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The Eli and Edythe L. Broad Institute

A Collaboration of Massachusetts Institute of Technology, Harvard University and affiliated Hospitals, and Whitehead Institute for Biomedical Research

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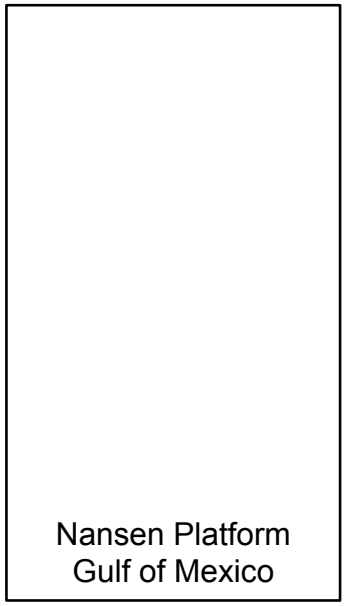
Process Improvement as a Catalyst for Innovation, Examples from High Throughput DNA Sequencing

Robert Nicol
Director, Sequencing Operations

Petrochemicals to Genomics

- 1st Life in Petrochemical Engineering and Construction
- Classic Enterprise Categories
  - Safety
  - Budget
  - Schedule
  - Performance



Nansen Platform
Gulf of Mexico

Conceptual Engineering

>Feasibility
>Scenarios
>Sourcing
>Estimates

Detailed Engineering

>Simulation
>Testing
>Integration
>Contracts

Construction and Startup

>Inspection
>Testing
>Operation
>Tuning

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Petrochemical Engineering - Craft

- Substantial Risk Mitigation Possible
  (Relative to Pharmaceuticals and Bio-Research)

But….

- Slow Technology Change (clockspeed*)
  - Well Understood Design Space
  - Established Supply Chain
- Long Product Lifecycle
- Few Design Interactions
- Limited Post Design Process Changes

Kerr-McGee Nansen Spar Platform -3,675 ft.

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* Clockspeed : Winning Industry Control in the Age of Temporary Advantage, Charles H. Fine

High Throughput Genomics

- Genomics Substantially Riskier - **Need Lean**

Primarily From:

- Fast Technology Change (clockspeed*)
  - Unexplored Design Space
  - Evolving Supply Chain
  - Changing Demands
- Short Product Lifecycle
- Many Design Interactions
- Continuous Post Design Process Changes

Whitehead Institute
Genome Center (ca. 2000)

The Broad Institute

History

Grew from Whitehead Genome Center (b. 1990)

Founding Gift by Eli and Edythe Broad ($100m over 10 yrs)

Launch: May 2004

New type of biomedical research institute to realize promise of genomics

Joint partnership of:

MIT

Harvard

Harvard Affiliated Hospitals

Whitehead Institute

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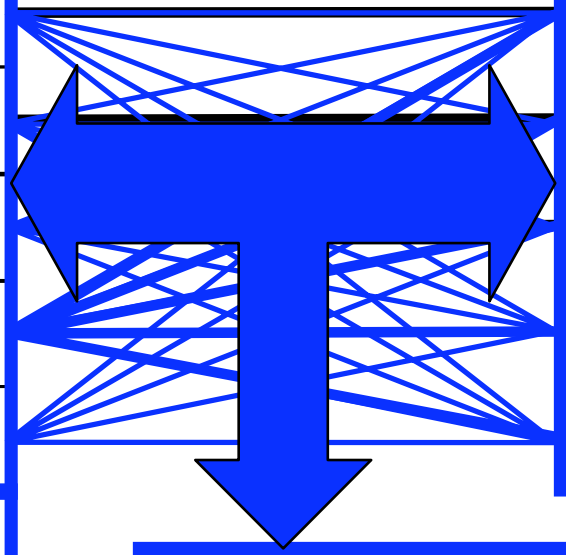
Scientific Programs

- Genome Biology and Cell Circuits Program
- Chemical Biology Program
- Medical and Population Genetics Program
- Cancer Program
- Computational Biology and Bioinformatics
- Metabolic Disease Initiative
- Infectious Disease Initiative
- Psychiatric Disease Initiative

Scientific Platforms

- Genome Sequencing Platform
- Chemical Biology Platform
- Genetic Analysis Platform
- RNAi Platform
- Proteomics Platform



Projects

Microbial Sequencing Center	Center for Genotyping and Analysis
Fungal Genome Initiative	Connectivity Map
Immune Circuits	International Haplotype Map
Cancer Genome Project	Mammalian Genome

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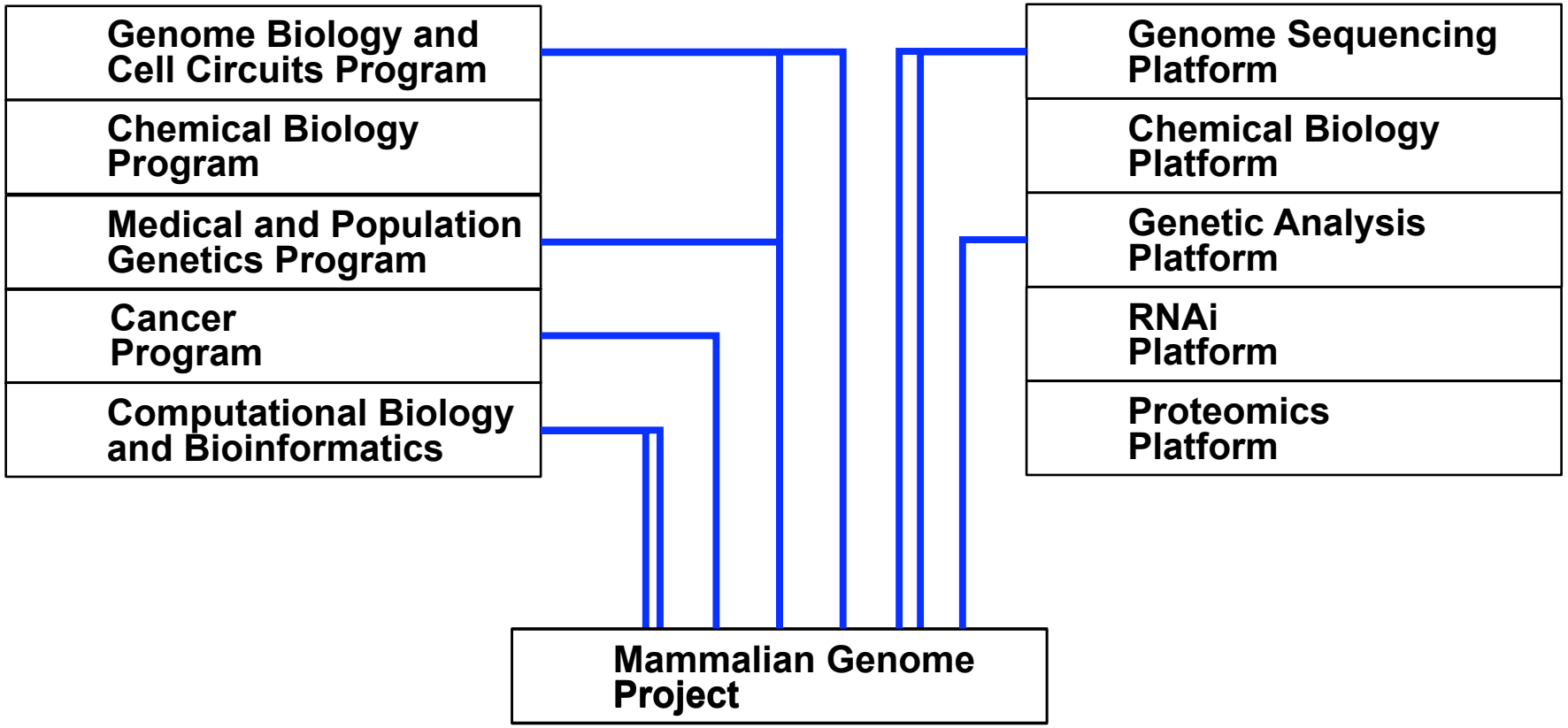
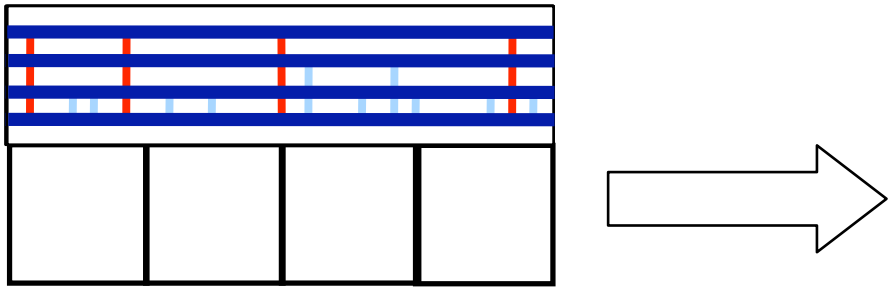
Scientific Programs

Scientific Platforms



Next Step: How does it work?

- Identify genes, regulatory elements, micro RNAs…
- Comparative Genomics to separate signal from noise
- Requires Substantial Data Set



Yeast ~13Mb

Interpret human genome, via evolutionary conservation

- Compelling proof in yeast
- Adapt strategy to human genome

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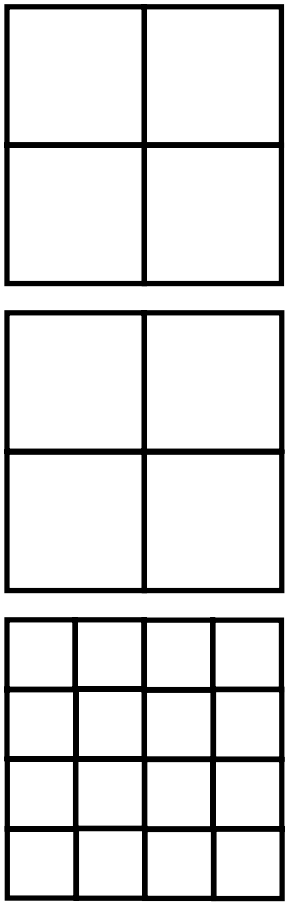
Sequencing and comparison of yeast species to identify genes and regulatory elements
Manolis Kellis, Nick Patterson, Matthew Endrizzi, Bruce Birren, Eric S. Lander
Nature 423, 241-254 (15 May 2003)

Broad Genome Sequencing Platform

Scale Comparison



4 Fungi
~0.4 Gb

4 Mammals ~60Gb

Cancer Genome Project

>>100Gb (proposed)

Broad Institute
- 60Gb* per Year Capacity
- Highest Throughput Center

- Cost is Driver
- Process Excellence Enables Science

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*Q20 bases

An order of magnitude Improvement
Comparison to Semiconductors

Gel Based Seq.

Craft production

- Highly skilled workforce
- Low production rates
- High cost

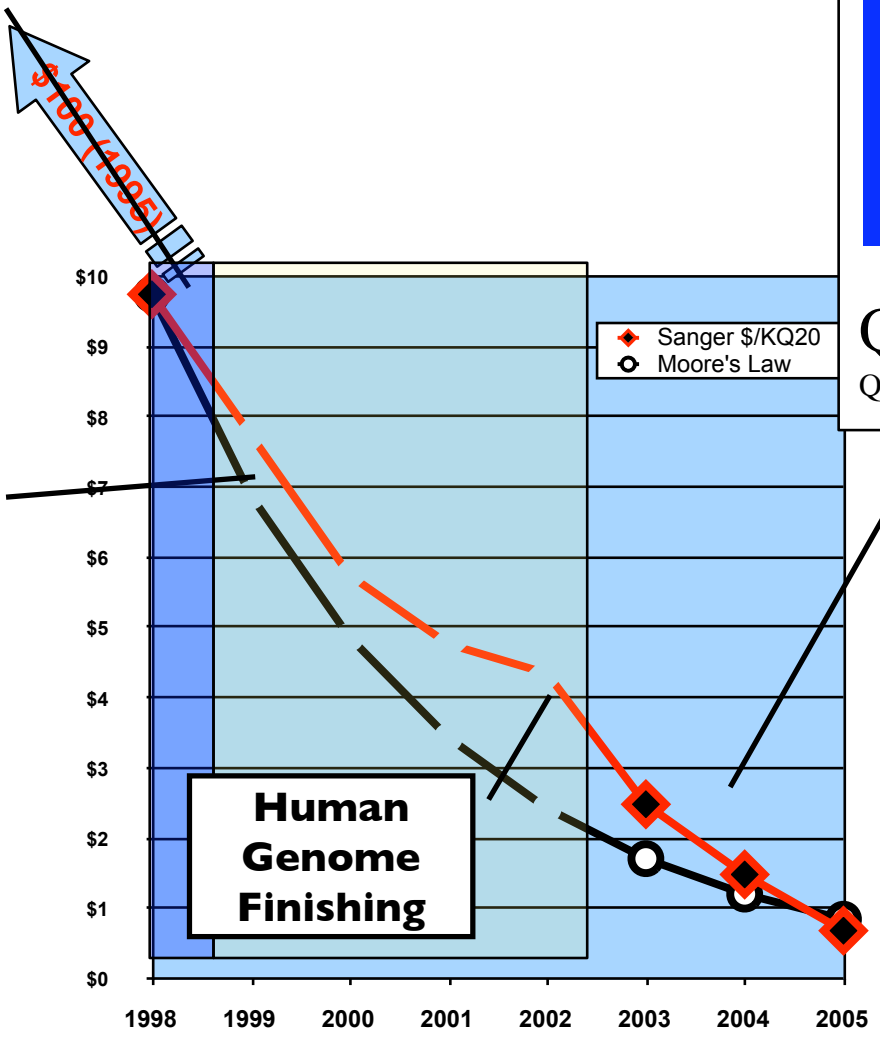
Apollo Guidance Computer MIT - 1968

SPRI/3700 Seq.

