Contents lists available at ScienceDirect

Chemical Engineering Research and Design

journal homepage: www.elsevier.com/locate/cherd

Design of large-scale manufacturing of induced pluripotent stem cell derived cardiomyocytes

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ABSTRACT

A new approach for design of large-scale manufacture of stem cell derived cells by using the biomechatronic methodology and computer-aided-design tools is described. The systematic conceptual design methodology for systems composed of active mechanical, electronic and biological components, here referred to as biomechatronics, is combined with the methodology for computer-aided design of bioprocesses. The objective has been to systematically investigate and compare by the combination of the methodologies what are favourable design alternatives in terms of equipment configuration and economic parameters. A demonstration case has been used for the manufacture of cardiomyocytes from human induced pluripotent stem cells. The results show how certain configurations are more favourable than others under given boundary conditions. The study indicates that the approach is possible to apply on other related bio-manufacturing systems.

Keywords: iPSC; CAD; Biomechatronics; Conceptual design; Pluripotent stem cells; Cardiomyocytes

1. Introduction

The request for stem cell derived products is increasing (Jensen et al., 2009; Braam et al., 2009; Mandenius et al., 2011a,b). In particular this includes cells for regenerative therapy, such as heart cells, liver cell and neural cells (Kane et al., 2011; Chen et al., 2008; Wu et al., 2007). The current improvements and understanding of the biology of stem cells and the efficiency of routes for their differentiation create new challenges for production, especially on large scale (Schriebl et al., 2010; Want et al., 2012).

Previous focus on differentiation of human embryonic stem cells to target cell types has now been turned to cell products derived from induced pluripotent stem cells (iPSC) (Huang, 2010). The iPSCs have the advantage of using a variety of starting cell materials from patients or population groups and by that allowing stratification of diseases.

However, if each stratified group shall be produced separately, production batches will be relatively small and may have a certain variation in culture requirements.

The production volumes of these batches may therefore be more difficult to assess and may require a larger degree of flexibility of culture conditions (Ratcliffe et al., 2011; Archer and Williams, 2005). For infarction heart diseases, it has been estimated that approximately 10^{16} human pluripotent stem cells (hPSCs) will be required to treat a yearly demand of 250,000 patients (Want et al., 2012). However, this value would probably have to be divided on at least ten different cell lines representing different patient groups. Based on this, we assume in this report a batch scale intended for 25,000 individuals using the same cell product but flexible enough to be adjusted to the other patient-specific cell lines.

These requirements call for a design methodology able to cope with this complexity. The biomechatronic methodology offers such an alternative design approach for developing the design of complex system where biological, mechanical and electrical components play an active role in the function of the system (Derelöv et al., 2008; Mandenius and Björkman, 2010, 2011). The methodology follows basic theoretical principles of systematic design of mechanical products

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Received 1 November 2012; Received in revised form 19 May 2013; Accepted 21 August 2013
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http://dx.doi.org/10.1016/j.cherd.2013.08.021

as previously been developed by Pahl and Beitz (1996) and Ulrich and Eppinger (2007) but expand their theory to the functionalities of biological systems. For manufacture of stem cell products the approach addresses such decisive issues as the interaction between stem cell differentiation, process monitoring and control and regulatory requirements (Mandenius and Björkman, 2009; Mandenius, 2012). By exploiting the systematics of the methodology the unit operation functions needed for differentiation and expansion of large scale production of stem cell derived products can be analyzed and designed.

Computer-aided design (CAD) has been applied to biotechnological processes (Heinzle et al., 2007) using well known CAD tools such as Superpro Designer (Rouf et al., 2001) and Aspen (Shanklin et al., 2001). This has demonstrated how stoichiometric and mass balancing methods are useful for simulation and comparisons of unit operation configuration alternatives and to carry out economical evaluation of these alternatives. Although the manufacture of stem cell products require new unit operations not yet described in the tools (Thomas et al., 2008, 2009), the CAD methods as applied are the same or could be adapted with relatively minor adjustments.

