automation Advancements – OPC

(Object Linking and Embedding for Process Control)

-**Solution** - OPC Foundation (1996) ensured interoperability in automation by creating and maintaining open specifications that standardize the communication of acquired process data, alarm and event records, historical data, and batch data to multi-vendor enterprise systems and between production devices.

- Before OPC, device drivers had to be written by every software company to communicate with every different hardware device. Like in the DOS days for printers.



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Automation Advancements - Fieldbus

-**Problem** – Every field signal required a separate electrical signal. (24VDC, 4-20mA)

-**Solution** - Intelligent networks based on open standards daisy chained to multiple devices.

-New open standard, fieldbus technologies.

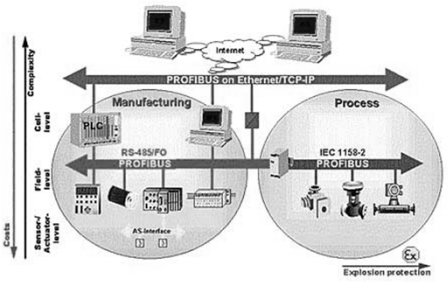
-Profibus

-Foundation Fieldbus

-EtherNet/IP

-ModBus TCP

-DeviceNet



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Automation Advancements – S88 (ISA 88, Batch Control)

Problem – Every batch control system programmed separately**.**

Solution - S88, shorthand for **ANSI/ISA-88**, a standard addressing batch process control. A design philosophy for describing equipment and procedures. It was approved by ISA in 1995. It was adopted by the IEC in 1997 as IEC 61512-1.

S88 provides a consistent set of standards and terminology for batch control and defines the physical model, procedures, and recipes.

Hardware model is separated from the recipes. Recipes can be selected by the user to run on any available batch. Each recipe only programmed and tested once.

Physical Model - enterprise, site, areas, process cells , unit, equipment modules, control modules.

Procedure Control Modules - *recipe procedures, unit procedures , operations*, *phases*.

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Automation Advancements – Server Technology

•Servers have dedicated functionality such as web servers, print servers, domain servers, database servers

•Servers have a faster CPU, and often, redundant hard drives, power supplies and network connections for disaster recovery.

• 2000 –VMware enabled servers to run multiple, virtual machines and operating systems simultaneously.

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Automation Advancements – Blade Technology

• **Problem** - multiple servers take up space, power, require cooling.

• **Solution** - Blade.org (2006) - provides open standards for Blade manufacturers.

• Reduced space, energy, wiring, redundancy, high speed (10G) Ethernet, hot swappable (128 blade server/rack vs. 42 conventional)

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Automation Advancements – MES

Manufacturing Execution System - a control system for managing and monitoring work in process on a factory floor to improve productivity and reduce cycle-time. Often integrated with ERP software.

Typically Include

- Scheduling
- Security Basics
- Equipment Tracking
- Materials Management
- Inventory Management
- Recipe Authoring
- Order Management
- Weigh and Dispense
- Electronic Batch Records
- Electronic Signatures
- Genealogy and Traceability

Software

- Werum
- Syncade
- Elan
- PMX
- Simatic IT
- Plant Apps

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Portable Wireless Workstations

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Why Disposables

- Improved return on capital
    - Reduced and deferred capital investment
    - Increased speed of deployment
- Reduced CIP, SIP requirements. Simpler validation, automation, labor
- Multiple products with no cross contamination
- Portability, improved ability to manage and implement change

Existing Disposable Systems

- Media mixers and storage systems
- Buffer Mixers and storage systems
- Bioreactors
- Sensors – temperature, pressure, pH, conductivity, UV, flow
- Separations – limited to filtration
    - Harvest
    - Virus removal / sterilization
    - Concentration / buffer exchange
- Purification – membranes