Mass Production

- Less skilled workforce
- High production rates
- Low cost
- Quality problems
- Inflexible processes

Veeco 2100 Ion Implanter – 1970's



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attacttttaatttggctcaaagtcctaattgaacacctggacagctagcatctct
cagcacctatcatatgacatagtcactgtgttcctgcctgtacatccaagagct
gtgaaagtatatgtgctccataa

Q20=99% accuracy

$Q20 = -10 \log_{10}(1-0.99)$

RCA/3730 Seq.

Agile Enterprise

- Adaptive workforce
- High Production Rates
- Low cost
- Flexible Processes
- Improving productivity
- Improving quality
- Stakeholder value focus

IBM Fishkill Semiconductor Plant - 2004

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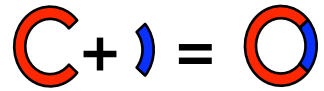
Production Models Credit: Prof. Deborah Nightingale MIT, Lean Aerospace Initiative

Bench Scale

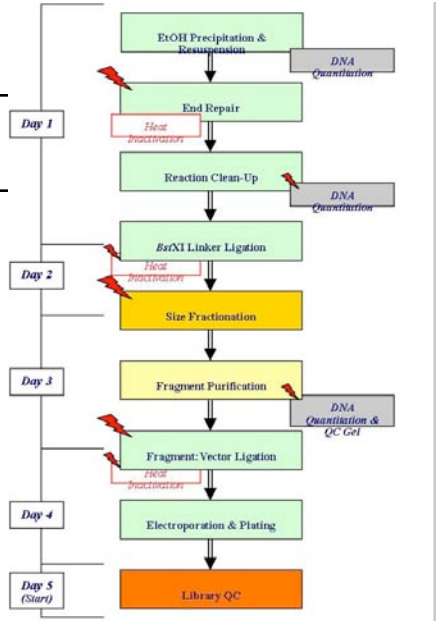
DNA Sample Receipt	DNA Preparation	Library Construction
•Registered •QC'd •Archived	•Sheared •QC'd •Prepared	•Repaired •Separated •Ligated

DNA Sample

Sheared DNA



DNA + Vector = Library

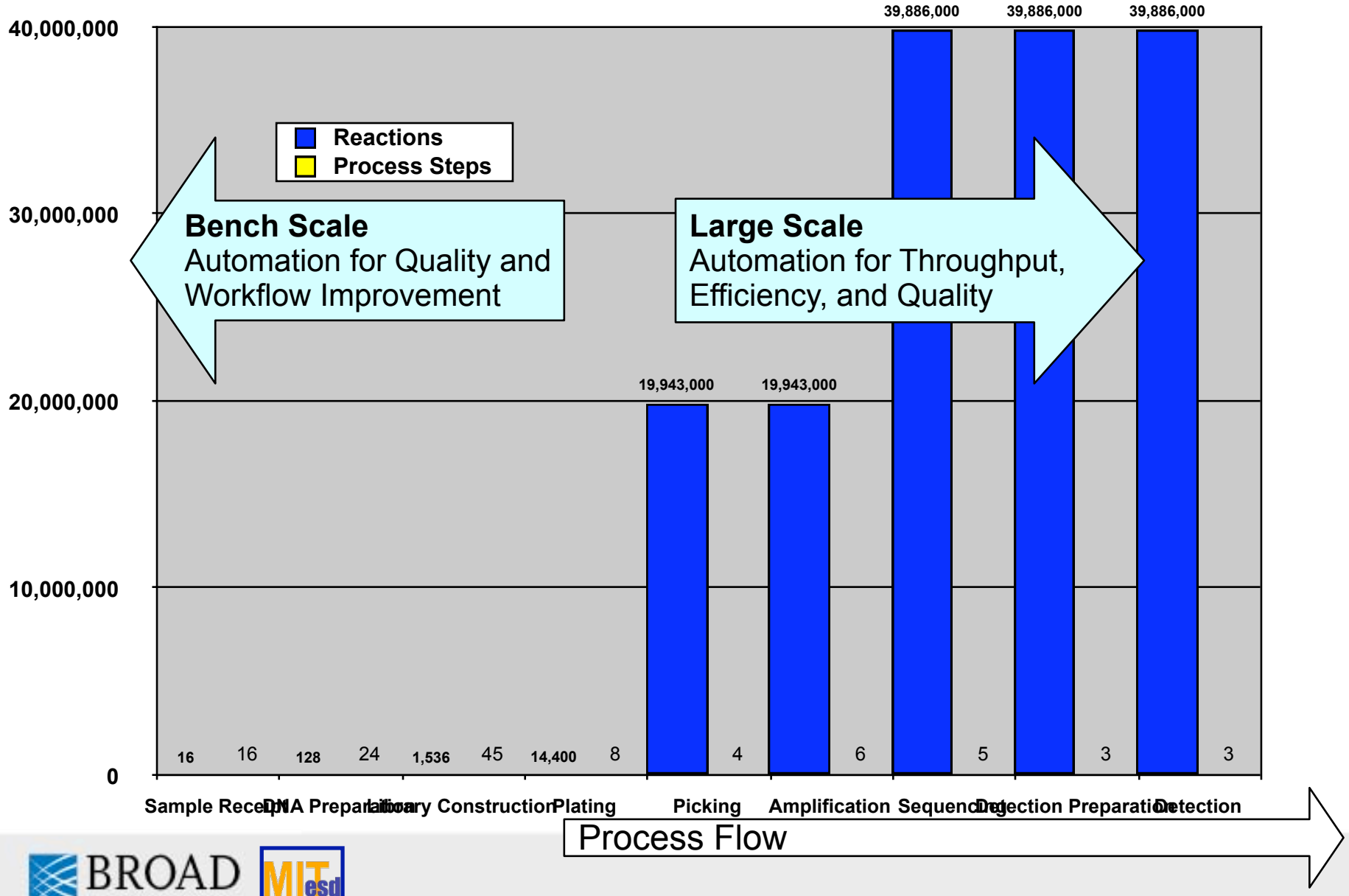


Large Scale

Picking	Amplification	Sequencing	Detection Preparation	Detection
•Mech. Separation •Automated •Barcoded •384 Microtiter Plate	•Enzymatic Amplification •Automated •Significant Cost	•Sanger Based Chemistry •Automated •Significant Cost	•Cleanup •Re-suspension	

ABI-3730xl
DNA Analyzer

Genome Sequencing Process (7X Mammal Example)



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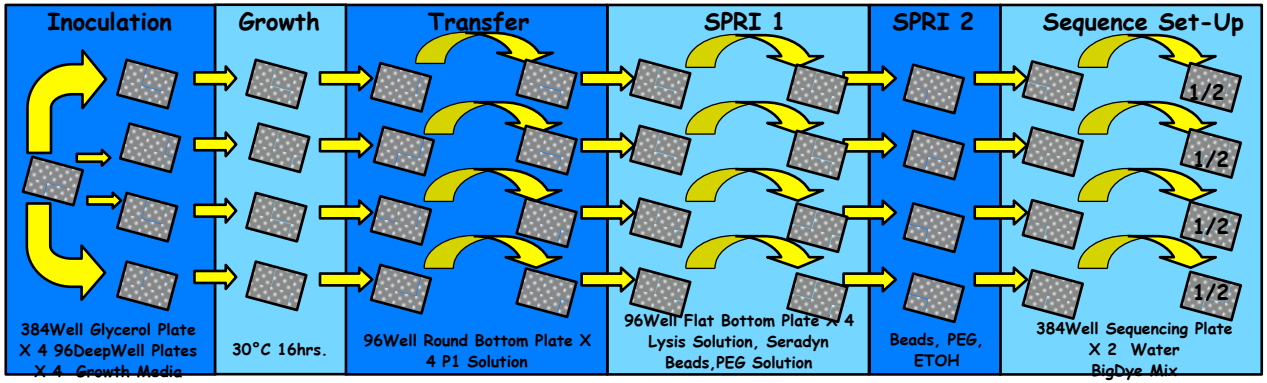
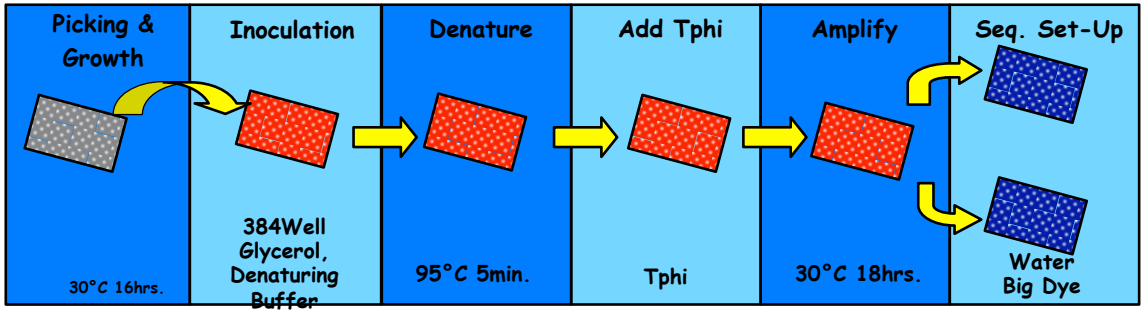
Evolution of the Large Scale Sequencing Process at the Broad Institute

SPRI 1998-2002

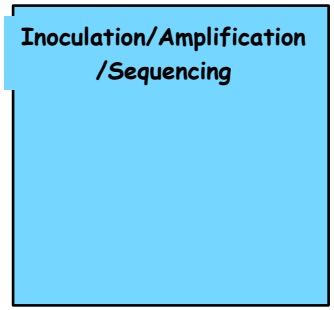


Detection

RCA 2002-2006



NanoFluidics 200?



	Consumables (Plates)	Transfer / Messaging Events	Operator Interactions	Total Reagant Volume (mL)	Total Liquid Volume Handled (mL)
SPRI	14	16	5	983.8	1084.8
Tphi	2	2	4	9.6	13.056
Chip	1	1	2	0.32	0.43

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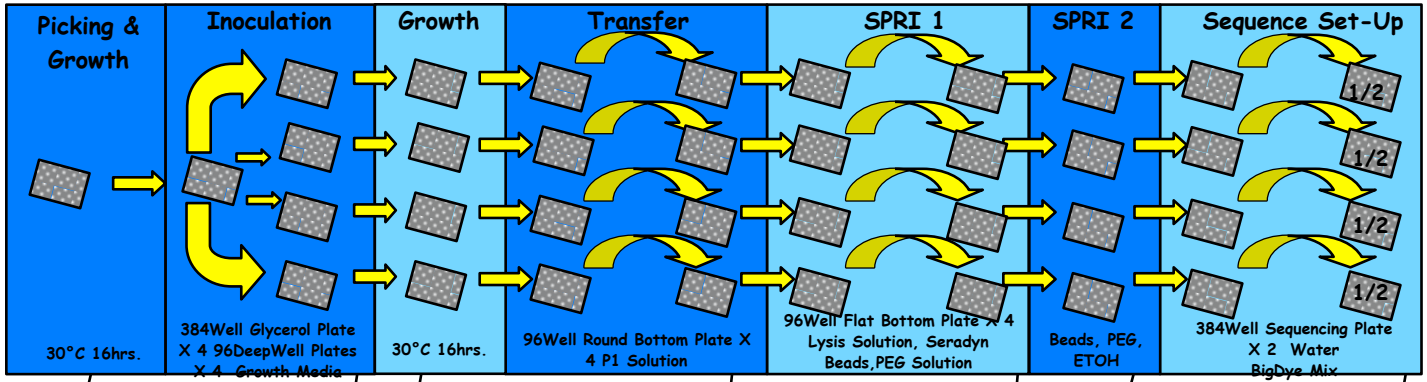
Evolution of the Sequencing Process at the Broad Institute

SPRI
1998-2002



Labeled DNA Yield f(???)

Growth Conditions (T, t, V, [TB]) QC

Inoculation (ΔV, Δt)

Growth Conditions (T, t, V, [TB], RPM)

Transfer (ΔV, Δt, [P1], pH, RPM) QC

SPRI 1 (ΔV, Δt, pH [SP1], RPM)

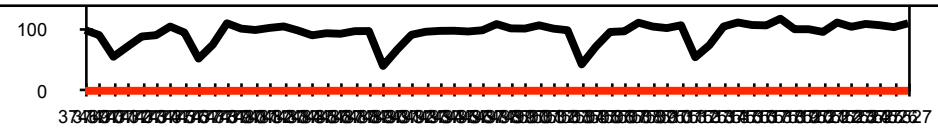
SPRI 2 (ΔV, Δt, [SP2], RPM)

Sequencing (ΔV, Δt, [BD])

- Complex: 16 Transfers
- Inherent variability
- Weak variable effects
- No intrinsic bounds
- Limited in-line QC

Learned how to improve from this process

- Toolbox: DOE, SPC, Pareto, etc.
- Design for Six Sigma Methodology
- Automation and Workflow for Control
- Supply Chain, Organizational Design



