Optimising Commercial Scale Autologous Cell Therapy Facility Design using Discrete Event Simulation

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Introduction

Design of a commercial scale Cell or Gene Therapy facility is a challenging undertaking. Achieving the required throughput, cost effectively, requires consideration of equipment, layout, staff, variability in the process steps, and issues with concurrent batch processing. Optimising the facility design to maximise throughput while adhering to spatial constraints can be difficult to achieve through standard calculation and assessment methods. Use of a Discrete Event Simulation modelling tool can create a Digital Twin of the facility prior to construction which can be assessed, challenged, and modified to create the most efficient design.

Why use Simulation?

The benefits of process modeling and simulation can be grouped into three main categories: communication, optimizing facility design, and improving operations.

Communication

There is value in seeing the facility, as its expected to operate, early in design.

- Data collection promotes communication between disciplines.
- Inefficiencies and excessive inventories are revealed.
- The impact of the layout and travel distances is highlighted.
- Design improvements can be shown in before and after views.

Facility Design

- Estimate throughput, find bottlenecks
- Equipment configuration, utilizations
- Size utility systems (WFI, PW, gasses)
- Warehouse sizing and configuration
- QC lab sizing, equipment, and staffing
- Understand variability, arising from:
  - Patient arrivals
  - Process step durations
  - Equipment reliability and repair
  - Testing: duration and results
  - Material arrival and logistics

Operations

- Production schedules and staffing
- Gowning and de-gowning
- Material logistics: Raw materials thru finished goods
- Waste flow

Is it worth it?

Process modeling and simulation projects can have a large return-on-investment (ROI). Results can reduce expensive equipment and save operating expenses. It removes risk, risk of over-design and risk of under-performance.

The ROI can be high, but a good model takes time and effort to develop properly. Data collection, model detail and model validation can be time consuming. Scenarios are much faster; allowing the best answers to be found quickly once the model is built.

The value side of the equation can take many forms (both quantifiable and softer).

- Confirmation of throughput
- Minimum total annual cost (capital and operating)
- Design for flexibility if product mix is uncertain
- Early identification of problems and hence cheaper mitigation

Discrete Event Simulation (DES) vs other simulations

There are many different technologies used for modeling and simulation. The selection of which should be appropriate for the system being modeled and the project objectives. For cell and gene therapy projects we often choose discrete event simulation.

Discrete event simulation (DES) – The manufacturing system is described using events, or system states, which are linked to other events. Each event requires the completion of a previous event and may require equipment, labour, and other resources. Durations and branching may use stochastic inputs as in a monte-carlo simulation; many replications are required to characterize the results. Often these models include graphical elements such as 3D views of equipment, materials in staging and animation views.

First principles – Material and energy balances can be used to solve for pressure, temperature, and composition anywhere in the process at any time. Reactions and material properties must be well known.

Data driven – Input and output data can be used to infer the relationships between variables. It may be difficult to understand cause-and-effect relationships.

Scheduling model – Typically built from recipes and campaigns, results are dependent on the schedule, equipment, and resource configuration. Difficult to represent complex dependencies and selections.

DES and Cell Therapy

Autologous Cell Therapy Manufacturing:

- Small-scale, labour intensive operations
- Scale-out to increase throughput
- Production model tracks all operations through the process:
  - Two operators per process step (one batch = one patient)
  - Manual transfer between unit operations

Allogeneic Cell Therapy Manufacturing:

- Small-scale, labour intensive operations
- Scale-up to increase throughput
- Production model tracks all operations through the process:
  - Reduced number of operators (one batch = multiple patients)
  - Manual or automated transfer between unit operations

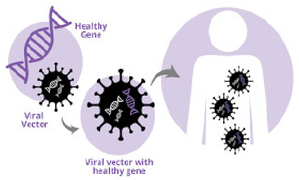
Applies to both:

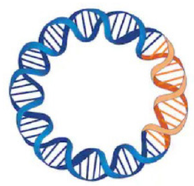
- Statistical model to accurately depict variances in deliveries and process step times
- Process Support (kitting, media prep / usage, waste handling) linked to production model
- Personnel model tracks shift change
- DES outputs accurately determine:
  - Equipment and Resource requirements
  - Room Sizes and Staging
  - Warehousing requirements

DES and Gene Therapy

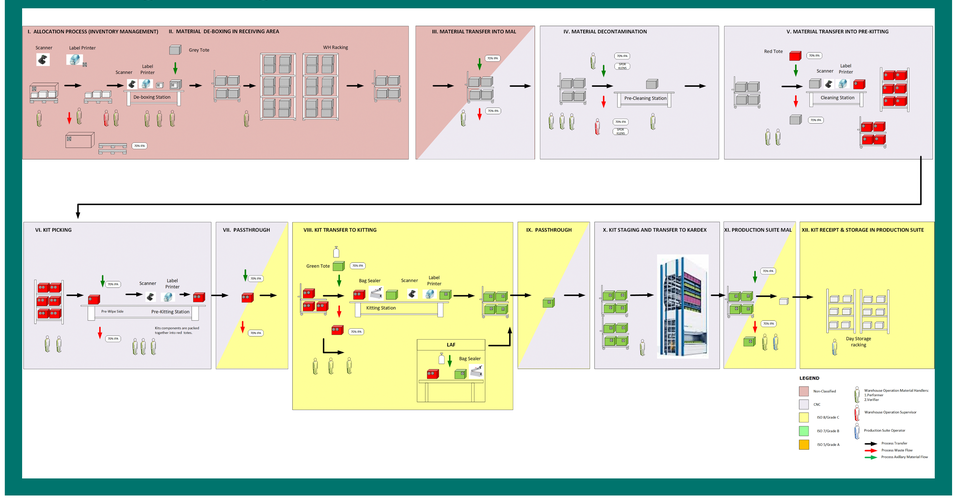
Gene Therapy (Viral Vector) and Plasmid (microbial cell) Manufacturing:

- Medium scale manufacturing operations
- Typically, single-use technology – manual set-up / disassembly
- Automated manufacturing operations
- DES model benefit more around support functions:
  - Warehousing, consumables kitting and consumables staging area capacities
  - Personnel movements (consumables handling / shift change)
  - Resource requirements
  - Manufacturing suite / airlock / locker room sizes
  - Biohazardous waste staging area
  - Decontamination autoclave requirements

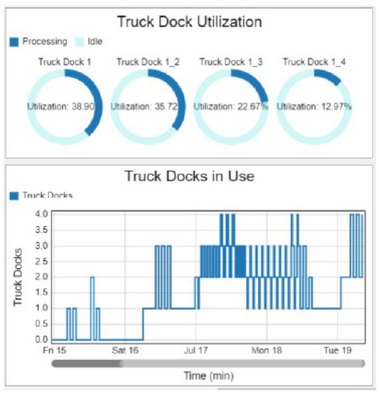




Warehousing and Kitting - Material Flow Example

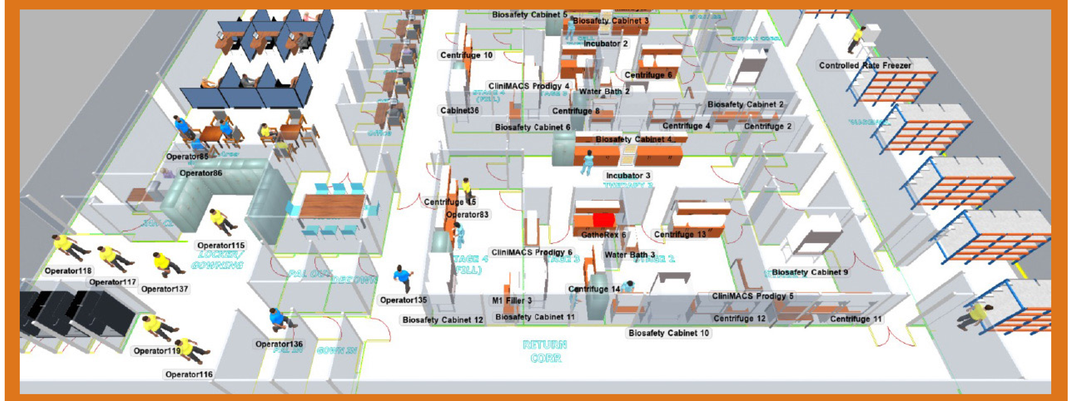


Warehouse Sizing



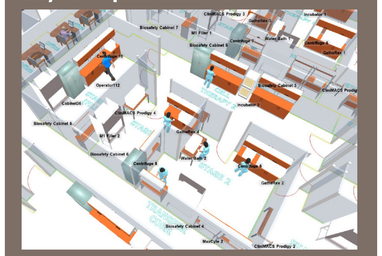
Warehouse design including pallet spaces, number of truck docks and logistics staff can be optimized by simulating the material logistics.

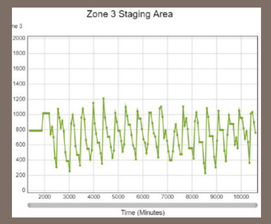
Cell Therapy Example



This model includes three (3) cell therapy production suites which access a common freezer and incubator ballroom. Animation helps to communicate expected operations and often reveals improvements to the design, layout and operations.

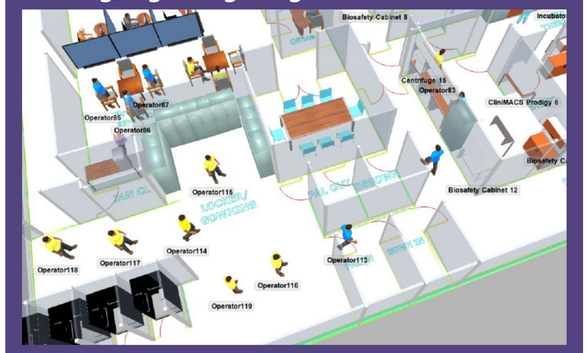
Layout Optimization





Busy clean rooms are minimized to save costs, restricting useful staging space. With simulation we can quantify staging requirements as a function of throughput and schedule.

Gowning/Degowning Sizing



Cell and Gene Therapy production is labor intensive. Simulations can help size gowning and support spaces to improve operational efficiency.

Conclusions

A discrete event simulation, detailed to match the design phase, provides a better design and improved operations. The payback for these projects can be large including capital and operating cost reductions. Simulation is particularly valuable in cell and gene therapy projects with the increased emphasis on labor and material logistics.