In this article we show how the biomechatronic methodology approach for analysing the manufacturing of iPSC-derived cardiomyocytes can be combined with a CAD tool method. In particular, the methodology is used to compare the potential design alternatives not yet considered versus production targets and their economic feasibility.

2. Materials and methods

2.1. Materials

The CAD programme SuperPro Designer™ (SPD version 6.0; Intelligen Inc., Boston, Mass, USA) was used for all simulations of flow chart diagrams using data provided in the database of the software or from other data sources as mentioned in the examples. The software was also used for the economic evaluations.

2.2. Methods

SuperPro Designer evaluated capital costs through an equipment list with specification of size and number of each item. A built-in model calculated total cost (C_{TC}) and fixed capital cost (C_{FC}) from equipment purchase cost (C_{PC}) by multiplying with appropriate cost factors (Rouf et al., 2001):

$$C_{TC} = C_{PC} \times f_1 \quad (1)$$

$$C_{FC} = C_{PC} \times f_2 \quad (2)$$

When evaluating total operating cost, prices for raw material were identified from literature or supplier data.

The raw material cost was estimated from amount of each material required according to mass balances. Utility requirements were estimated based on energy balances and number of labour hours. The software also assessed annual profit and return on investment (ROI) according to Ostwald (1992) as:

$$ROI = (S - C)/C_{TC} \quad (3)$$

and gross margin, G_M, according to:

$$G_M = (S - C)/S \times 100 \quad (4)$$

3. Theory

Biomechatronic methodology is a design approach recently described by Mandenius and Björkman (2011). The methodology is founded on design principles described in the mechanical design theory by Pahl and Beitz (1996), Hubka and Eder (1996) and Ulrich and Eppinger (2007).

The biomechatronic methodology applies a consecutive and iterative procedure where graphical and tabular tools are used. Fig. 1 shows the recommended order for executing the steps of the procedure. In the first step, the design mission is concisely stated. This is followed by identifying the needs of the users of the intended product or production process. These needs are further specified with target values. With the help of these specifications an overview flow chart showing the functions required for accomplishing the specification is drawn. The functions in this chart are represented in abstract functional components that are combined in as many alternatives (permutations) as imaginable. This is the key step in the design and is referred to as concept generation. The concept alternatives are screened and scored towards the specified target values. This results in a ranking from which just a few design alternatives are selected. First at this stage, actual physical objects, chemicals or cells, are brought into the design work. These objects, so called anatomical components, are identified as chemicals, biologics, technical devices, instruments or other technical gears, usually commercially available, or feasible to construct or prototype. After analysis and evaluation of these anatomical structures the final design solution of the product is settled (Mandenius and Björkman, 2011).

In this study the biomechatronic design procedure has been combined with computer-aided design (Fig. 1). The CAD is used at the stage of the anatomical analysis where the

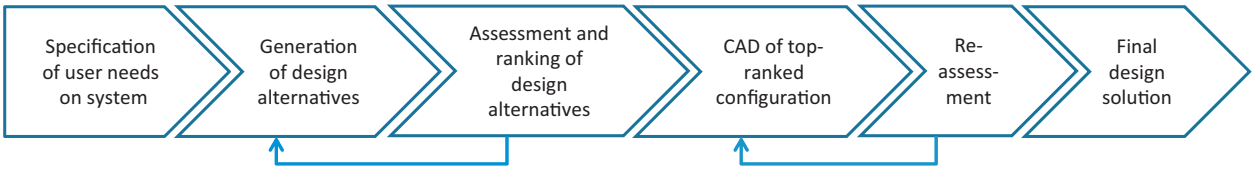

Fig. 1 – The main steps in the work process when applying the biomechatronic design approach as applied in this study. The consecutive steps include the initial specifications of the user needs on the stem cell process, the generation of design alternatives based on the specification restrictions, the assessment and ranking of the alternatives based on collected information from available sources, the CAD design of the top-ranked alternative(s) based on the outcome of the assessment, using a simulation tools of the CAD to reassess the ranking, and, finally, reaching a preferred design solution. The work process is to a large extent iterative (indicate by the reverse arrows), and where specification details and assessments are reviewed several times.