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Review

High-throughput automation design considerations for biotechnology processes involving RNA purification protocols using multi-centrifuge bioseparation steps

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ABSTRACT

Design of an automation line is a multi-objective optimization problem involving throughput, yield, floor space and cost constraints. The paper examines the feasibility of a computer-aided automation design for biotechnology applications using Arena™ software. A generic case study chosen for this study involves a sequence of steps in a preparation process of RNA from tissue-cultured cells. These steps involve repetitive usage of centrifuging operations to perform separation of biochemical substances. A sample must be loaded onto a centrifuge by a pick-and-place device (typically a robot manipulator). Consecutive centrifuging steps may involve multiple centrifuges as well as robots, or some measure of equipment sharing. The paper proposes a unified simplified cost model for all design objectives (throughput, space utilization, process capital and operational cost) and a quantitative selection criterion to allow for an optimal automation design.

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Contents

1. Introduction

The design of any automation system strives to minimize capital and operational costs as well as floor space and maximize throughput, yield and product variety. The latter is referred to as Flexible Automation [1]. There are typically multiple constraints such as limited footprint, a limited budget and the protocol-specific constraints (i.e. timing, reaction conditions and environmental condition constraints). Such multi-objective optimization problem is large-scale thus often requiring computer-aided design [2]. The optimization often starts with a construction of an ad-hoc "feasible solution" that meets a given set of cost, space and throughput constraints and proceeds with incremental design modifications aimed at yielding incremental performance improvements.

Automation plays an increasing role in Life Sciences and especially in Biotechnology. With advances in automation, the human genome and other genomes have been sequenced. One of the earliest examples of rigorous automation design for biotechnology is described in [3]. Modern molecular biology and biotechnology have contributed to new assays that, whenever automated, provide more accurate and rapid large amounts of information [4]. Similarly,

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the pharmaceutical industry is heavily dependent on automation, especially as it shifts from products that treat diseases, to analytical methods that detect and classify diseases. Automation for the Life Sciences includes fluid handling and assay processing, high-throughput screening and drug discovery, high-throughput production and analysis of protein and DNA microarrays, devices for analyzing living cells, lab-on-a-chip analysis tools and numerous detection methods.

A large percentage of biotechnology and drug discovery research and advances take place in small to medium size laboratories [5]. These laboratories study diseases and their interaction at the molecular level and try to devise new therapeutic answers. These laboratories often do not have the resources to conduct a high-throughput screening for a Drug Discovery campaign. This paper targets small to medium size laboratories that may perform Drug Discovery research. The paper evaluates high-throughput flexible solutions, with common equipment (that may already be available at such laboratories), which can be reconfigured to serve multiple kinds of protocols and techniques.

Some stand-alone equipment such as QIAcube from QIAGEN laboratories [6] is available in the market. Even though such solutions perform a wide range of sample purification protocols used in biotechnology and in upstream stages to Drug Discovery high-throughput screening campaigns, these are limited to perform only one kind of a technology, such as column chromatography, not making available protocols that use for example magnetic beads technologies. Another key point to keep in mind is that "turn key systems" often have a limited throughput.

Whenever assembling biotechnology processes into production lines various challenges and constraints are encountered. First, biotechnology operations need to be reasonably accurate as there is almost no possibility of automatically monitoring by direct feedback every single step in a process. In order to assure that the output is within specifications, the essentially open-loop operations require precision. Another unique feature of many biotechnology processes is the relative high cost of processed materials. The samples and reagents involved in such processes tend to be expensive and scarce and therefore waste must be kept to a minimum [5]. The liquid samples themselves tend to be small with each volume in the range of tens of nano-liter to a few milli-liter. Some biotechnology process steps may require strict environmental conditions and tight timing constraints [7].

A key component in many biotechnology protocols is a centrifuge performing bio-separation operations. This type of equipment is somewhat challenging [8] from an automation design viewpoint as loading and unloading of the equipment generally require a pick-and-place device as it is done from the top of the equipment. Separation is one of 12 key Lab Unit Operations (LUO) for biotechnology automation, as listed in [5]. In order to illustrate automation design choices and optimal selection we focused in this paper on biotechnology protocol steps that involve centrifuges.

The paper discusses different configurations of repeating centrifuge steps. Section 2 describes the specific biotechnology process, which is the subject of this study; the complete process is outlined as a manual labor production line. This section also discusses issues related to automation implementation. Section 3 contains a detailed description of a multi-centrifuge process subset that requires computer-aided automation design optimization. Section 4 describes the throughput, cost and footprint considerations and available choices when selecting an automation configuration. Section 5 focuses on high-throughput implementation. Section 6 outlines open issues and future research directions.

2. Case study: preparation of RNA from tissue culture cells

Let us present a typical biotechnology process in full detail. The preparation of RNA from tissue-cultured cells is shown in Fig. 1. The set of process steps are first laid out conceptually as a manual-labor production line. Such a production line presentation, with its sequential stages, serves as a basis for a further deductive process as to how each station might be automated.

The goal of this case study process is the isolation of RNA from Drosophila Schneider 2 cells that were transfected with a plasmid expressing dact mRNA (RE37047) [9]. The manual production requires the following equipment and reagents: homogenization columns, silica-based membrane columns, lysis buffers, ethanol, wash buffers and elution buffers, all shall be explained next. Generally

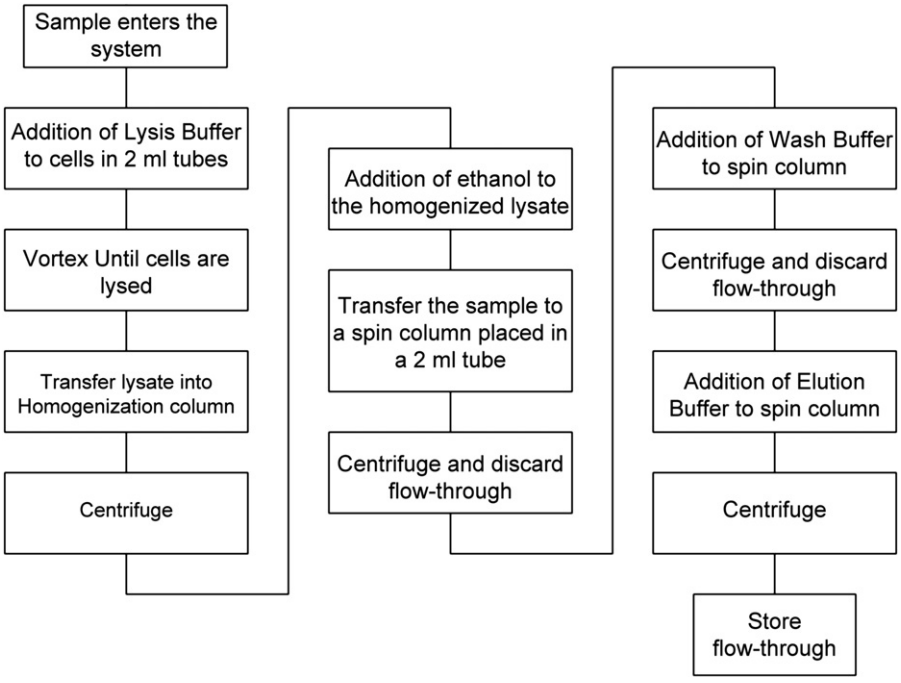

Fig. 1. Preparation of RNA from tissue culture cells.

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