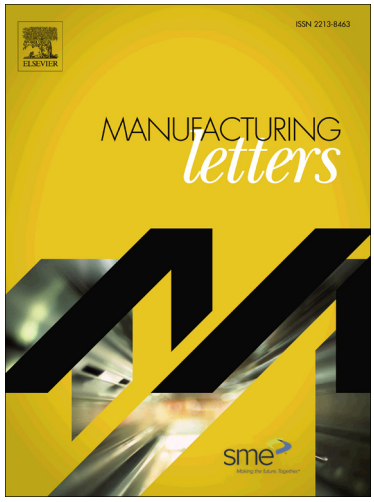

Letters

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Opportunities to apply manufacturing systems analysis techniques in genetic manufacturing systems

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Abstract

Breakthroughs in molecular and synthetic biology are pivotal to understanding the function of cells and creating new pharmaceutical applications. These advances in biological processing present a new class of manufacturing systems, defined here as genetic manufacturing systems, which produce a final product with a genetic construct. Genetic manufacturing systems rely on molecular events for success, and this aspect is a key difference from traditional manufacturing systems. Analysis techniques for manufacturing systems have been successful in providing valuable insights for complex manufacturing environments and have the potential to transform how genetic constructs are currently produced. This paper provides an introduction to the interdisciplinary field of genetic manufacturing systems and outlines the similarities and primary differences between traditional manufacturing systems and genetic manufacturing systems. Mathematical modeling and simulation opportunities are presented as they relate to reducing cost and time as well as increasing efficiency in genetic manufacturing systems. Finally, several challenges for genetic manufacturing systems are presented.

Keywords: Advanced manufacturing systems, Genetic manufacturing systems, Gene synthesis, Mathematical modeling, Quality control, Simulation modeling, Synthetic biology

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1. Introduction

Synthetic biology, and more specifically *de novo* gene synthesis, has progressed significantly during the past two decades with advances in both the application of the science and advancements of technology allowing unprecedented breakthroughs in the creation of DNA constructs. In infectious disease research, the synthesis of viral genomes led to new vaccine engineering strategies [1-3] and vaccine production workflows [4]. Within industrial biotechnology, computational approaches can be used to design genes, which code for enzymes with new or improved catalytic activities [5, 6]. Genes can be designed to maximize the production rate of a desired protein [5-8]. Additionally, it is now possible to create much larger synthetic constructs including a bacterial genome [9] and yeast chromosome [10].

With these recent breakthroughs, *de novo* gene synthesis is changing the face of biology. The manufacture of products created through molecular biology processing is increasingly becoming commonplace within the industrial biotechnology sector. Molecular and synthetic biology continues to develop new tools to manipulate and control biological systems with immense precision and understanding. For example, gene synthesis techniques can create segments of DNA that do not occur naturally with precision down to the individual base pair ordering of a sequence.

Molecular and synthetic biology have spawned a new manufacturing production environment referred to here as *genetic manufacturing systems* (GMS). A GMS is defined as any production or manufacturing environment in which the final product is a genetic construct. This could range from a system that creates a genetic sequence of only a few base pairs or creates an entire genome comprised of billions of base pairs. While these two product outcomes may seem drastically different, many of the process operations are foundational and employed in an

iterative fashion to create the desired genetic sequence. Similar to traditional manufacturing systems, these complex process flows can be deconstructed, and manufacturing systems analysis tools used to better understand the dynamics of the production environment.

With the immense interest in gene synthesis research, funding and commercial opportunities in the sector have also increased. The US biotechnology sector has doubled in size over a ten year period and grown into a $98.5 billion industry [11]. The amount of capital within gene synthesis research tends to increase the speed of innovation where efficiency may not be the primary concern. Thus, many of the processes and operations have not yet been optimized to minimize production costs or time.