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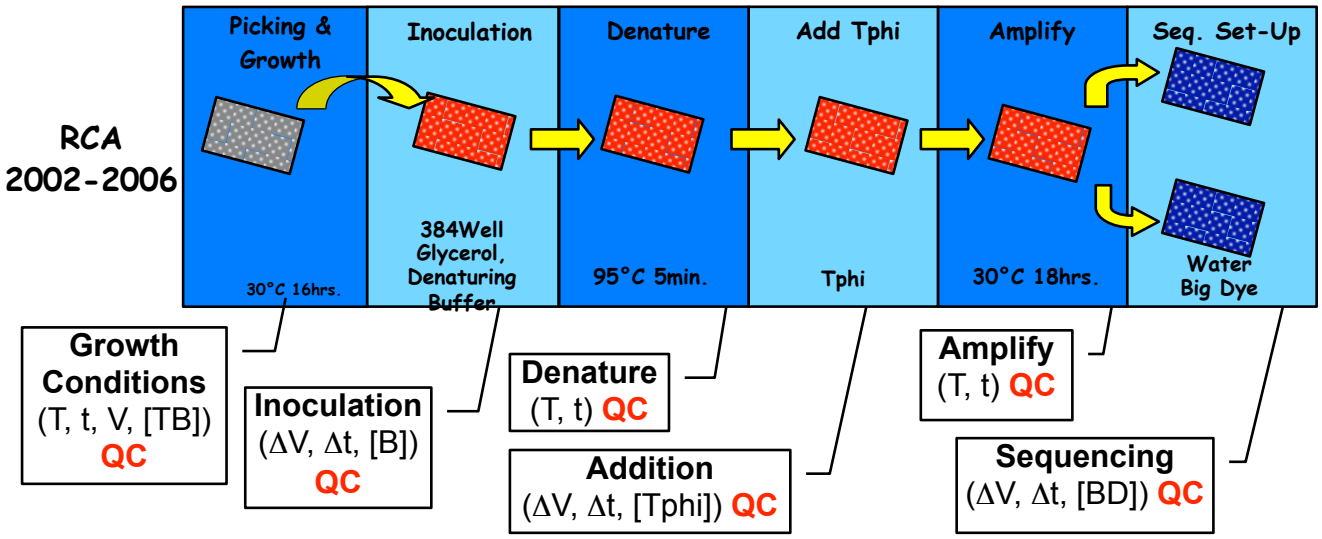
Evolution of the Sequencing Process at the Broad Institute



Labeled DNA Yield f([Tphi], t, [BD])

- Simple: 2 Transfers
- Inherent stability
- Strong variable effects
- Intrinsic bounds
- Greater in-line QC

Applied many lessons to this process

- Design in control / measurement points
- Test limits and identify design space
- Flexible Automation and Workflow
- Push Controls Back Into Supply Chain

Many Lean Elements

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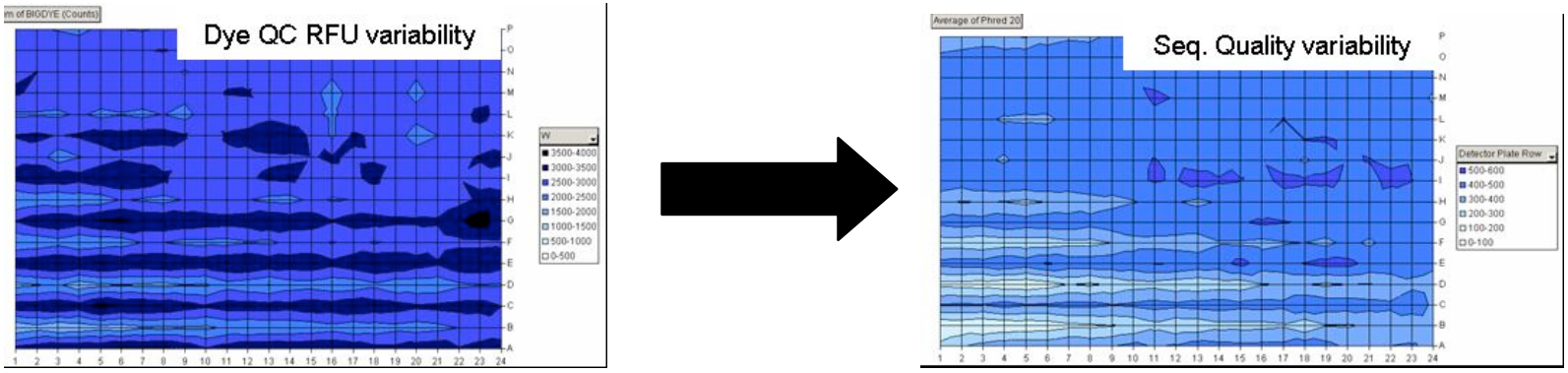
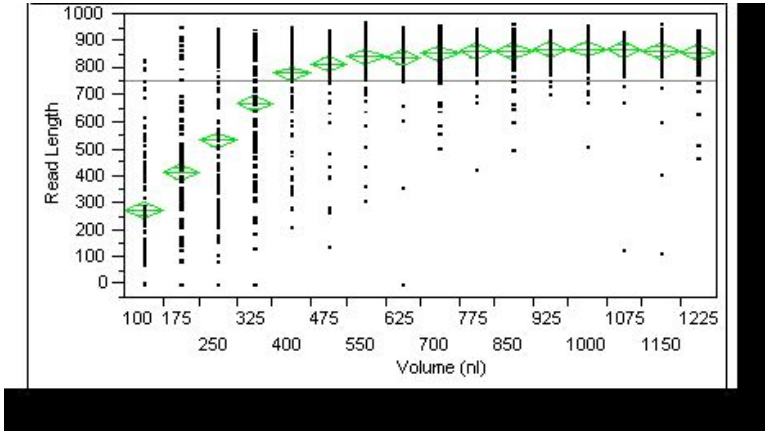
In Line QC Example



ANOVA analysis of reagent volume vs. quality



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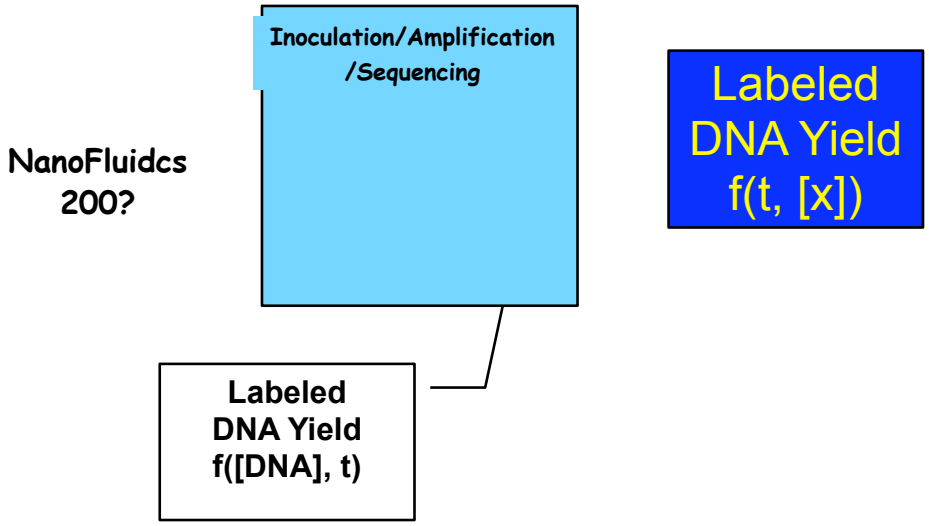
Evolution of the Sequencing Process at the Broad Institute



- 1 Transfer?
- No external effects
- Strong variable effects
- Intrinsic bounds
- In line QC

Next Generation… Same Lessons

- Design in control / measurement points
- Test limits and identify design space
- Flexible Automation and Workflow
- Supply Chain Matters

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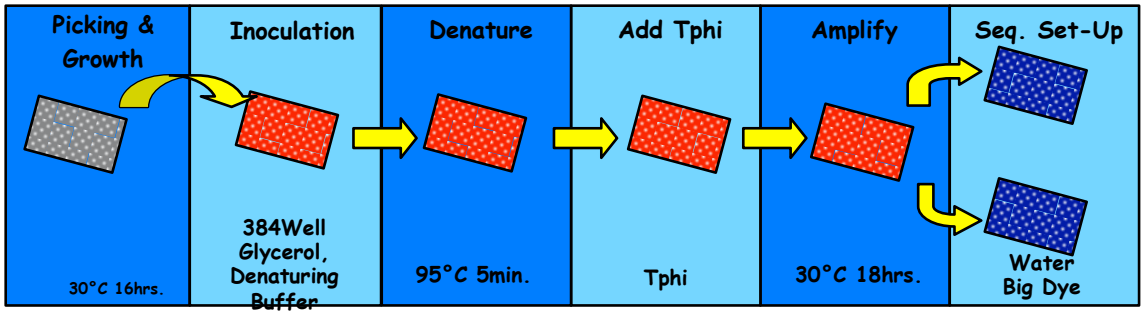
Devices Pictured: (1) Micronics, MIT / Broad Development Group (2) S.R. Quake, Caltech

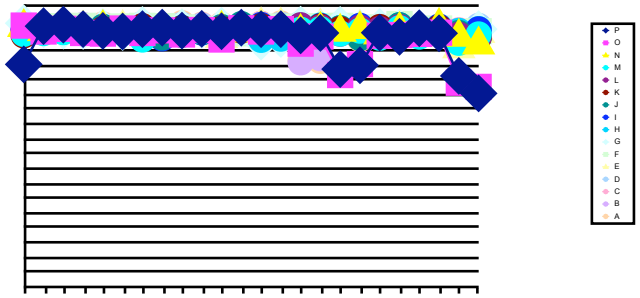
Remember Those Plates?
Lessons in Supply Chain Selection

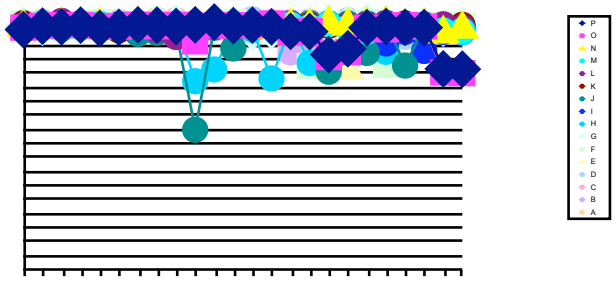
RCA



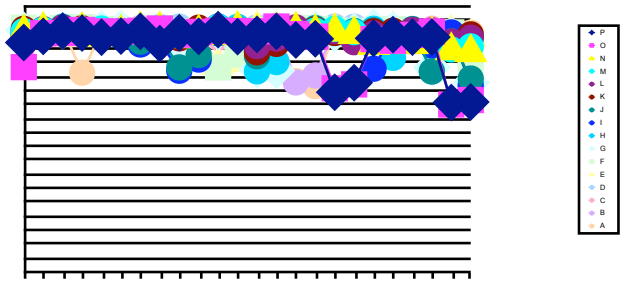
Only 3 plates
- 384 Well
- Plastic

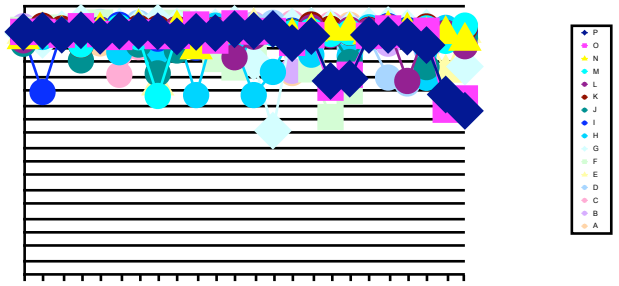
- Need ~207,000 plates for a 7x mammalian project
- Select the cheapest? Just plasticware, right?
- Process design validates all elements of supply chain
- Concurrent engineering – integration with other elements
- Impact of key elements on *overall system*





- Most Expensive!
- But Optimal For System





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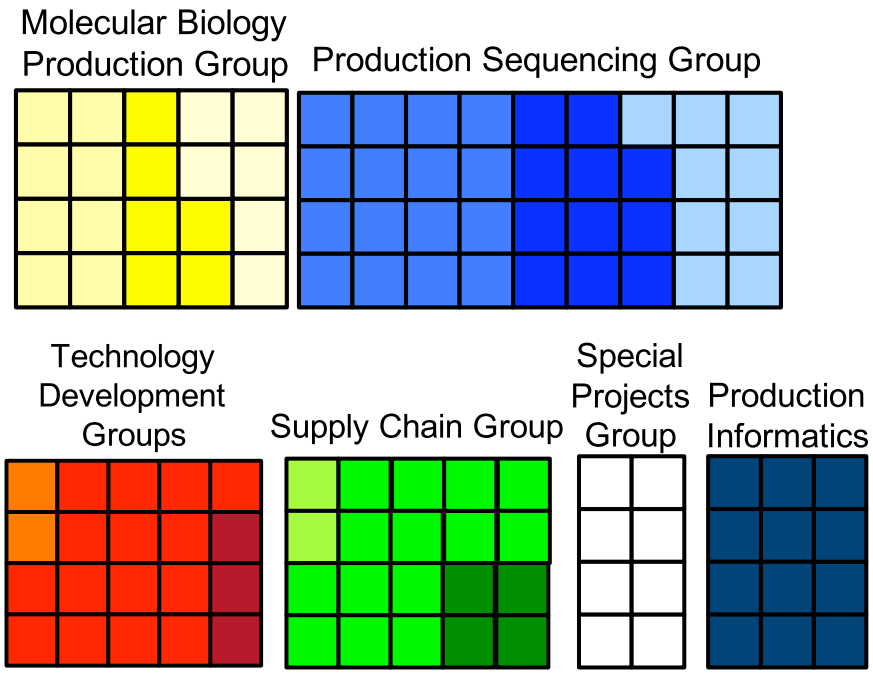
Organization Design
The Key to Lean Design

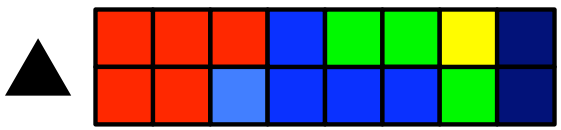
- Plate example required coordination of supply chain groups, development, and production
- >110 People in High Throughput Sequencing Platform
- How to ensure coordination and cooperation?