Fully Integrated Disposable Factory

Courtesy of Xcellerex

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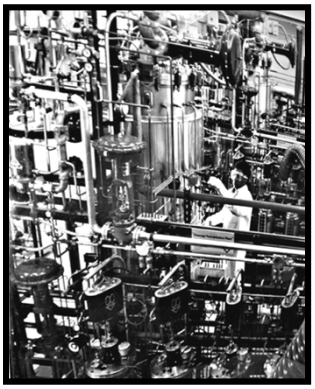
Bioreactors

1980's



1990's

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Bioreactors Today

GE Healthcare (Wave)

ThermoFisher (Hyclone)

Xcellerex

Disposable Bioreactors

- Disposable bags include disposable sensors – temperature, pressure, pH, UV, O2, conductivity, flow.
- Eliminates the need for CIP, SIP and associated chemicals, energy, labor, controls and validation.
- Reduces the need for clean room space and likelihood of cross contamination.
- Disposable bags are Gamma radiated with the sensors and mixer blade inside.
- From 3 liter (Millipore) to 2000 liters (Xcellerex) and testing with 5000 liters
- Disposable bioreactor market growing at greater than 20%. Total bioreactor market growing at 5%. Disposable sensor market growing at 100%.
- Currently an estimated 20% of all new bioreactors less than 1000 liters are disposable

Shire –Lexington, MA
Reference - ISPE Boston – Keynote - Oct. 6th

Using Xcellerex disposable reactors (up to 2000L)

- Reduced building sized by 35%
- Reduced energy requirements by 50%
- Reduced water usage by 85%
- Saved 6 months off construction schedule
- Will be producing licensed product first quarter 2011.

New Disposable
Downstream Technology

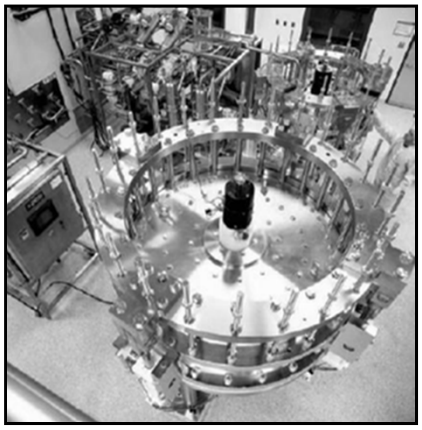
- Single use tubular bowl centrifuge – Pneumatic Scale
- Single pass ultra filtration - Pall
- Pre-packed chromatography: GE, Repligen, Natrix
- Expanded bed chromatography – Upfront
- Genderless, re-useable sterile connectors
- Simulated moving bed chromatography – Tarpon, Novasep

The Down Stream Bottleneck

- **Titers increasing to 5 -10 g/L, require smaller reactors**
- **Purification cost is now 80% of manufacturing costs**
- **Traditional chromatography is labor intensive, prone to mistakes, expensive, and time consuming to set up.**

Lonza Biologics

Portsmouth, NH Facility



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SMB Chromatography

Simulated Moving Bed

Tarpon - SMB made for Biopharm applications

- Fully disposable fluid path including valving
- Flexible configuration modular design
- Multi-column or Multi-device mode with unlimited scale

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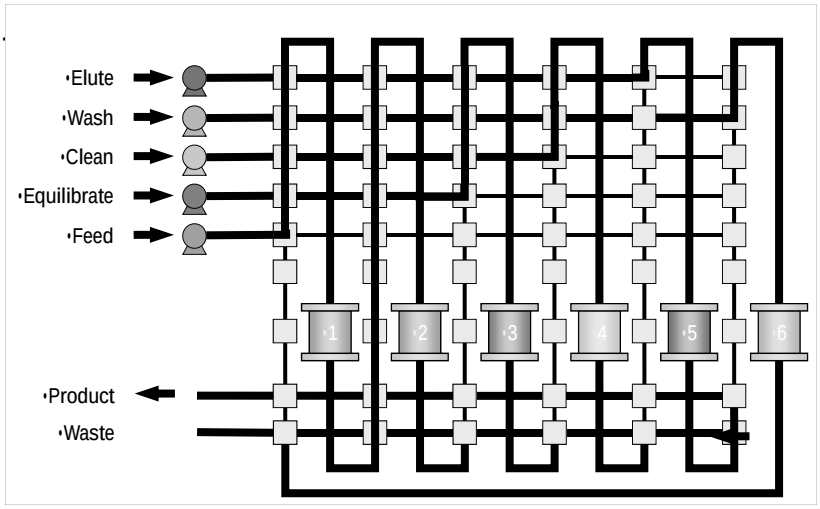
Simulated Moving Bed Chromatography

