



Process Optimization and Simulation

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CRB Introduction



1100+ design + construction professionals nationwide

90% of CRB's work is focused on FDA-regulated facilities



International Society for Pharmaceutical Engineering (ISPE) Facility of the Year Awards

1



Largest, privately-held engineering firm in the Life Sciences Industry



Established **1984**

18
offices

Atlanta
Basel
Boston
Dallas
Denver
Kalamazoo
Kansas City
Los Angeles
Marshfield
Oakland
Philadelphia
Raleigh
Rockville
Saint Louis
San Diego
San Juan
Stuttgart
Tustin



#4
#5

Pharmaceutical Design
Pharmaceutical Construction
Engineering News-Record (ENR)

\$640 million in revenue



Single Resource for Clients



STRATEGIC CONSULTING

- Business planning
- Operations modeling
- Cost of goods
- Master planning
- Risk assessments

PLANNING

- Capital planning
- Process development
- Technology transfer
- Facility consolidation/Optimization
- Compliance consulting/Regulatory assessments
- Strategic Facility Planning (SFP)



REGULATORY/GMP CONSULTING

- Equipment evaluations, risk assessments, CGMP audits

PROCESS ENGINEERING

- ATMPs, biologics, API & pharma
- Fermentation, cell culture, fill finish, aseptic processing

MEP

- HVAC, process piping, backup power, central utilities, filtration, pressurization, hazardous area classification

ARCHITECTURE

- Master planning, feasibility, concept, programming, interior design, lab planning & design

INSTRUMENTATION & CONTROLS

- systems optimization, network architecture, PLC-SCADA systems

PROCESS UTILITIES



PROCESS MODULES / SKIDS

- Design
- Procurement
- Management
- Construction

PRE-CONSTRUCTION + PROCUREMENT

- Program and project management
- Design management
- Estimating and budget
- Development
- Scheduling
- Value engineering
- Construction logistics
- Life cycle costing



CONSTRUCTION

- Project management
- Field supervision
- Equipment procurement
- Cost estimating/cost control
- Constructability and scheduling
- Value engineering
- Quality control
- Safety and security management
- Startup and commissioning

COMMISSION/QUALIFY

- Test plans
- Startup assistance
- FAT/SAT
- Testing/balancing
- Commissioning planning
- Validation master plan
- FDA review planning /documentation



OPERATIONS IMPROVEMENT

- Process evaluation
- Cost-of-goods analysis
- Risk assessment
- Process modeling
- Cost reduction
- Improved compliance
- De-bottlenecking



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Agenda

- Artificial Neural Networks
- Discrete Event Simulations



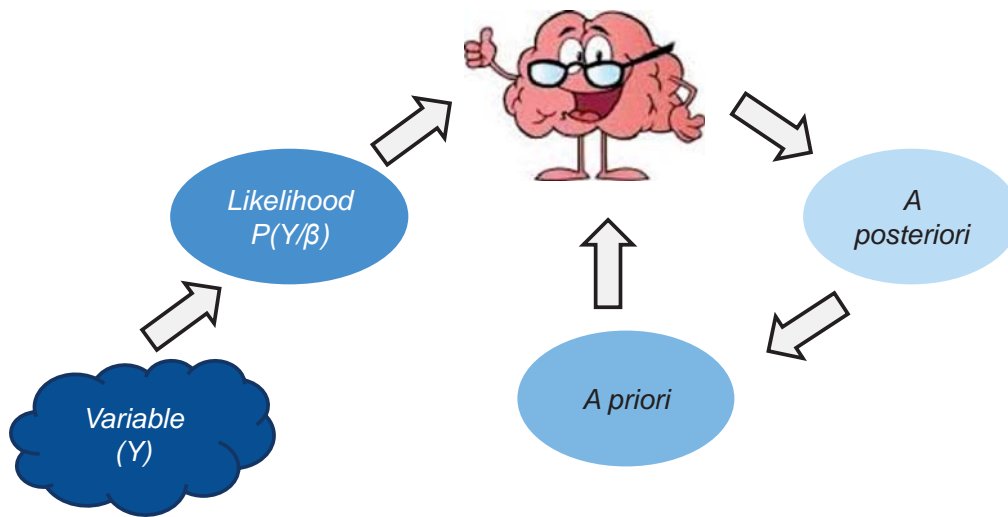
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Lack of Uncertainty = Information



Artificial Neural Networks

Brain does not manufacture thoughts. Thoughts shape neural networks

(Deepak Chopra, 2012)