The analysis of traditional manufacturing systems (TMS) has progressed dramatically over the past century with mathematical modeling, simulation, and data analytics being vital contributors to the growth of this field. These techniques also provide the basis for improvements within GMS. Process flow optimization, sequencing and scheduling for genetic production facilities, inspection and resource allocation problems, and facility layout and design are a few areas in which methods from manufacturing systems analysis can be applied to this burgeoning field. With cost and time reductions being commonplace in traditional manufacturing settings, the real question is how to translate these gains into the world of GMS. This paper serves to introduce GMS and provide a selection of research areas in this promising interdisciplinary research field.

2. Differences between traditional manufacturing systems and genetic manufacturing systems

Traditional manufacturing analysis techniques can be applied within GMS, however, there are some key differences dictated by the characteristics of synthetic biology and more specifically, gene synthesis. Operations to create the final genetic product may be well defined, but the production process requires rare molecular events to occur, which introduce more sources of variability into the system. This leads to highly complex and iterative process flows.

In general, protocols are used to describe many of the common processing steps in gene synthesis [12, 13]. Differences in the application of these protocols can impact the success of any given processing step or the entire process flow. In addition, even if two identical protocols are conducted in the exact same fashion, an opportunity exists for the molecular event to not occur or a random mutation to change the final product.

Another key difference between traditional and genetic manufacturing systems is quality monitoring. Deriving the quality of mid-stream constructs and final products is difficult, costly, and time consuming for GMS. Strategies are available for mid-stream quality assurance within biological processing, but it is unclear if these approaches reduce the cost or time of processing. Visual optical inspection of DNA is impossible; therefore, inspection techniques indirectly infer the quality of a sample. Both gel electrophoresis [14-16] and capillary electrophoresis [17, 18] are common methods for deriving different types of mid-stream process data regarding a DNA sample. The interpretation of these results introduces another source of variation into the processing flow.

DNA sequencing technologies are capable of detecting the exact sequence of a construct and the costs of these technologies have decreased considerably over the last ten years [19, 20].

However, sequencing is still cost prohibitive to apply after every processing step and typically requires the samples to be outsourced to a third-party vendor, increasing the lead time. Figure 1 illustrates the differences between a TMS with an inspection step and a common gene synthesis processing flow with an inspection and final sequencing quality step.