(courtesy of Tarpon Biosystems)



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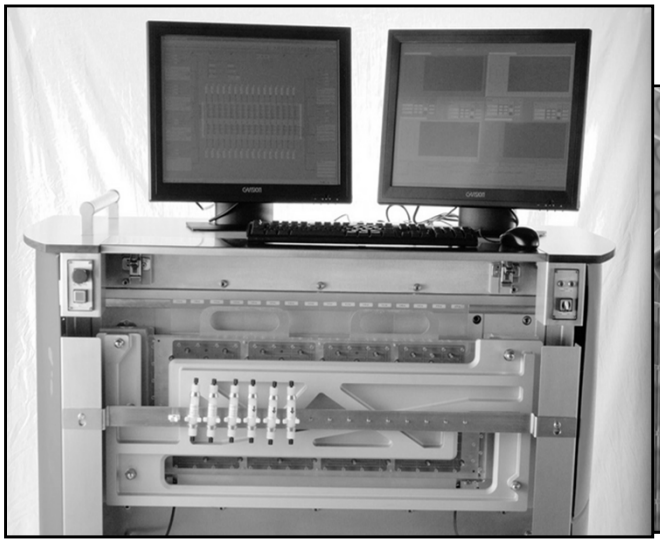
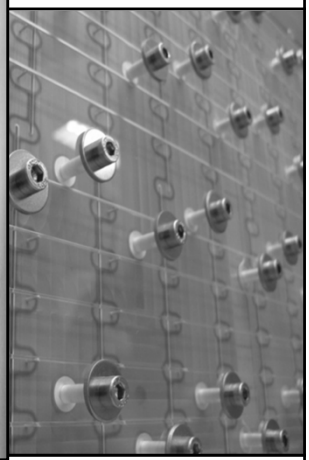
SMB Chromatography



The Valve Block



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SMB Example 1

Courtesy of Tarpon Biosystems

Clinical Manufacturing of MAb (Protein A step) *

- Bioreactor volume: 2000 L
- Expression level: 5 gm/L
- Protein A media: MabSelect SURE**

- ** Assuming 48 hr processing time for the Protein A chromatography step*
- *** GE Healthcare Product packed into 8 cm Diameter X 6 cm Height disposable column format*

	Batch	BioSMB
• Column Volume	71L	2.5L
• No. of column	1	8
• Cycles per Batch	5	88
• Column diameter	60cm	8cm
• Column height	25cm	6cm
• $ Protein A Resin	$921K	$32K

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SMB Chromatography – Ex. 2

(courtesy of Tarpon Biosystems)

Scenario		Low titer		Medium titer		High titer	
Titer	gm/L	1 gm/L		5 gm		10 gm/L	
Volume	L	10,000 L		10,000 L		10,000 L	
Pr.time	hr	22 hr		22 hr		22 hr	
		Batch	BioSMB	Batch	BioSMB	Batch	BioSMB
Pr.A media	L	100	12	200	25	380	37
Buffer	L	8450	5500	35000	25000	63400	47800
Columns		1	8	1	12	1	16
Cycles		1	20	6	43	6	56

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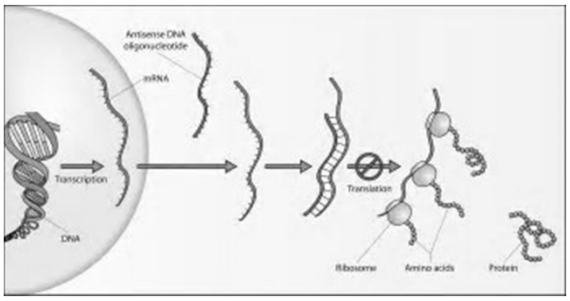
Oligonucleotide Manufacturing 2017



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Biotech Manufacturing Automation - The Future

- Automation hardware and disposable sensors will continue to drop in price. Purchased equipment will have built in transmitters.