Hybrid Design

- Explicit cooperative projects resourced from Groups
  - Matrix like
  - Limited Number
  - Temporary
- Ongoing intra team work (and projects)
- Rotations for employees to provide system view

Organizational Design





- Integrated Process Teams
- Designated Leadership (▲)
- Large Scale Efforts Only

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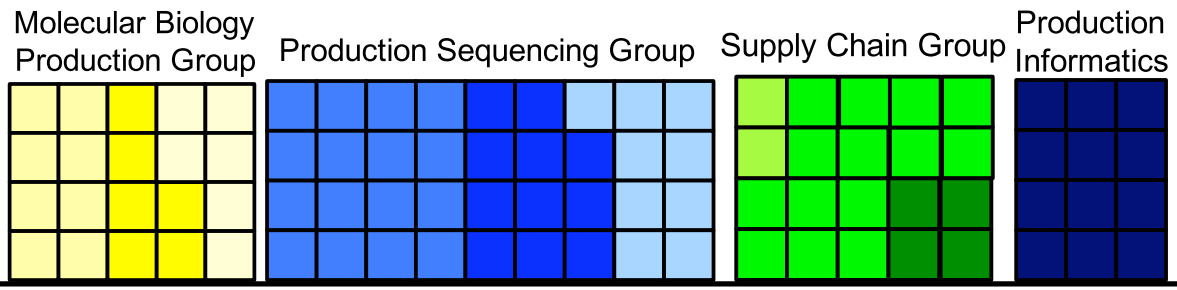
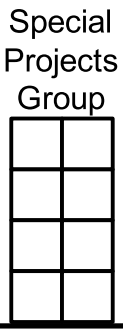
Organizational Design

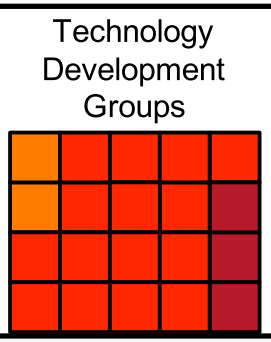
Production
- Stability
- Efficiency
- Improvement
- "Pilot Plant"

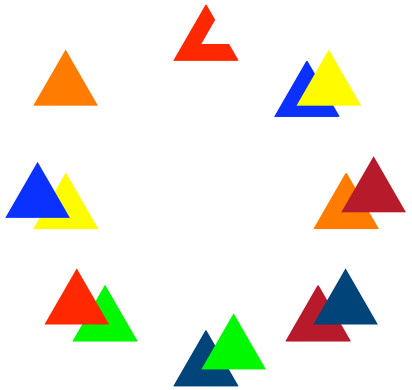


Special Projects
- One-Off
- External Interface
- R&D and Production
- Triage



R&D
- Next Generation
- Fast Cycle Time
- Risk Taking
- Prototyping





- Networked Leadership
- Cross-Group Backups
- Resource Balancing

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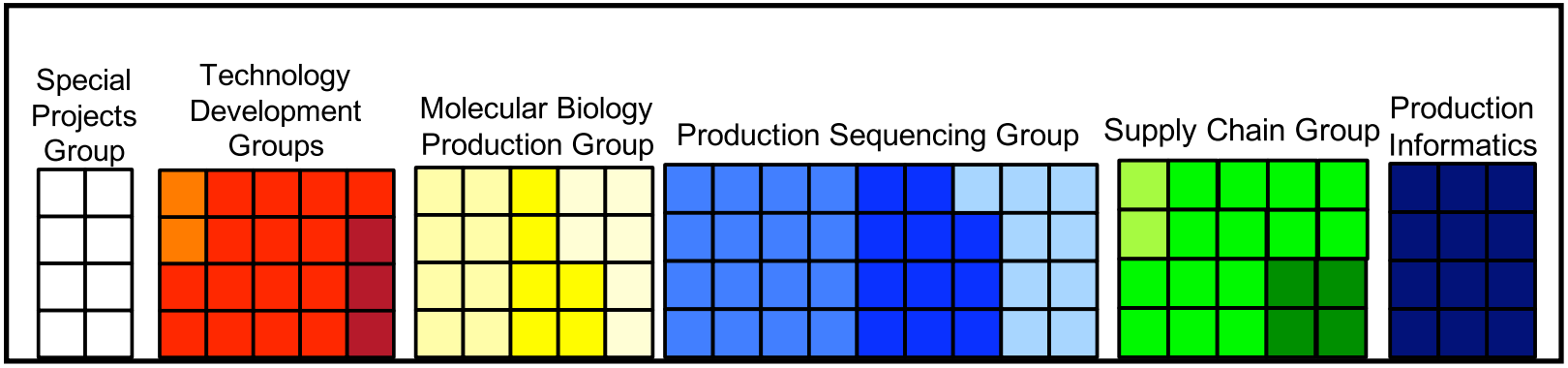
Organizational Design



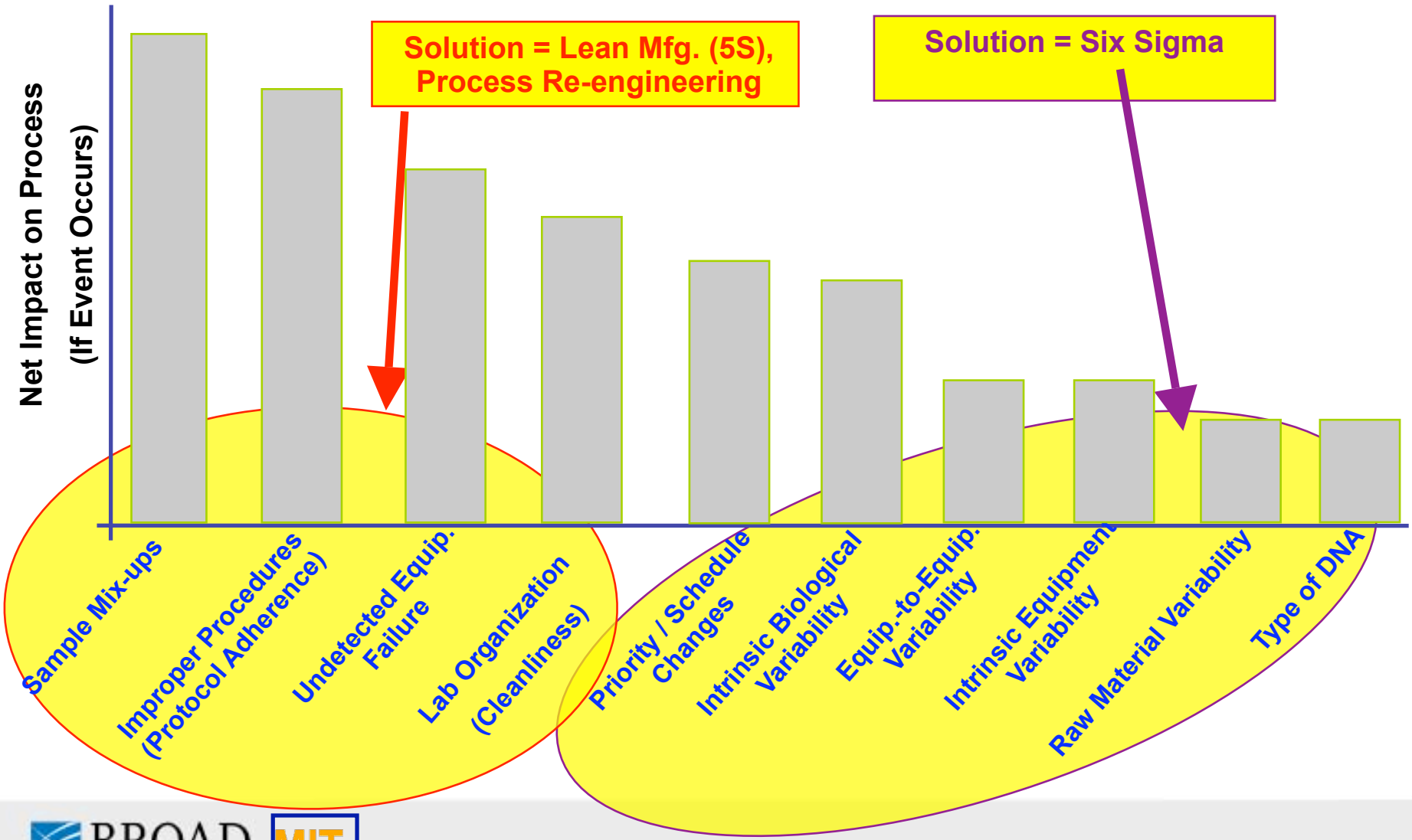
- Common Language
  - Process Improvement (Six Sigma, 5S)
  - Knowledge Sharing / Management (e-Lab notebook)
  - Bioengineering / Bioinformatics
- Integrated Supply Chain (protocols, MRP)
- Extensive Training (PMI, SAS, others)
- **System View, Lean Thinking**

Case Study: 5S Implementation

- Risk Analysis May 2004
  Molecular Biology Production Group (MBPG)
- Identified most likely failure modes and ways to address
- Pareto Categorization of Risks Showed Majority in workflow improvements: these dominated process variability
- Within process improvement toolbox most appropriate method for workflow is 5S
  - 5S* is a Japanese quality methodology to create a lean manufacturing process - walk into a Honda plant

***Sort, Straighten, Shine, Standardize, Sustain**

Risk Analysis - MBPG



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Ligation Workstations - Before

Problems

- Little dedicated equipment
- Most equipment in other locations
- No local stock of consumables
- No visual separation between two workstations
- Individual variation in workspaces

Ligation Workstations - After

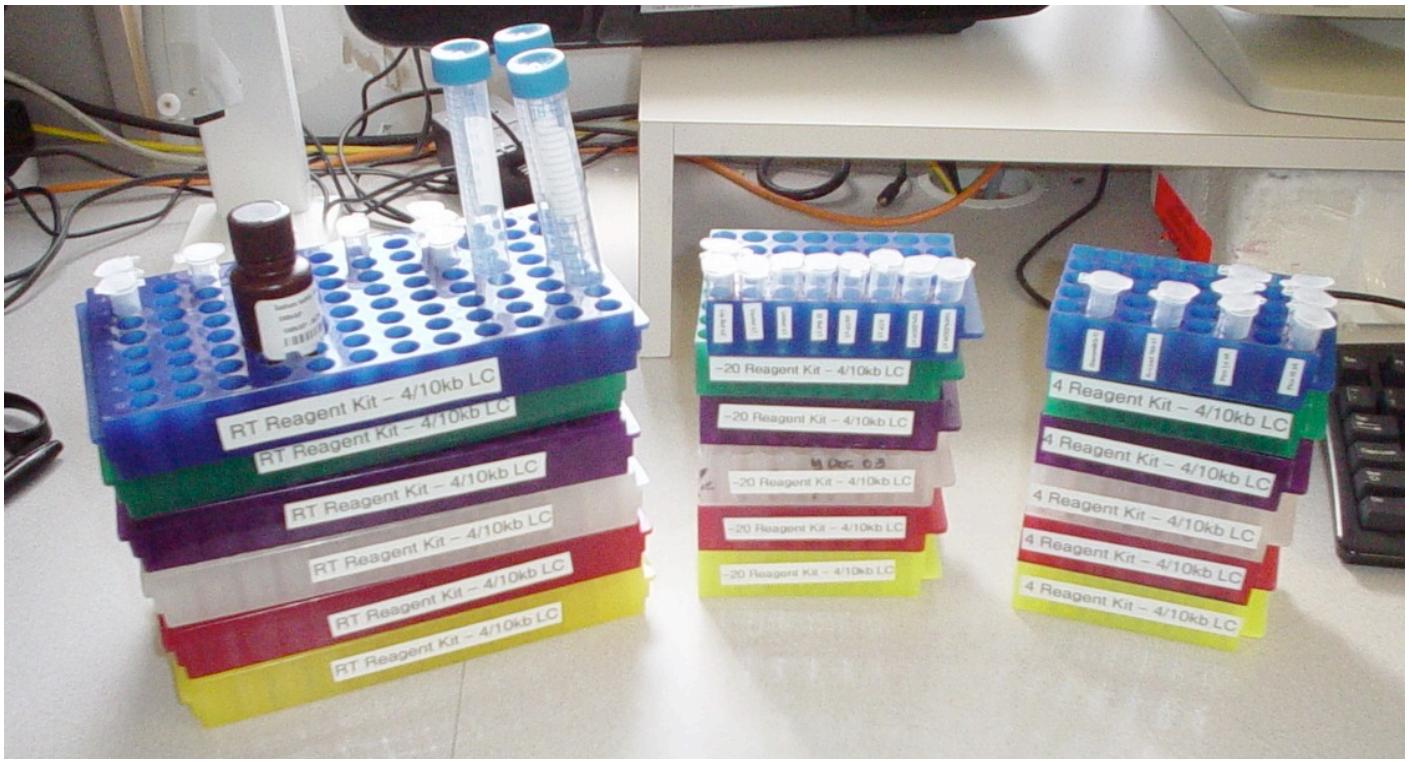
Solutions

- All dedicated equipment
- Most equipment local
- Full local stock of consumables
- Visual separation of workstations (red vs. blue)

Cycle Time Reduction

- **34% lower manual time**

Material Flow Improvement – Reagent Kits



Ligation Reagent Kits → **One for each temperature & color-coded for each workstation**

Purpose → **Eliminate multiple trips to mini-marts; Provide visual progress of week-long process**