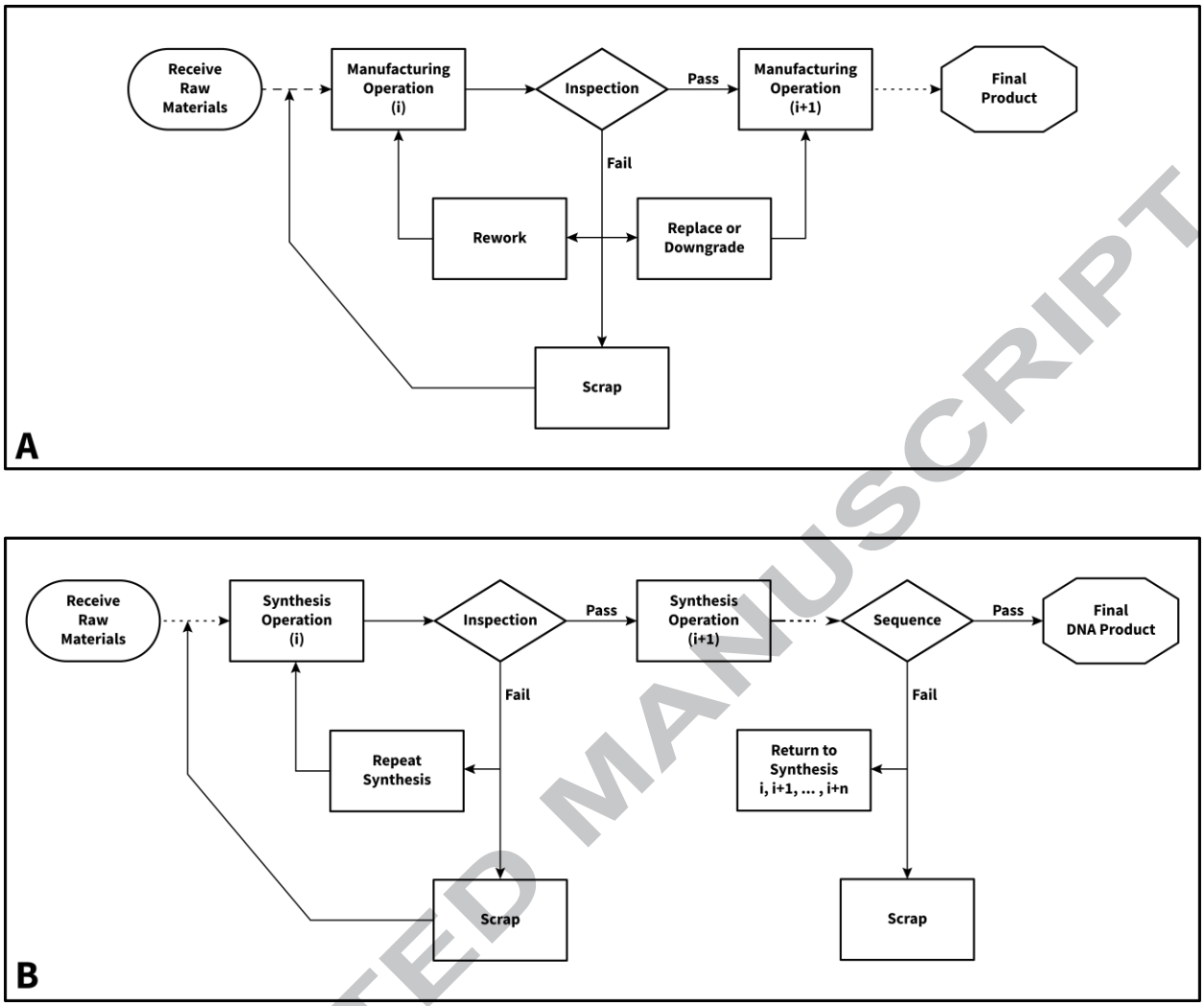

Figure 1: Panel A shows a traditional manufacturing process flow with an inspection step and routing options following the inspection result. Panel B shows a genetic manufacturing system process flow with both an inspection and sequencing step with the different routing options.

The end product of a GMS is a single genetic product that matches a desired reference sequence. This difference and many of the other differences discussed in this section are outlined in Table 1.

Table 1: Major differences between traditional manufacturing systems and genetic manufacturing systems.

	Traditional Manufacturing Systems	Genetic Manufacturing Systems
Quality Control	Established tools and techniques including some visual methods	Limited tools and techniques with few reliable visual methods
Variation	Processes designed to maintain a specific quality level	Final sequence must be a 100% match to the desired reference sequence
Rework	Common for many manufactured products	Not common due to cost and complexity of processing
Process Flow	Standardized methods to describe process flows	Lack of unique way to describe protocols across disciplines
Modeling & Simulation	Models available to understand and predict system performance	Models used to understand the interactions between cellular events

As highlighted in Table 1, there is usually no room for error or variation in GMS as even a single base pair inserted incorrectly or misplaced could drastically change the function of the sequence or final product. After a sequence is created, *perfect* clones can be produced through established cloning techniques, meaning much of the time and cost of a GMS is spent on creating the first *perfect* sequence. Another primary difference in a GMS is the lack of models specifically tailored for process improvements to reduce the cost or time associated with production of genetic products. These differences from TMS motivate the need for solutions to address the unique processing considerations found in GMS.

3. Modeling and simulation opportunities in genetic manufacturing systems

Traditional manufacturing systems have relied on modeling and simulation for significant reductions in cost and time as well as increases in efficiency. However, given the differences between traditional and genetic manufacturing systems as outlined in Section 2, opportunities to directly apply these models are limited. Instead, there is potential to adapt the modeling and simulation techniques, given the constraints of genetic processing, to provide insight on how to most efficiently undertake various processing flows and operations.