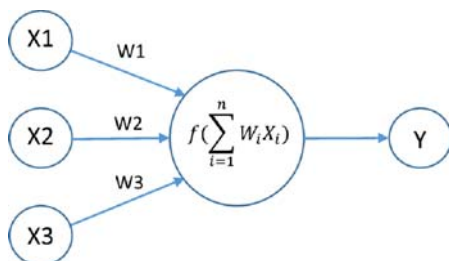
Artificial Neural Networks

- Neurons work by processing information, i.e., receive and provide
- Many (artificial) neurons linked together according to a specific network architecture

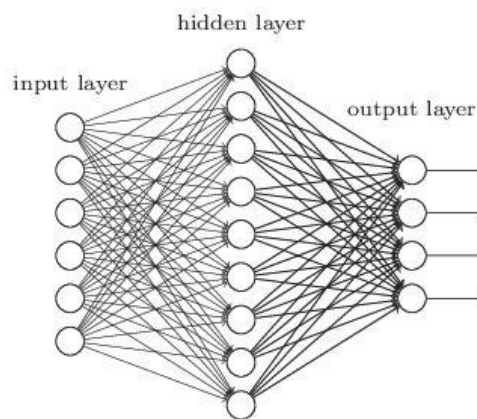


Artificial Neural Networks (cont'd)

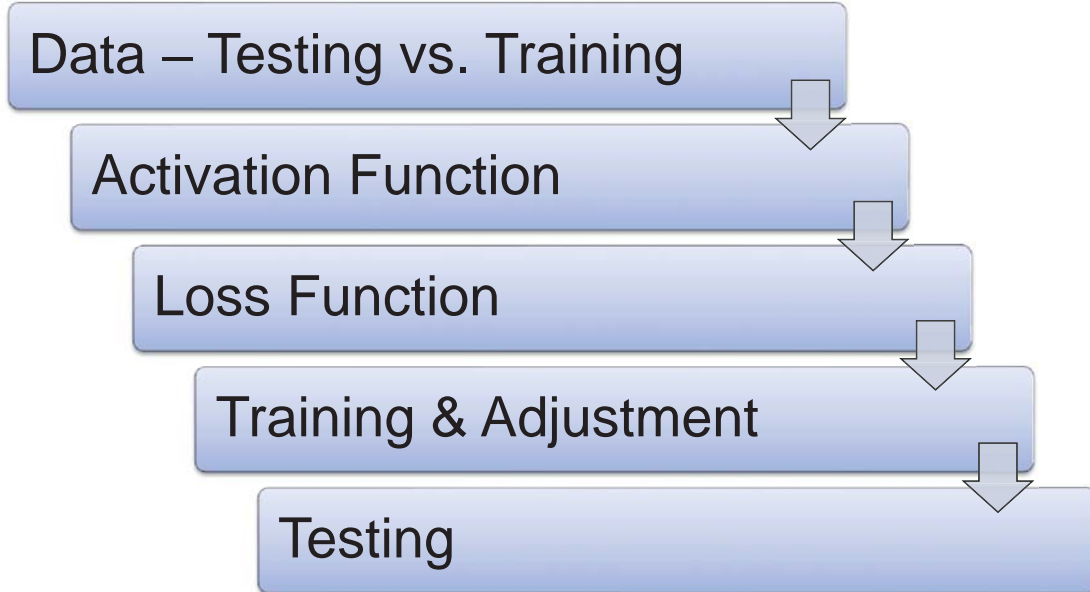
ANN's objective is to transform inputs into meaningful outputs



McCulloch-Pitts model, 1943

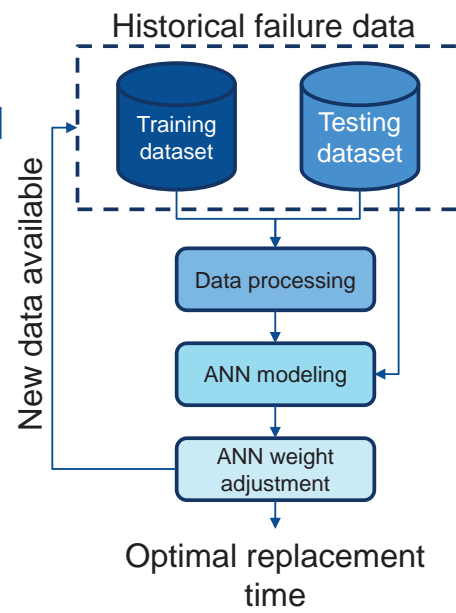


ANN Study Methodology



Condition-based Maintenance

- Predictive maintenance
- Feed forward back propagation NN



Things to keep in mind...