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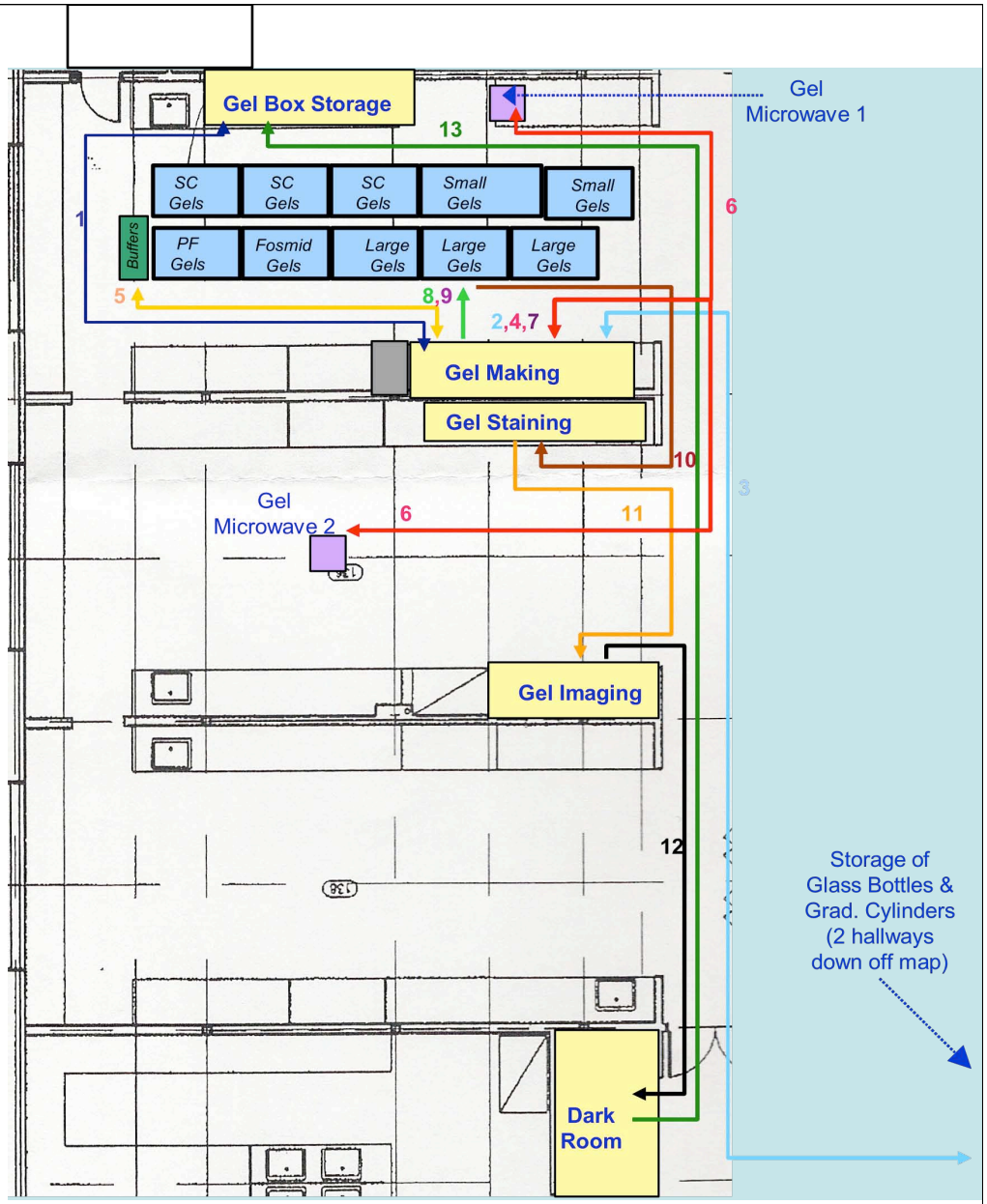
Gel Workflow – Before

Process Background

- Gels used for library construction, sizing, QC, and other uses

- 9 Work Locations
- 5 Rooms
- 6 Material Inventory Locations
- 8 Long Walks



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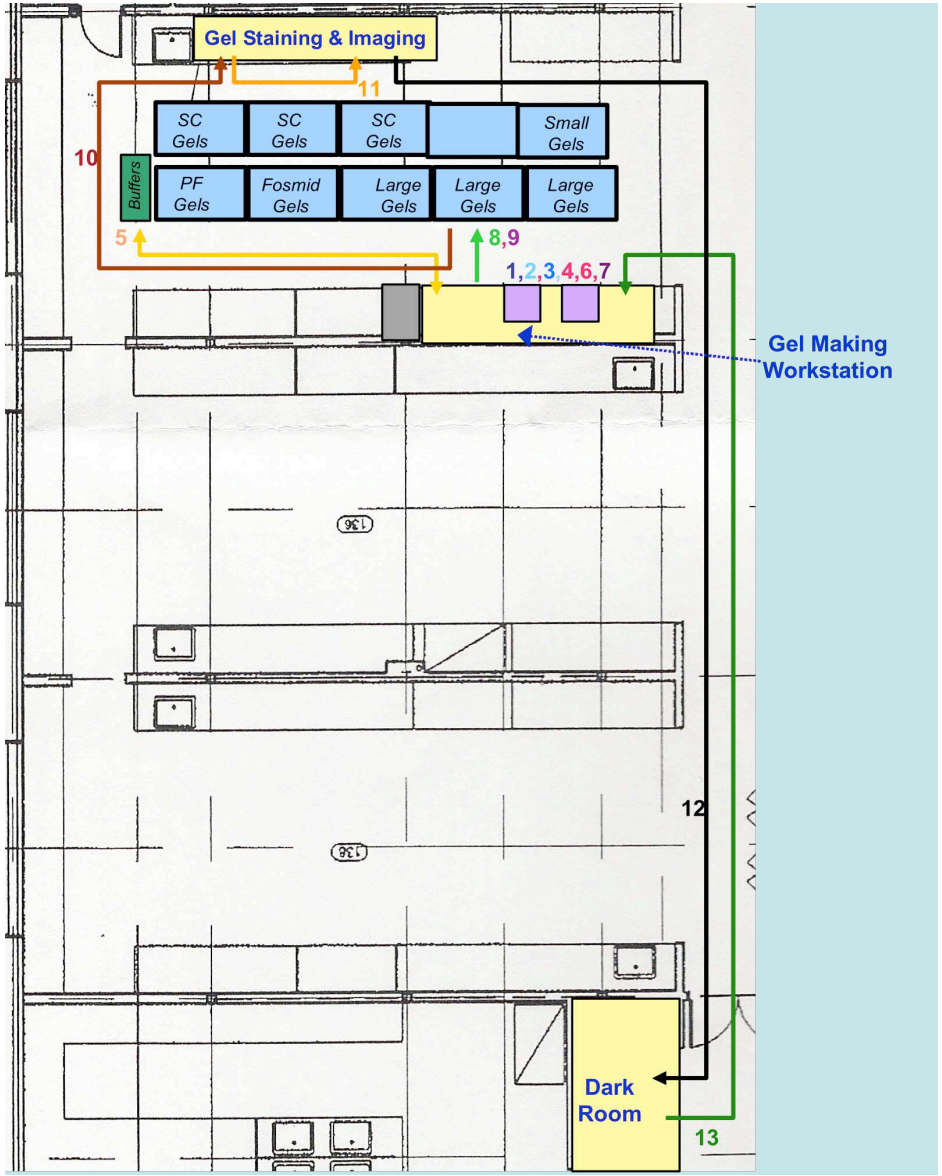
Gel Workflow – After

- 4 Work Locations
- 2 Rooms
- 3 Material Inventory Locations
- 4 Long Walks



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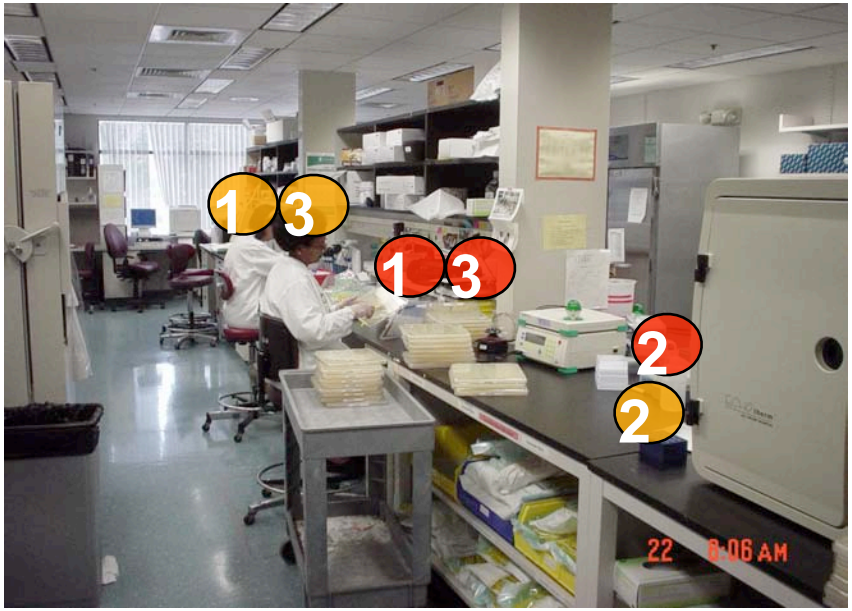
Creating a 5S Culture:

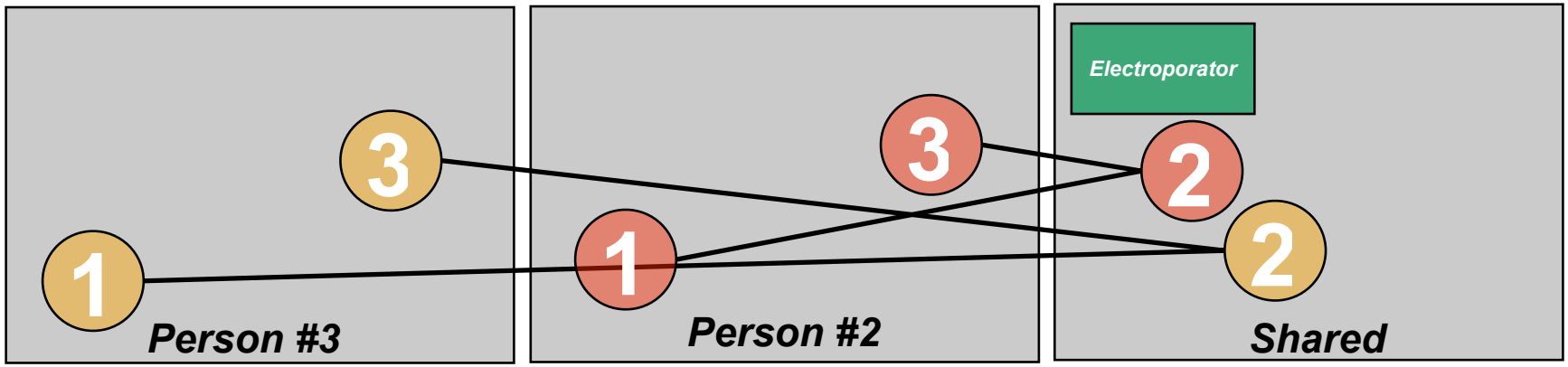
2-Person Transformation Workstation Before 5S



Transformation Steps

1. Set-up
2. Shock
3. Plate

Top View of Workstations



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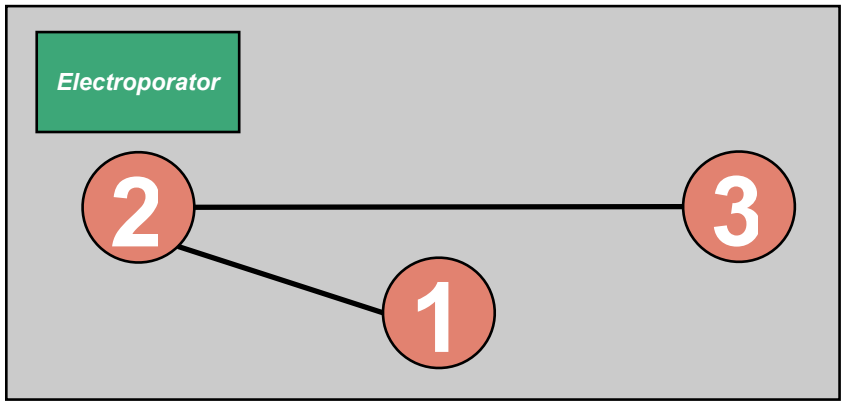
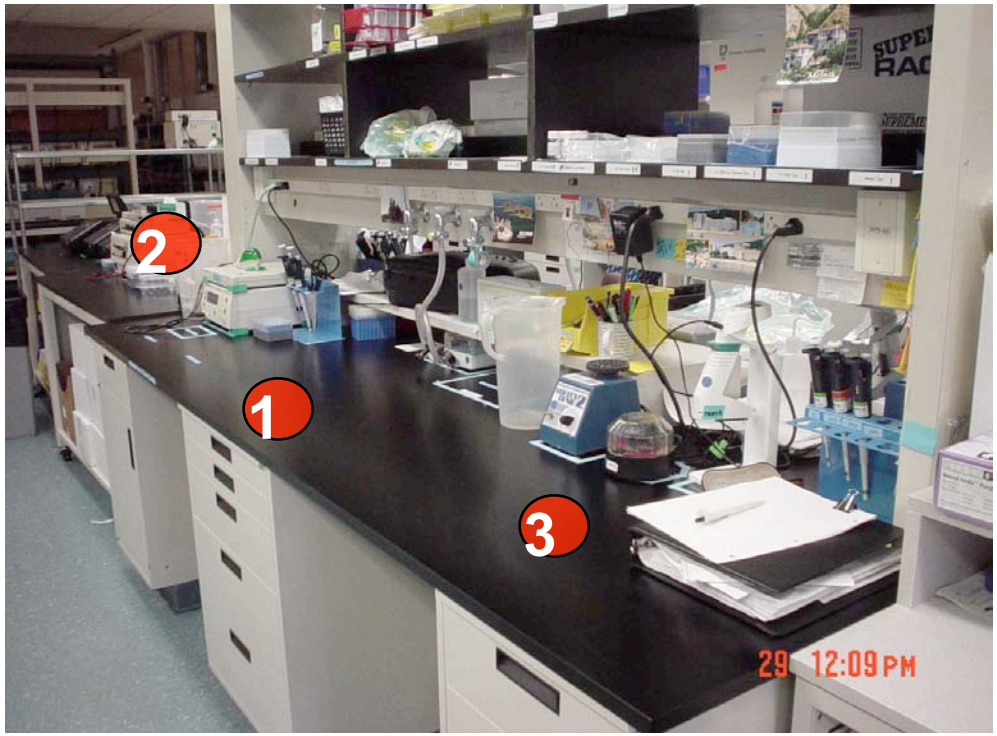
Creating a 5S Culture:

Prototype Workstation

Created By: Group Coordinator, LFM Intern

Top View of Workstation





Transformation Steps

1. **Set-up**
2. **Shock**
3. **Plate**

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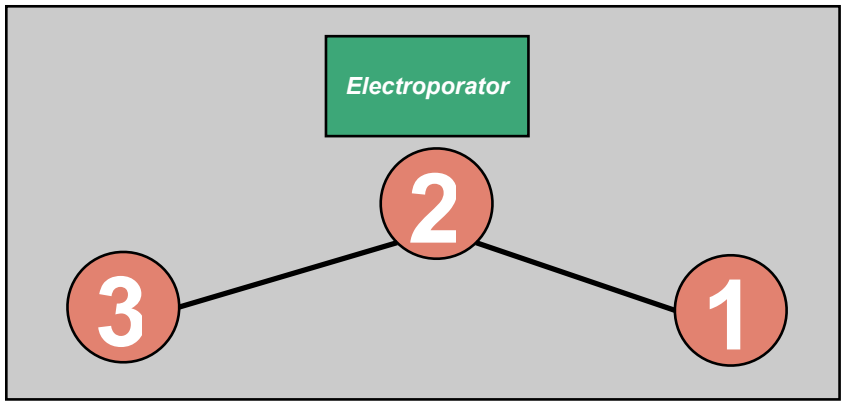
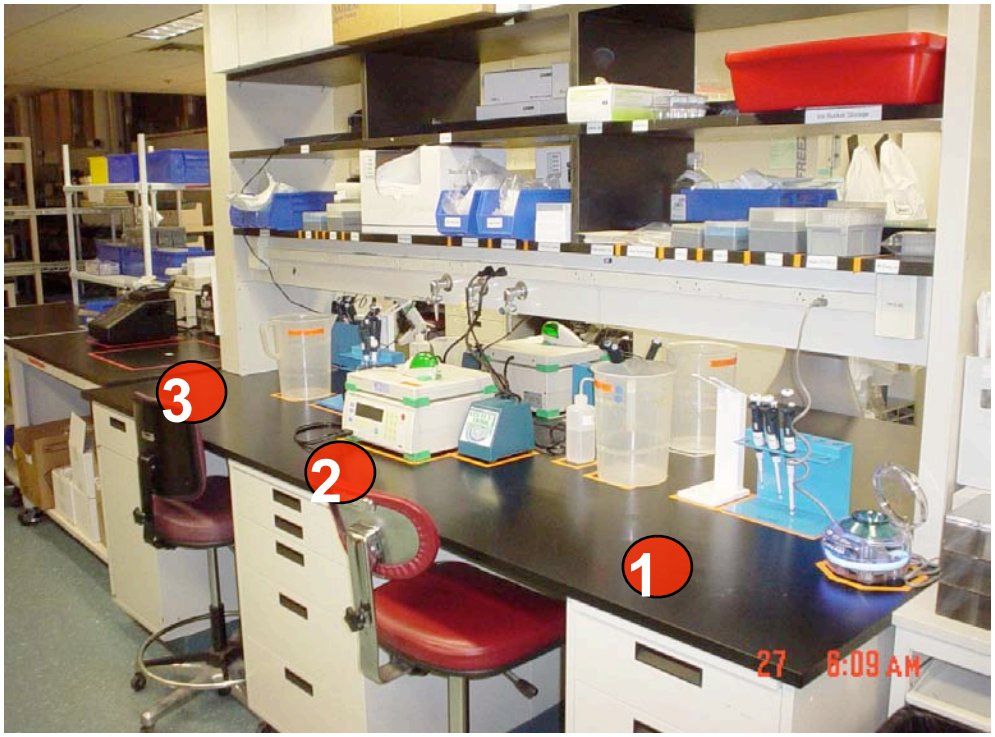
Creating a 5S Culture

Final Workstation

- Created By: *Research Technician, Lab Assistants*

Top View of Workstation





Transformation Steps

1. Set-up
2. Shock
3. Plate

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Metrics

Metric	Month				[Current] / [Baseline]
	May-04	Jun-04	Jul-04	Aug-04	
High-Level Measurements					
Number of Potential Sample Mix-up Points	71	71	54	36	50.7%
No. of Improved Workflows *(before & after floor maps)*	0	0	3	9	n/a
5S Checklist Score					
Material Efficiency Measurements					
Material Consumption per Month *(total units)*	24,570	13,734	8,665	7,508	30.6%
Material Consumption per Month *($$)*	$82,536	$78,828	$78,995	$53,248	64.5%
[Required Materials *(units)* ***/ Supplied Materials*** *(units)* ***]***	22.0%	40.2%	63.8%	80.3%	364.9%
[Required Materials *($$)* ***/ Supplied Materials*** *($$)* ***]***	64.9%	68.6%	78.6%	121.8%	187.7%
Number of Inventory Locations	24	24	19	17	70.8%
Number of Materials Replenishment Locations	13	13	10	10	76.9%
No. Labeled Materials & Reagents	168	168	531	1074	639.3%
Capital Productivity Measurements					
Cumulative Amount of Recovered Lab Floor Space *(sq. ft.)*	0.0	0.0	68.1	141.2	n/a
Recovered Floor Space / Total Floor Space	0%	0%	2.8%	5.8%	n/a
Recovered Capital	$0	$0	$2,899	$6,010	n/a
Cycle Time/Productivity Measurements					
Transformation Team Output *(# passed plates / month)*	3313	4096	3864	3580	108.1%
Transformer Productivity *(# passed plates / person / month)*	60.8	58.3	52.8	51.8	85.2%
Agar Plate Pass Rate *(proxy for "Right 1st Time")*	96.8%	96.5%	93.4%	90.9%	93.9%
Cycle Time per Library Attempt *(hr.)*	72.3	72.3	72.3	69.1	95.6%
Manual Cycle Time (hr.)	*9.3*	*9.3*	*9.3*	*6.1*	*65.8%*
Machine Cycle Time (hr.)	*63.0*	*63.0*	*63.0*	*63.0*	*100.0%*
Available Ligation Capacity *(library attempts / month)*	17.8	17.8	14.8	12.6	70.6%
Individual Ligator Capacity *(library attempts / month / person)*	3.0	3.0	3.0	3.1	106.0%
Library Construction Team Output *(# libraries / month)*	52	35	48	55	105.8%
Library Construction Team Output *(# attempts / month)*	13	11	20	15	115.4%
Ligator Productivity *(# libraries / person / month)*	8.7	5.8	9.6	13.8	158.7%
Ligator Productivity *(# attempts / person / month)*	2.2	1.8	4.0	3.8	173.1%
Library Pass Rate *(proxy for "Right 1st Time")*	87.9%	76.5%	95.8%	90.5%	103.0%

Baseline

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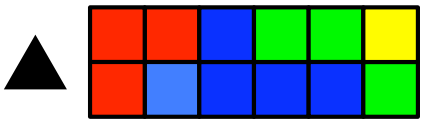
5S Project Key Results

- Reduced # of potential sample mixup points by 50% (71 to 36)
- Reduced MBPG material cost by 35%
- Reduced # of material storage areas by 30%
- Reduced manual cycle time by 34%
- Reduced hazardous reagent travel by >75%

- **Implemented sustainable improvement system owned by employees**



Process Risks Example: Sequencing

#	Process	Suspected Source of Variability	Source Type	Potential Impact	Expected Detection Result	Root Cause Validated?	Current Preventive Action	Current QC Measure	Proposed Preventative Action	Proposed QC Measure
1	1_Colony Picking	Contamination from machine surfaces	Machine	Contamination of Culture	Mixed Sequence				Routine cleaning	Routine swab test?
2	1_Colony Picking	Picking Machine Min. Diameter too low	Machine	potential of missed colonies	Empty Sequence				enforcement, checklist, LIMS feedback	
3	1_Colony Picking	Picking Machine Proximity Too Low	Machine	Increased potential of double picks	Mixed Sequence				Standardized imaging settings, Protocol enforcement, checklist, LIMS feedback	Automated seq. Characterization - correlate with plate densities, automated tracking of plate
4	1_Colony Picking	Picking Machine Wash Bath Contamination	Machine	Contamination of Culture	Mixed Sequence				Regular bleach soak	inoculate pins into control glycerol after first and last wash/station, O/N Growth Control plates
5	1_Colony Picking	Picking Machine washing is insufficient	Machine	Contamination of Culture	Mixed Sequence				Protocol enforcement, checklist, LIMS feedback	O/N Growth control , Logs/LIMs Reports
	ony Picking	Picking Pins bent or broken	Machine	Increased potential of missed colonies	Empty Sequence		Pin Maintenance, Pin Fire Test	Visual Inspection	Visual inspection by operators or maintenance team, Pin alignment tool?	SQUID: Quality by deck by well?
	on	Plate Density		Increased potential of	Mixed				Define "Dense plates" and picking	Automated logging of instrument settings, LIMS
8	1_Colony									

There are 108 more rows....just for production sequencing

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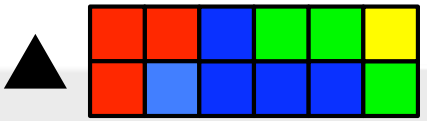
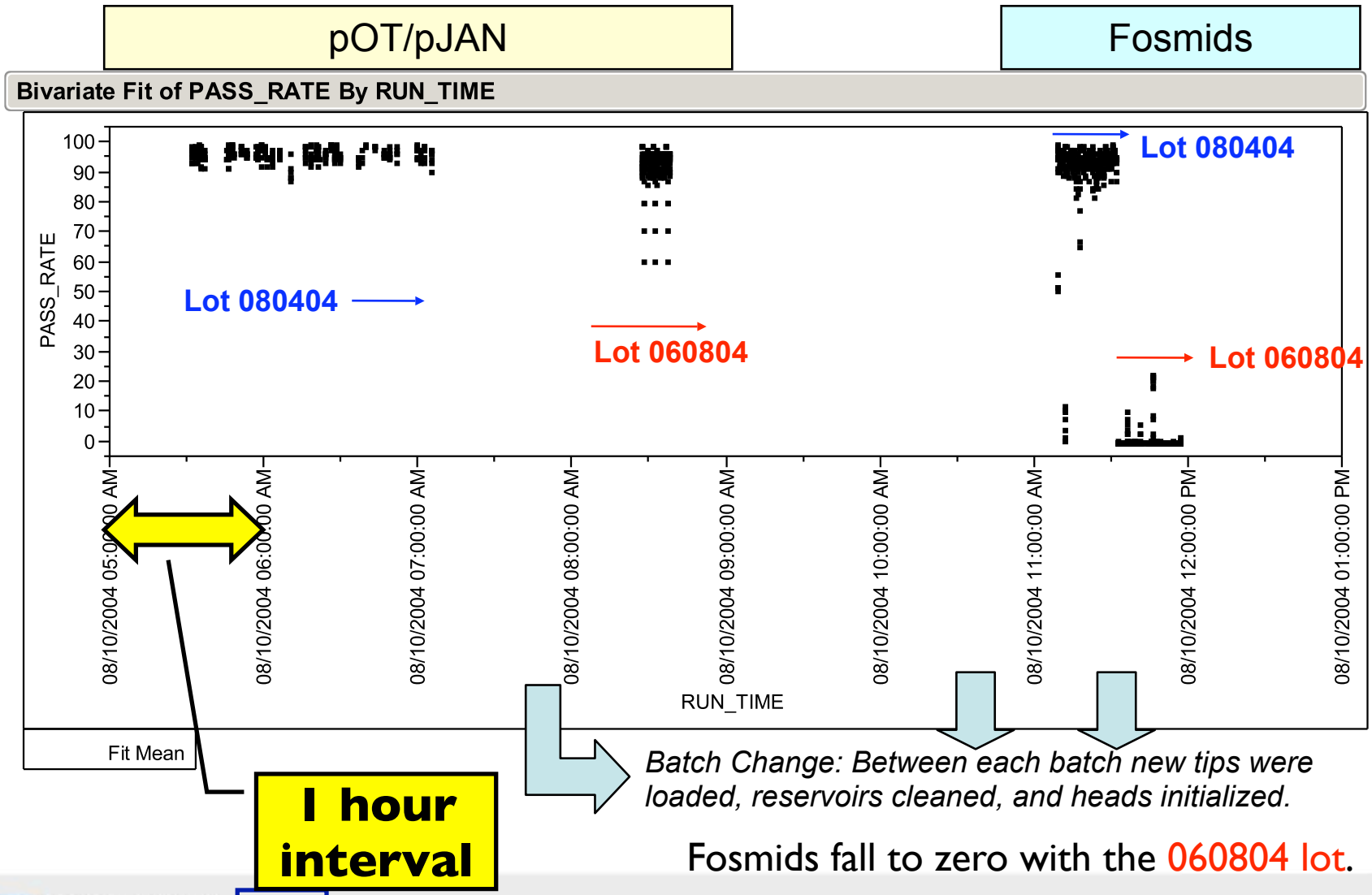
Case Study: Supply Chain Risk
Tphi

- June-August 2004 received planned Tphi orders from General Electric ($1.6 Million cost)
- GE production lot **#060804 received first**
- **Failed** routine QC to certify material for production
- Broad MRP system rules ensured adequate safety stock of current production lot **#080404**
- Began Integrated Troubleshooting



Lot #060804 Process Test



Fosmids fall to zero with the 060804 lot.