3.1. Inspection allocation

An example of utilizing TMS analysis within GMS is determining the proper inspection resources to allocate for a process flow. Inspection can reduce the prevalence of errors and limits repeated work on non-conforming samples. Inspection allocation models determine if and where inspection allocation resources should be placed within a production flow. Various optimization strategies can model the inspection allocation problem for TMS with imperfect inspection and utilize a wide-range of direct and heuristic solution techniques [21-36].

Adapting these types of models for GMS is possible, but requires accounting for the differences associated with producing genetic final products. The techniques available for mid-stream inspection of genetic material do not necessarily provide the specific sequence of the DNA construct. Both gel electrophoresis and capillary electrophoresis provide information on the relative concentration of DNA molecules at specific lengths with differing levels of accuracy and do not identify the sequence order. DNA sequencing is capable of providing the specific base pair ordering, but significantly increases the cost and time following each processing step if outsourced to a third-party provider.

Another complication involves the mathematical models commonly used to describe the inspection allocation problem in TMS. The serial, single-line, multi-stage inspection allocation formulation is well suited to modeling the problem in GMS [21-24, 27-31, 34-36]. However, with these mathematical models, the number of parts or units entering the system is typically a parameter of the model. High volume production systems found in the industrial biotechnology sector can use a modeling strategy similar to the traditional inspection allocation formulations. In high volume GMS, the end product will be a certain number of genetic products reaching a specific quality threshold. For this case, the quantity of starting raw material will be known to produce a given quantity of final product which is similar to the starting number of parts or units entering the systems for TMS models.

Research and development (R&D) laboratories, in the academic and industry space, seek to produce a single conforming clone with a perfect match to the target reference sequence. Therefore, the amount of starting materials or number of operations necessary for this objective is unknown. This complicates the inspection allocation model for R&D environments as the starting number of parts or units must also be found through the problem formulation. While this increases the complexity of the formulation, these types of differences also provide context for the unique nature of GMS when considered as a multi-stage manufacturing production process.

3.2.Rework decisions

An added complication to the inspection allocation problem involves the potential for rework in a GMS. TMS often rely on downgrading and rework to retain value for products that do not meet a certain quality threshold. Rework is technically possible for gene synthesis as individual base pairs can be changed following the results of certain inspection steps or when dealing with imperfect initial raw materials [37, 38]. Techniques based on clustered regularly interspaced

short palindromic repeats (CRISPR) are increasingly used to enable base pair specific genetic editing [39-43]. However, it is unclear what the optimal rework threshold is for a GMS. How many erroneous base pairs are too much to warrant the cost of conducting the rework operation? This question is illustrated in Figure 2 depicting a common two-stage GMS process and decision