- PLC, DCS hardware will become a commodity or be replaced by PC like devices.

- Disposable reactor bags with disposable sensors all built in, with one network connector or wireless communications.

- Automation companies will focus on software.

-PAT will become a reality with NIR, Raman Spectroscopy, and multivariable monitoring providing real time information.

- Software modules will be purchased over the internet (like Applets for the iPad).

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Biotech Manufacturing
The Future

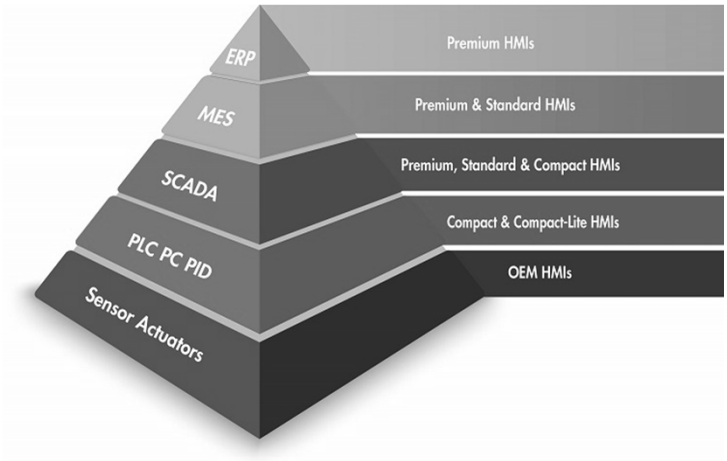
- Smaller, flexible, multiproduct, multiplatform facilities.

- Entirely disposable systems following standards for interconnection.

- Current batch manufacturing will shift toward continuous manufacturing like other mature industries (oil, commodity chemicals, paper, semiconductor).

-Continued outsourcing of noncore activities. Outsourcing to CMO's, CRO's.

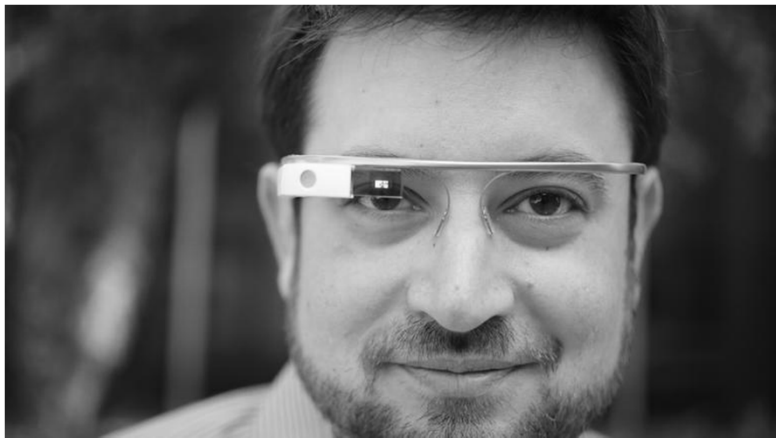
The Automation Pyramid is Changing



Biotech Manufacturing
2017 – The Cloud?

Data Center

Smart Glasses



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Validating the Operators Sight

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Biotech Manufacturing
2018 - The Future

-Hardware, networking, becoming a commodity.

-Software Control/Equipment modules sold as Apps from the Cloud. GMP data stored in the cloud.

-Artificial Intelligence used to identify statistically significant upsets and automatic corrections/notifications.

- Continuous Manufacturing is already a reality

- Google like glasses – video of all manufacturing steps.

THE END

Thank You