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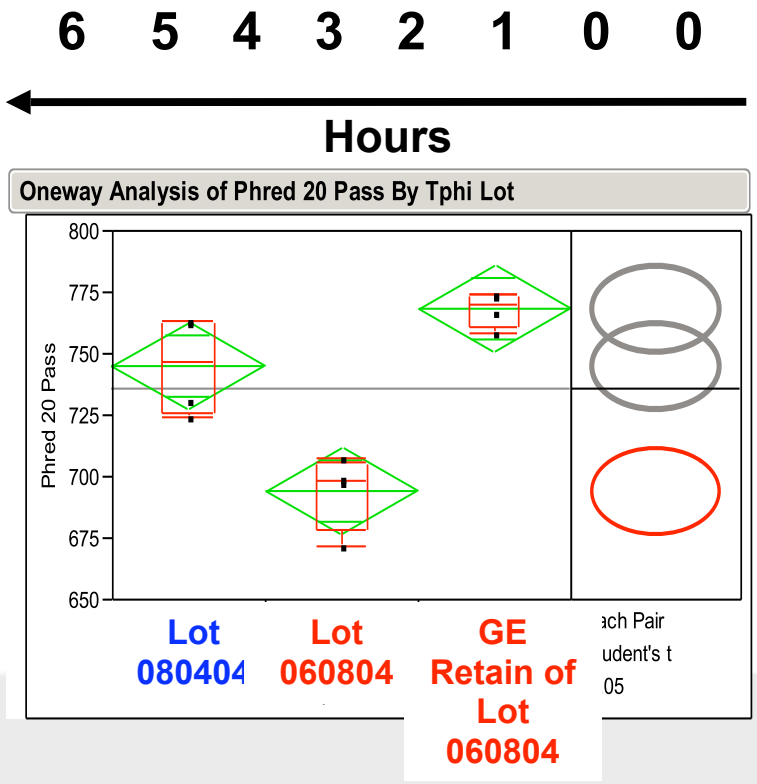
Lot #060804 GE Fill or Shipment Failure?

- Broad Process development program had identified phenotypes of failure modes, one very similar
- Short term heating of Tphi premix above 4ºC causes non-specific amplification
- Partially activated Tphi reduces overall yield
- Requested retain sample from GE manufacturing Facility (from original lot)



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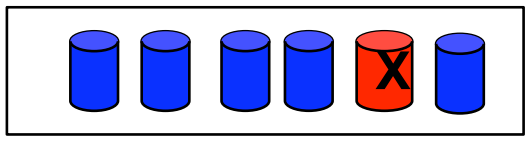
Lot #060804 Shipment Failure Confirmed

- Instituted additional gel validation as part of QC
- And Cold Chain monitoring (temperature tags)
- In August received a ***second Tphi lot #082504*** which *failed* new gel QC
- GE retain samples now also showed decreased yield
- Lot data also showed variation in individual bottles
- Pointed to fill stage at GE

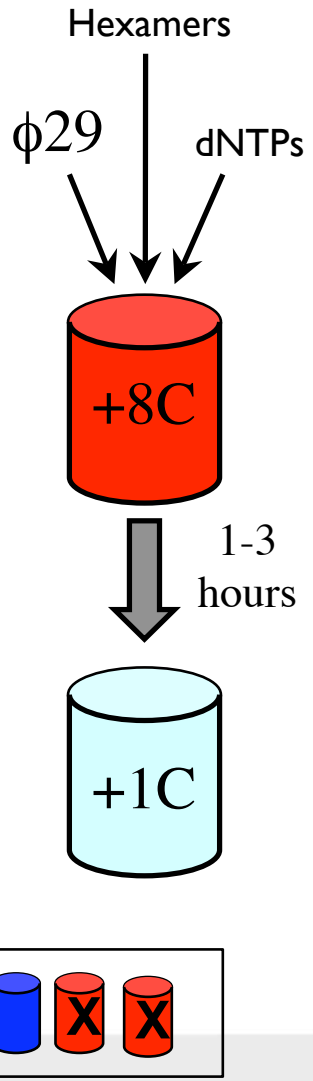


Temperature Tags OK

Lot #082504 Fill Failure Confirmed

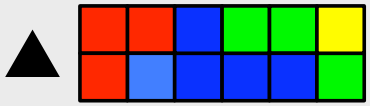
Broad/GE task force narrows failure to cold room

- Cold room keeps large vessels filled with buffer, before critical reagents are added
- Temperature was not closely monitored, could range from +1C to +8C (above activation temp.)
- When a “warm” vessel was used, the enzyme would become active and begin amplification
- First bottles filled received activated material explaining the low performing bottles, and improving as the vessel cooled



Lots #060804 and #082504 Summary

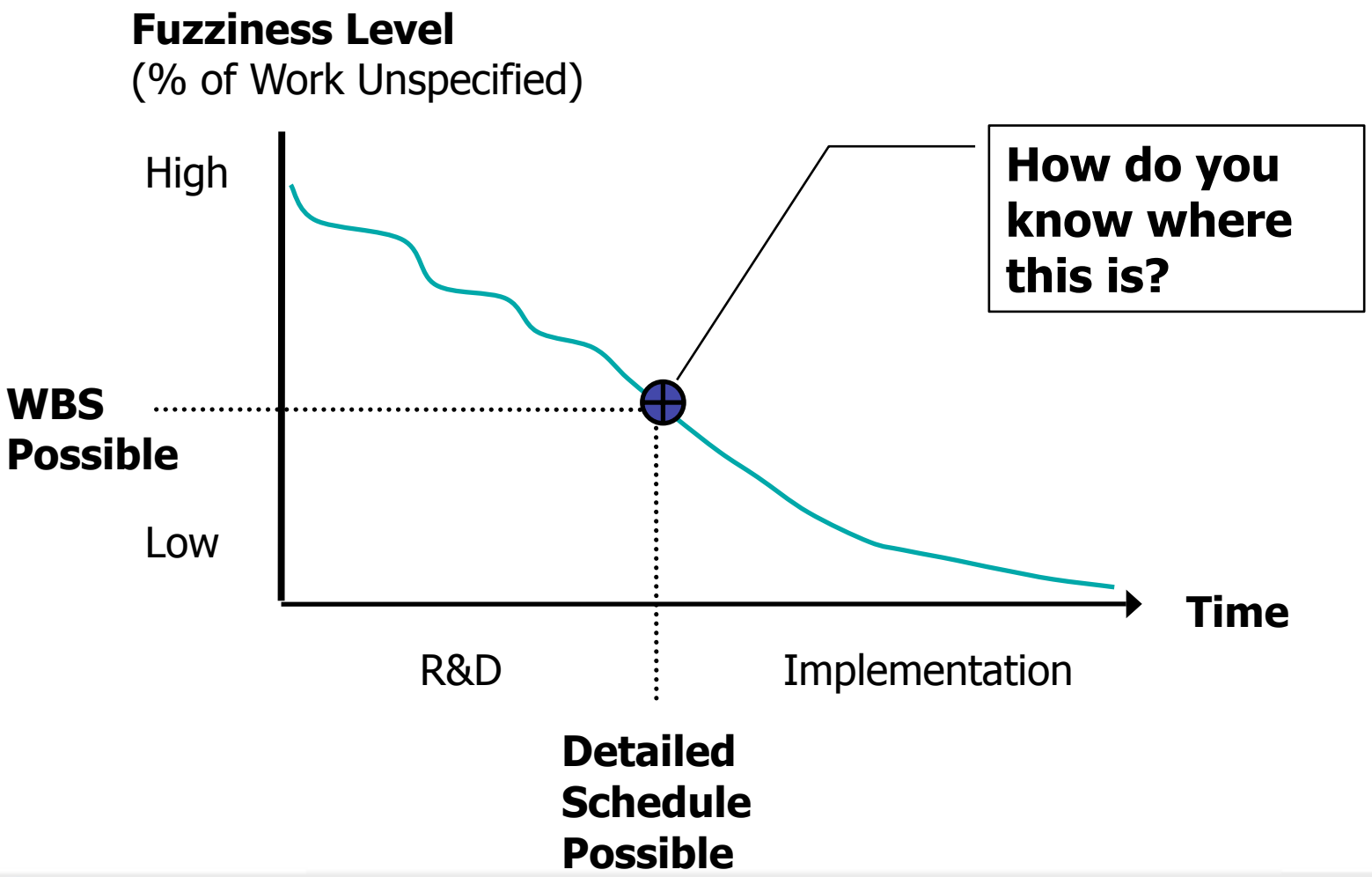
- Entire diagnostic process took ~5 weeks and involved nearly all teams and tools
- Broad and GE both six sigma organizations – greatly facilitated troubleshooting
- GE changed process to eliminate failure modes identified
- GE replaced $1.6 Million of Tphi material for Broad
- Broad has redesigned all Tphi QC processes adding gel, kinetics, cold chain, and in line assays
- This never impacted quality, throughput, or cost, but added significant value to GE, Broad, and NIH/NHGRI



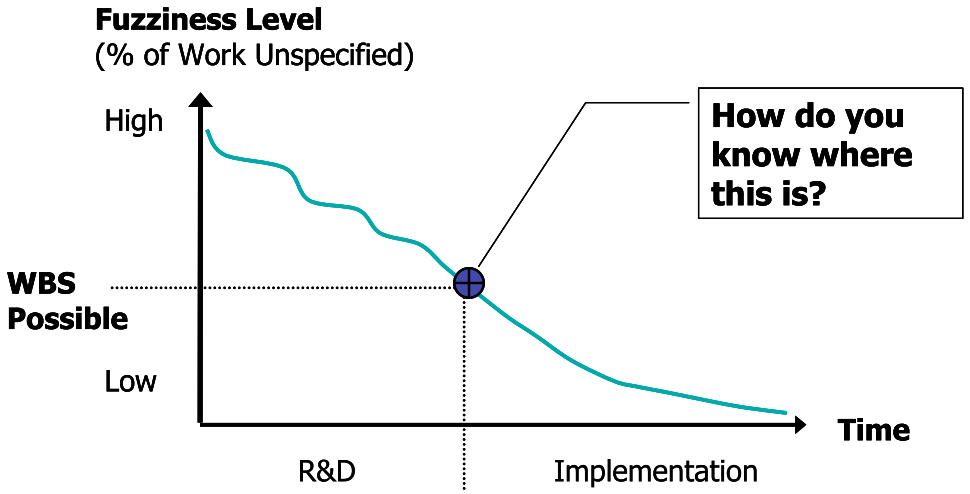
MIT Leaders for Manufacturing Internships at The Broad Institute

- **Louis Herena – LFM 1999**
  - "Application of Manufacturing Tools to the DNA Sequencing Process"
- **Scott Rosenberg – LFM 2003**
  - "Managing a Data Analysis Production Line: An Example from the Whitehead/MIT Center for Genomic Research"
- **Julia Chang – LFM 2004**
  - "Control & Optimization of the Colony Picking Process"
- **Kazunori Maruyama – LFM Class of 2005**
  - "Optimization of Detection Process in Genome Sequencing"
- **Matt Vokoun – LFM Class of 2005**
  - "Sources of Variability in Molecular Biology Processes used in DNA Sequencing"
- **Dave Penake – LFM Class of 2006**
  - "Quality, Consistency and Sample Tracking in Genomic Library Construction"
- **Kerry Person – LFM Class of 2006**
  - "Buffer Reduction and 5S Implementation at The Broad Institute"
- **Scott Couzens – LFM Class of 2006**
  - "Materials Change Management at a Genome Sequencing Center"

Process Design Phase Curve



Process Design Phase Curve



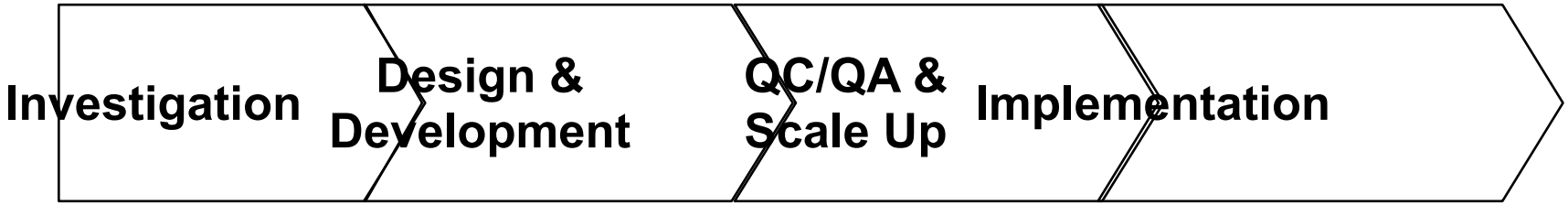
R&D

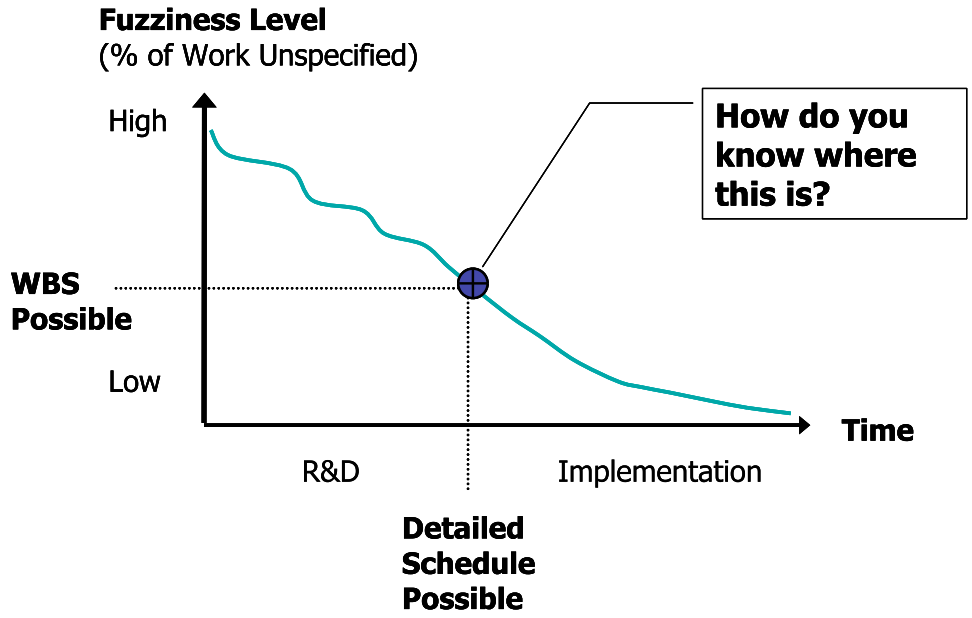
- Same Tools
- Design Space
- Control Variables
- Simplification
- *Rapid Cycle Time*