- Large amount of data required for training
- Over fitting (lack of testing dataset)
- Not truly probabilistic in nature
- Modeling sequence of stochastic events

Simulations

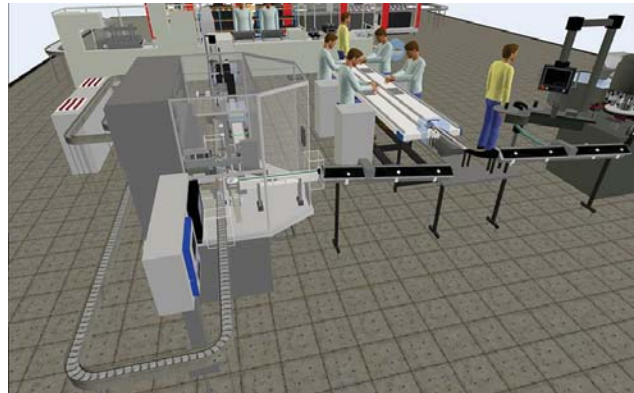
Welcome to the 'real'
world!

(Morpheus, 1999)

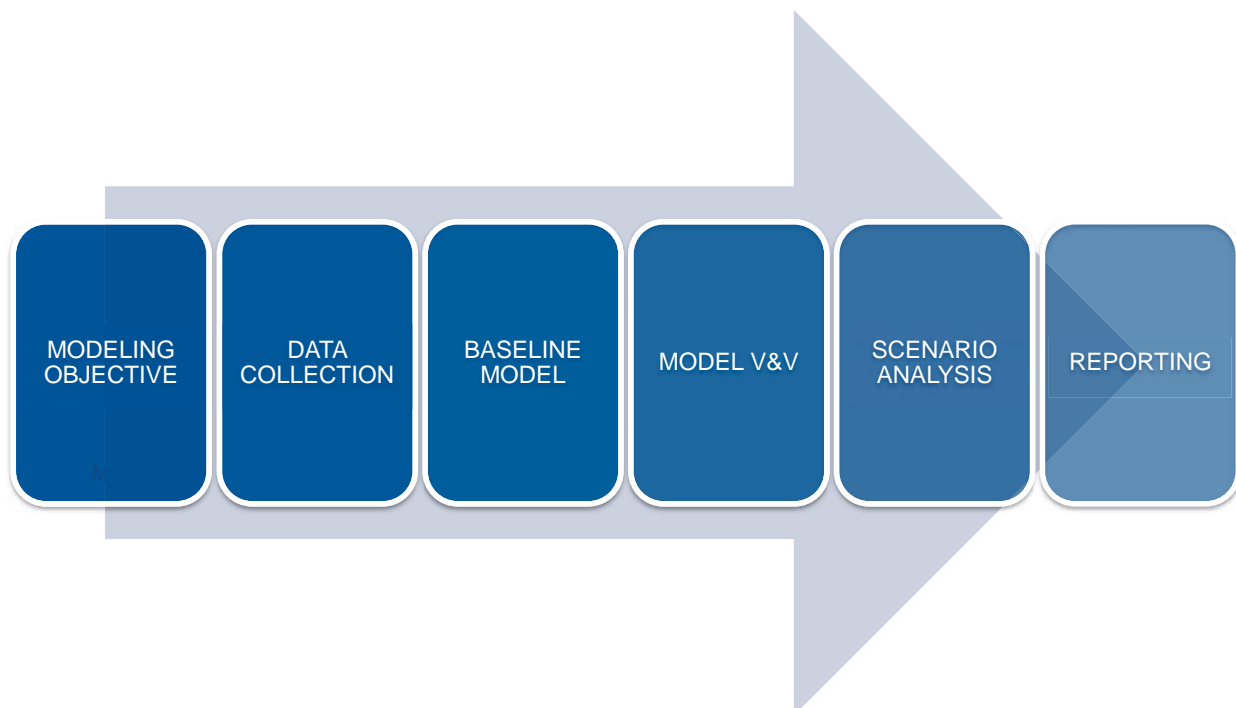


Discrete Event Simulations

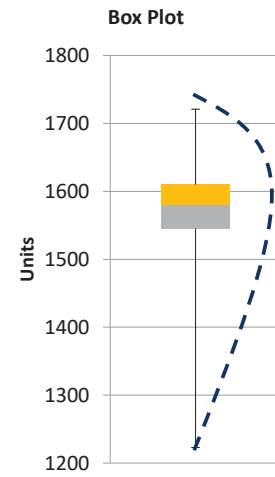
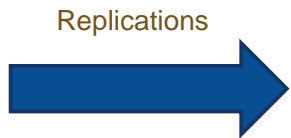
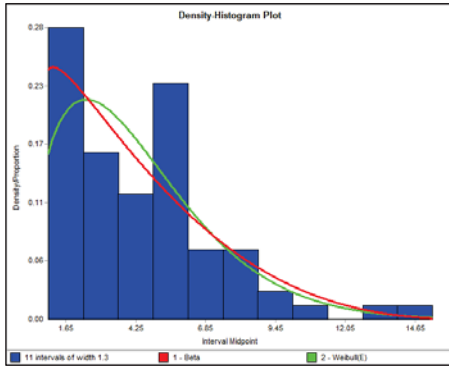
- Technique which simulates an ordered sequence of events in complex systems
- Special case of Monte Carlo Simulations + Time-Advance Mechanism
- Markovian queuing models
- Customize using C++
- Good animation capabilities



Simulation Study Methodology

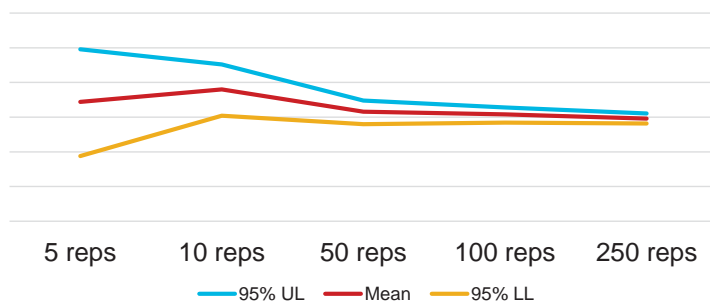


Simulation Characteristic



Deciding # Replications

Average Bag Freezer Content



Simulations for right-sizing resources to meet target throughput



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DES for Facility Design and Operation

- **Determine Objectives of Model Output**
 - Desired product output per year