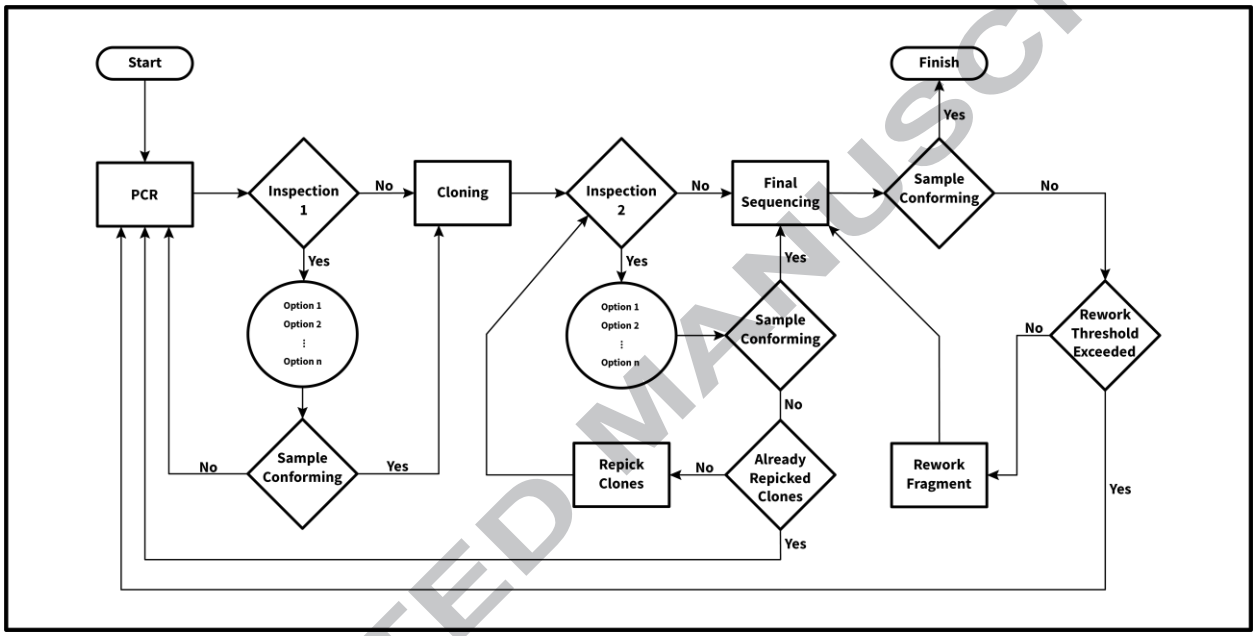

Figure 2: Process and decision routing for a two-stage genetic manufacturing system with the opportunity for rework.

flow with multiple inspection opportunities and the potential for rework.

From Figure 2, the inspection allocation problem for this type of system is more complicated than a TMS. The typical objective of minimizing cost or time will have the added constraint of determining the rework threshold during model execution. Determining the appropriate type of inspection and rework threshold would provide practitioners with more information on process decisions according to the specific parameters of their system.

3.3. Workload allocation

Process routing and resource considerations are another interesting challenge within GMS. Many research and development laboratories will have one technician conducting all of the work for a given project, completing all of the processing operations and steps to achieve a desired final sequence over the course of days, weeks, or even months. Typically, a technician may also be working on multiple projects, leading to the question how resources and equipment should be allocated in the laboratory. Should a single worker be assigned to a project or should that worker be in charge of specific process operations? Would it be possible to increase equipment utilization by combining batches from two different technicians? These types of considerations have been investigated for TMS as the worker assignment [44-53] and process scheduling [54-60] problems. Assigning human resources in GMS research and development laboratories has similarities to the worker assignment problem for job shop manufacturing systems [61-63]. Additionally, the random molecular interactions of genetic processing could provide an opportunity to look at the scheduling problem considering uncertainty in the iteration number of an operation until success [64].

While there are similarities to the worker assignment and process scheduling problems from TMS there are still added complications in GMS highlighted in Section 3. Additionally, how do the worker assignment and process scheduling considerations change when looking at more automated production processes within the industrial biotechnology sector? The variety of interesting challenges of GMS motivates the need for modeling solutions to compensate for the random nature of genetic processing to identify areas for process improvement.

4. Conclusions

The processes used in gene synthesis to generate novel genetic constructs require costly and time consuming iterative processes. Ultimately, the goal is to produce a sequence which is a 100% match to the desired reference sequence. Once this *perfect* sequence has been created, identical clones can be made in high volumes with great precision using established techniques. This major difference from traditional manufacturing processing provides a unique opportunity to investigate genetic manufacturing systems in order to increase their efficiency as well as reduce production cost and time.

Systems producing genetic constructs require a steep learning curve to grasp the processing considerations for production. The interdisciplinary field of genetic manufacturing systems can benefit from modeling and simulation techniques used in other manufacturing environments taking into considerations the differences between the two areas. The research questions posed in this paper are just the beginning of the possibilities available for analyzing GMS with TMS analysis tools. Combining the complexity and random nature of biological organisms with the structured examination brought from traditional manufacturing analysis yields an opportunity to provide logical processing rationale for a number of challenges facing gene synthesis and the broader field of synthetic biology.

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