Implementation

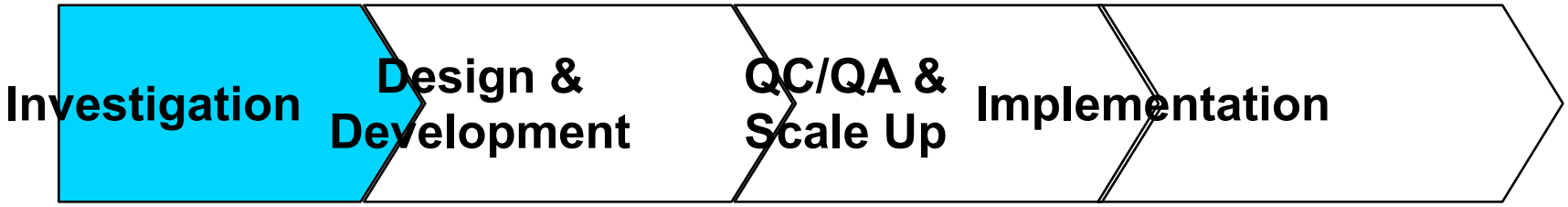
- Robustness
- Efficiency
- Quality
- Modularity
- *Flexibility*

Process Design at Broad



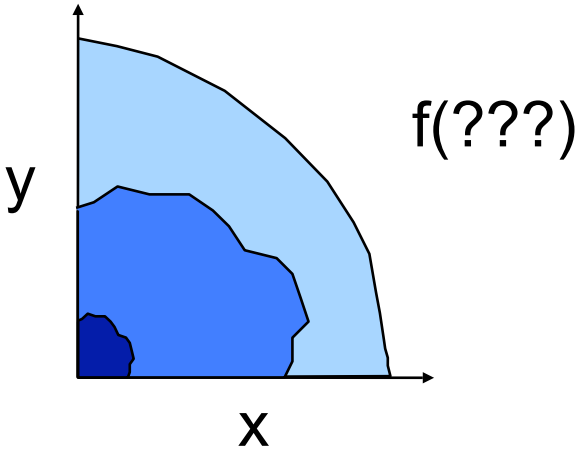


Process Design at Broad

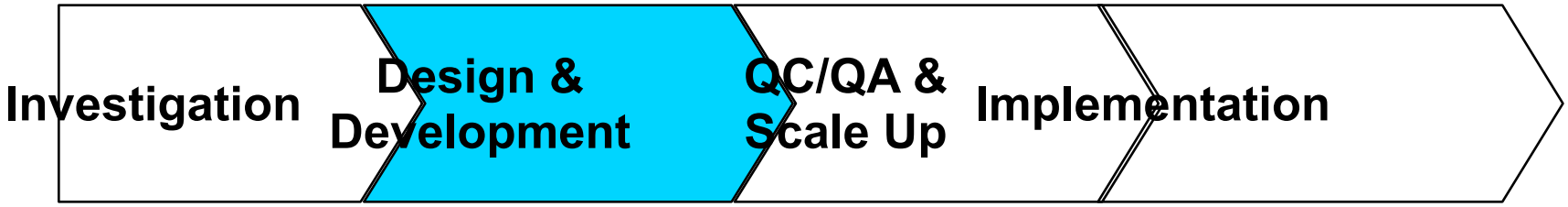


- Define Goals
  - Specific
  - General Understanding
- Feasibility Check
- Design Space Hypothesis
  - Process Variables
  - Constraints

Design of Experiments
Scheduled Testing
Idea Pipeline
Speed

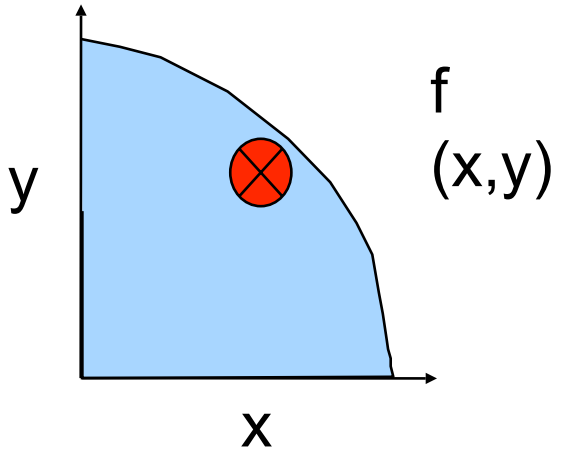


Process Design at Broad

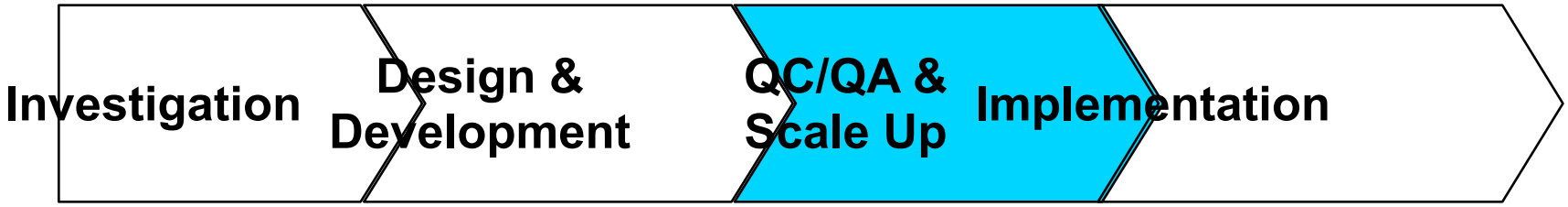


- Narrow Operational Space
  - Robustness
  - Ease of Implementation
  - Optimality
- Characterize Operational Space
  - Variable Interactions
  - Extreme Conditions
  - Likely Failure Modes
- Supply Chain

Design of Experiments
Process Maps (interactions)
Prototypes

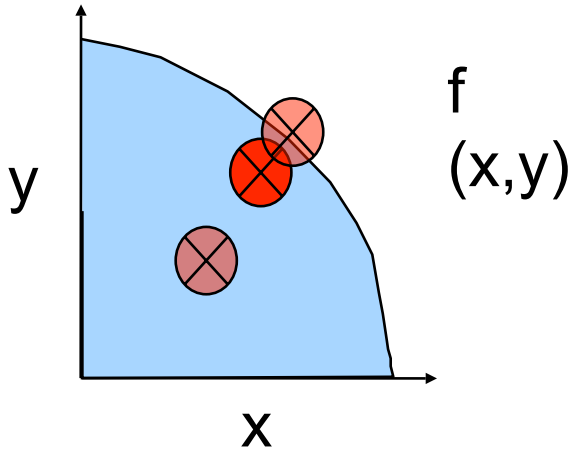


Process Design at Broad

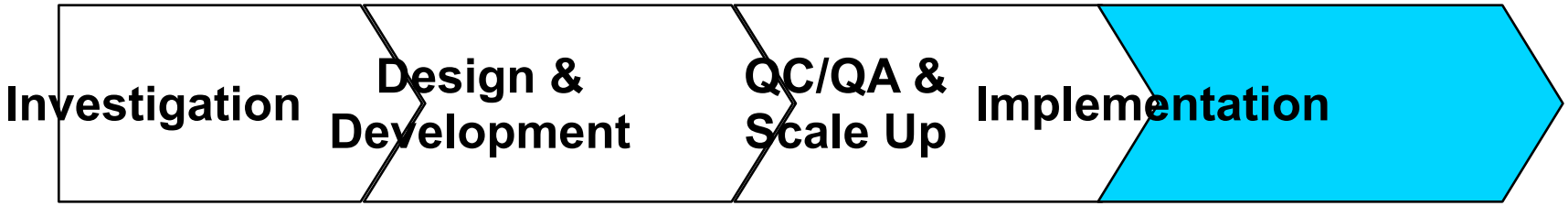


- Verify Control Variables
  - QC sensitivity
  - System Response to variation
- Scale Effects
  - Response changes at scale
  - Unforeseen interactions
  - Design Point Change
- Supply Chain

Design of Experiments
Full Scale Prototypes
Six Sigma Analysis
Workflow Design

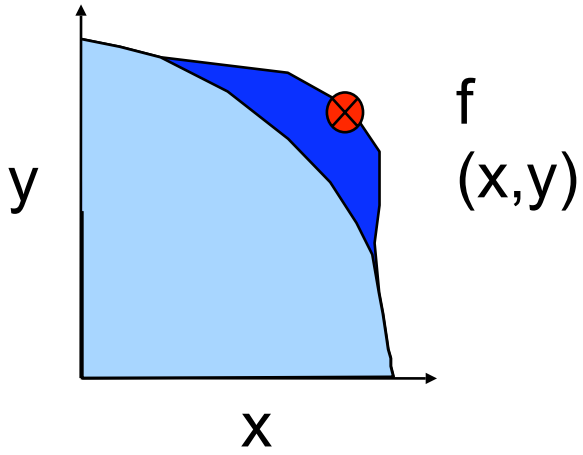


Process Design at Broad



- Stabilize Process
  - Bills of Material (MRP)
  - Equipment
  - Procedures
  - Training
- Ongoing Improvement
  - Process Owner
  - Feedback
  - Optimization

Six Sigma, 5S



Lessons Learned

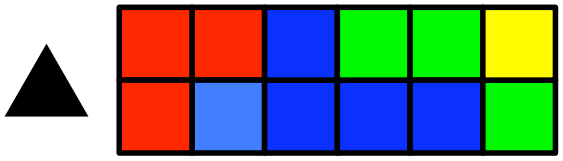
Lean requires a systems view

- Understand system constraints
- Organization must match goals
- Interconnections matter
- Process Improvement tools matter

Kerr-McGee Nansen
Spar Platform -3,675 ft.

vs.

Whitehead Institute
Genome Center (ca. 2000)



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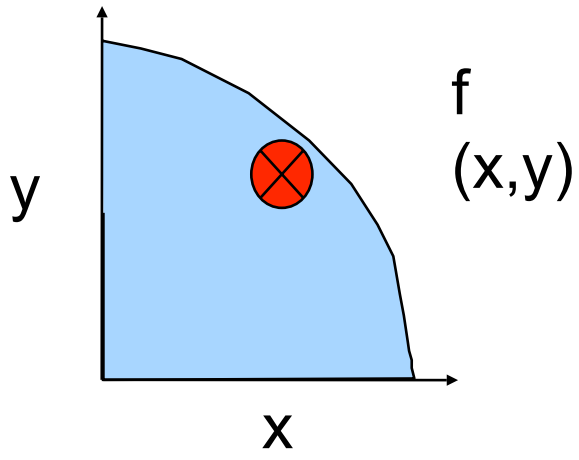
Lessons Learned

"Process Options" are critical in Lean Enterprises

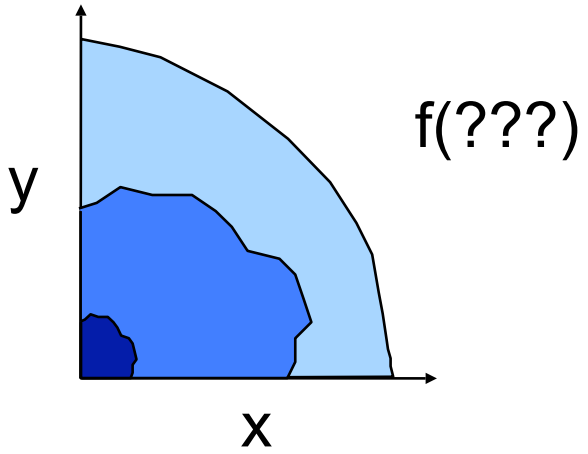
- Supply chain redundancy and buffers are one aspect
- Operational flexibility is another
- Must understand design space
- Cost versus value can be analytic



Lessons Learned

Innovation is hard work - Lean Ideas can help

- Organization should enable it
- Schedule opportunities for Eurekas
- Process Improvement culture is great foundation
- Cycle time is absolutely critical



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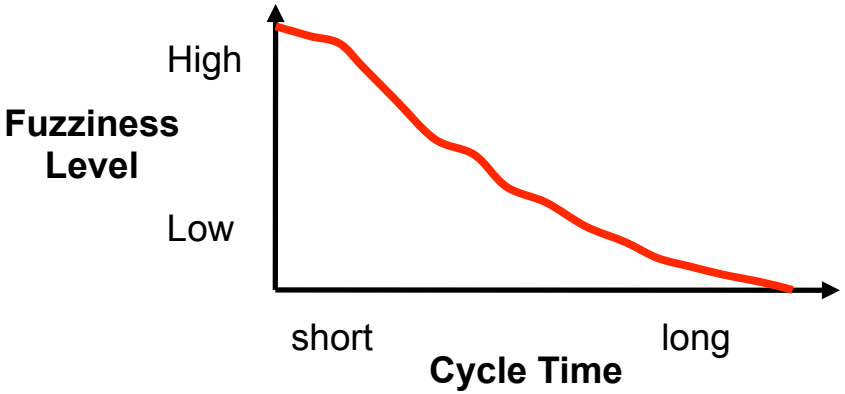

Scientific Programs	Scientific Platforms	Projects
Genome Biology and Cell Circuits Program	Genome Sequencing Platform	Mammalian Genome
Chemical Biology Program	Chemical Biology Platform	Cancer Genome Project
Medical and Population Genetics Program	Genetic Analysis Platform	International Haplotype Map
Cancer Program	RNAi Platform	Connectivity Map
Computational Biology and Bioinformatics	Proteomics Platform	Microbial Sequencing Center
Metabolic Disease Initiative		Center for Genotyping and Analysis
Infectious Disease Initiative		Immune Circuits
Psychiatric Disease Initiative		Fungal Genome Initiative

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