 - Equipment requirements to meet output (Manufacturing & QC Labs)
 - Staffing plan for Manufacturing, QC, and Support Functions
 - Utilization Rate of Equipment & Staff
 - Environmental Monitoring Sampling Plan
- **Model Outputs Assist with Facility Design**
 - # of Manufacturing suites for optimal operation
 - General arrangement of equipment
 - QC Lab space requirements
 - Office space requirements
 - Warehouse space




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Data Input / Output

- **Determine Assumptions for Model Input**
 - General - Operations time (days/wk., shifts, etc.)
 - Manufacturing Process
 - QC Samples and Process
- **Rubbish In, Rubbish Out** 
 - Understand your manufacturing process
 - Good data input is critical to model output
- **Scenario Planning**
 - Good model build allows us to easily run new output scenarios



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Simulating Cell Therapy Production Operations



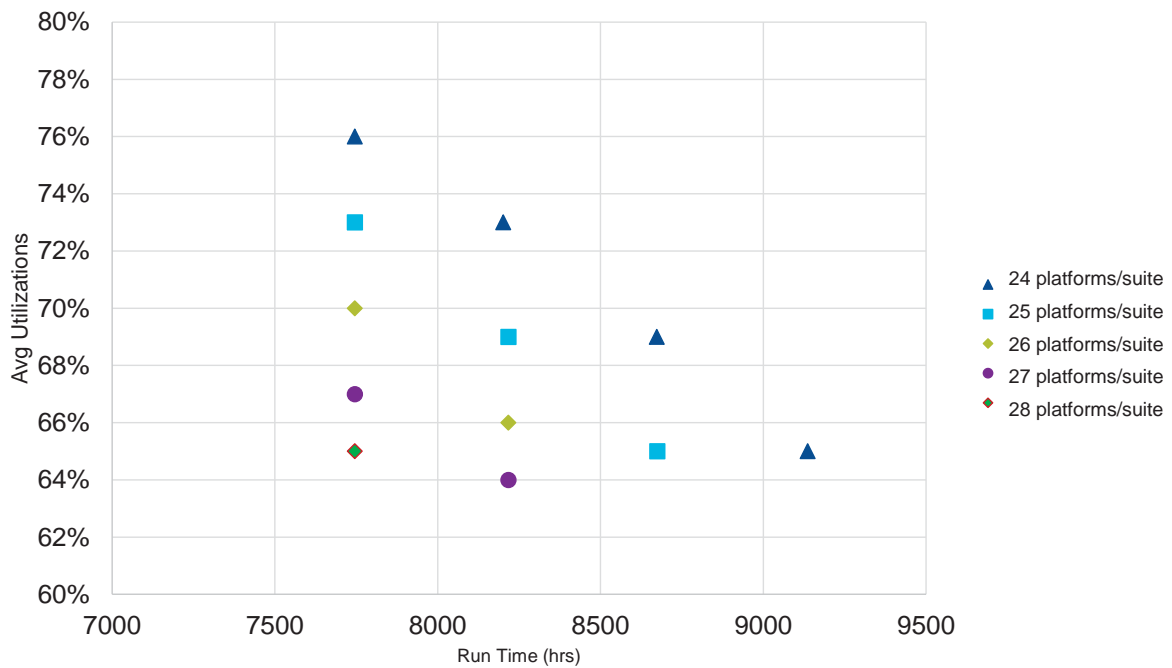
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Sensitivity Analysis to Estimate Equipment



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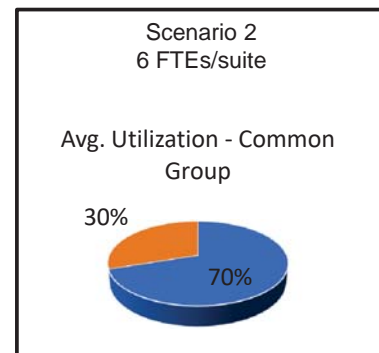
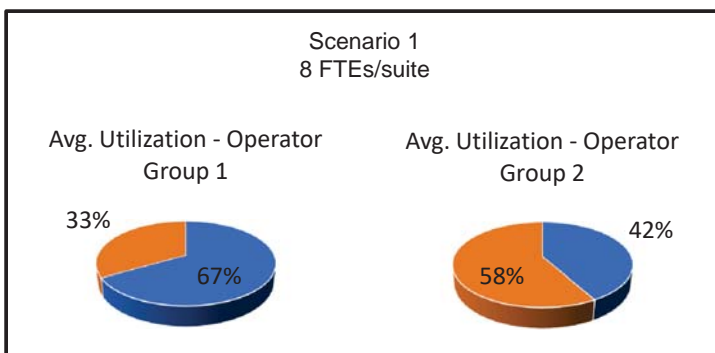
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Headcount Estimation

- Scenario 1: Employees split between Thaw through Harvest Fill/Freezing processes
- Scenario 2: Full cross-training within each suite

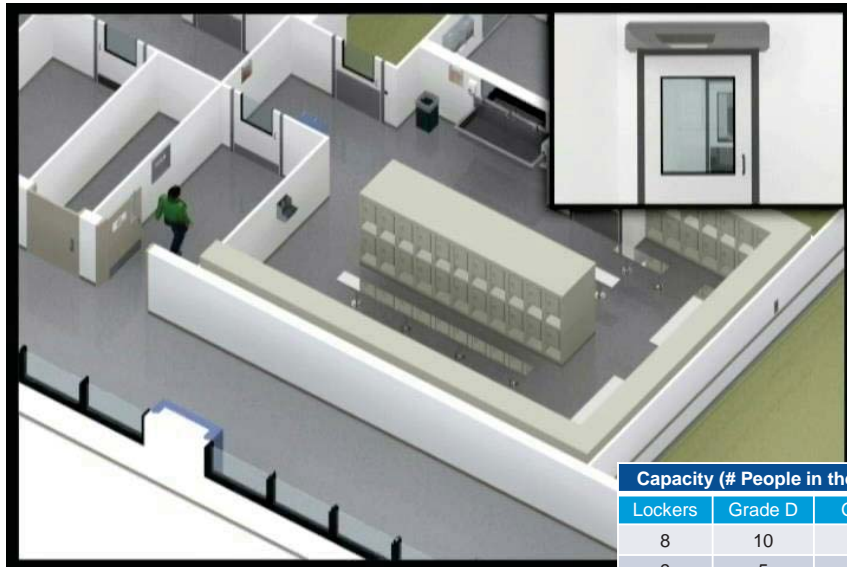


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Simulations to right-size gowning room capacities

Capacity (# People in the space)			Performance Metrics (Mins.)	
Lockers	Grade D	Grade C	Avg Lead Time	Max Lead Time
8	10	10	17.1	20.7
9	5	9	16.6	19.3
10	5	9	16.4	18.5
10	5	9	16.3	18.4
10	5	8	16.5	18.8
10	4	8	16.5	18.8
10	4	8	16.5	18.9
10	4	7	16.9	20.2

Conclusions and Take-away

- Simulate before you implement
- Models should be developed for a defined scope
- Replications is the key
- Define (limited number of) scenarios upfront
- Stay away from averages

Did you hear about the statistician who had his head in an oven and his feet in a bucket of ice? When asked how he felt, he replied, "On the average I feel just fine". (G. Litman, ND)



Questions?

Please use the microphone indicated so our recording includes audio of your question

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For further information,
please contact

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