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A systematic framework for the design, simulation and optimization of personalized healthcare: Making and healing blood

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ABSTRACT

We review the key building blocks of a design framework for modeling and optimizing biomedical systems under development in the Biological Systems Engineering Laboratory and the Centre for Process Systems Engineering at Imperial College. The framework features the following components: (i) *in vitro* environment, where model parameters can be obtained and new setups can be tested; (ii) *in silico* environment, including a simulation module for representing relevant physical or biological processes, and an optimization module, for calculating improved *in vitro* or *in vivo* outcomes; (iii) *in vivo* environment, from which organ and patient-specific parameters are collected and which can also implement personalized suggestions for improved outcomes. Two applications in the area of healthy and diseased blood are thoroughly discussed to exemplify the framework's characteristics. We discuss progress in the different areas and the way in which they are connected and finally propose a hybrid *in vitro/in silico/in vivo* platform.

1. Introduction

One of the most prominent features of modeling biomedical systems is the existence of phenomena occurring at multiple scales. Between molecular, cellular, patient and population scales, appropriate translations are necessary for evaluating the effects small-scale processes have at large scale and vice-versa (Hall et al., 2011). Deriving patient data directly is not always possible, thus making *ex vivo* observations and studies imperative. For the latter to be accomplished it is essential to develop appropriate experimental setups that reproduce *in vitro* the biological characteristics and behavior of the *in vivo* system. *In silico* techniques may bridge the gap between the *in vitro* and *in vivo* scales, through simulating the patient response (Androulakis, 2014; Chen et al., 2012; Harrold and Parker, 2009; Ho et al., 2013). The study of normal and abnormal blood production faces these challenges and many others related to the complexity of the underlying biological system and the heterogeneity observed in hematological malignancies.

The current trends and developments in genomics, proteomics and metabolomics open the possibility for obtaining specific information related to the genetic characteristics, together with the proteomic and metabolomics profiles of an individual patient, which can then be used toward *personalized medicine* (Saha et al., 2014). In this context, personalized healthcare is expected to deliver a *step change* in quality and value of care, through more precise and personalized diagnostics as well as cost-effective and targeted therapies. Some of the challenges in the delivery of personalized medicine lie in (a) *In vitro*: the *fidelity and validity of current experimental systems used to investigate human diseases*; (b) *In silico: the integration of patient-specific and disease-specific datasets and the development of validated predictive adaptive models*; and (c) *In vivo:* the application of these models to identify *simple targets* and *more efficient, yet less toxic therapies and drugs* for a specific condition.

Here, we present the fundamental features of an integrated framework which aims to address (some of) these challenges—with

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main focus on healthy and diseased blood. An earlier version of this manuscript appeared as a conference manuscript (Velliou et al., 2014e); this full length manuscript clarifies and extends the previous work.

2. Design framework

Fig. 1 presents key building blocks of the integrated design framework under development at the Biological Systems Engineering Laboratory (BSEL) and the Centre for Process Systems Engineering (CPSE) at Imperial College. As a whole, the framework aims at closing the loop by collecting relevant data *in vivo* and/or *in vitro* in order to predict and/or improve real outcomes through *in silico* calculations.

From the scale point of view (represented as rows on Fig. 1), biomedical systems' circuitry can be defined as the abstract representation of physiological processes into a network of compartments where exchange and/or reaction can take place at different levels. These physiological processes are subject to external cues that are tunable depending on medical/biological needs. Thus, the backbone of the design framework is composed of the following elements, under all three environments (*in vitro, in vivo, in silico*): (i) chemical stimulation: administering molecules capable of interacting with cellular material for inducing the desired transformation; (ii) molecular transport, either with biological modification (activation, degradation, elimination) or unmodified, to the target point of action; (iii) effect: molecular interaction with the target cells to transform their characteristics toward the desirable outcome; (iv) cell growth: stem cell proliferation, defining overall cell number which could then become susceptible to transformation; and (v) cell metabolism: cellular interaction with its environment to exchange the resources needed to sustain cell growth. Note that not all systems need accurate representations at all scales.

From the environment point of view (represented as columns on Fig. 1), biomedical systems' processes are captured *in vivo, in vitro* and *in silico*. A particular system can incorporate two or more of the three environments: we will refer to *in vitro*/*in silico* systems as type 1, corresponding to laboratory setups, and to *in vivo*/*in silico* systems as type 2, tackling clinical treatment at the patient level.

Type 1 systems feature an existing *in vitro* component which delivers a valuable product (cells, proteins, etc...) whose quality/quantity/cost is not satisfactory enough. Experimental data can be readily obtained (in accordance to sensitivity analysis findings) and used to determine model parameters. The *in silico* component features mathematical representations of the relevant biological and physical processes occurring *in vitro*, simulating the experimental setup based on the aforementioned parameters. *In silico* optimization then computes an optimal scenario in which values of the operating variables are found that minimize cost/maximize production/achieve a certain quality (all according to *in vivo* specifications), while satisfying the required constraints.

Type 2 systems are composed of an *in vivo* component, corresponding to a particular patient undergoing medical treatment. Patient characteristics (*in vivo* specifications) and details of the treatment clinically administered are used to derive patient-specific parameters. Body processes affecting or affected by the medical treatment *in vivo* are rendered *in silico* through appropriate mathematical equations simulating patient response. Sensitivity analysis on the model points out which model parameters are most significant. If those parameters are not available from *in vivo* measurements, experiments have to be designed in order to specifically obtain the required parameters *in vitro*. Finally, *in silico* optimization calculates the optimal scenario on a case-by-case basis, by delivering values of the operating variables for maximizing treatment efficiency/minimizing side-effects/minimizing treatment cost, in accordance with medical constraints.

This manuscript applies our systematic framework to two healthcare domains that exemplify type 1 and type 2 systems respectively (Sections 3 and 4): artificial blood production and personalized leukemia treatments. A brief overview of how the framework is applied to the treatment of diabetes and the control of anesthesia is given in Section 5.

3. Artificial blood production: An example of a type 1 system

Over 15 million whole blood units are collected in the USA yearly (National Blood Collection and Utilization Survey, 2011); 1.9 million blood units were collected in the UK between 2012 and 2013 (NHS Blood and Transplant). But despite the success of coordinated blood collection and utilization: 3.3% of hospitals delay surgery because of blood shortages and 10.3% of hospitals experience at least one day yearly when blood needs cannot be met (Timmins and Nielsen, 2009; Whitaker and Henry, 2011). Beyond shortages of commonly-stocked blood types, patients undergoing regular transfusions may require expensive rare blood donation to mitigate the risk of an immune response to foreign antigens (Tahhan et al., 1994; Meny et al., 2013). *Ex vivo* blood production is an attractive solution for filling shortage gaps and scaling-up rare blood donations. Current blood expansion protocols however require $8330 per unit of blood when an average hospital in the USA pays only $225.42 for a typical unit of blood and $1150 to $3025 for a unit of rare blood (Timmins and Nielsen, 2009; Whitaker and Henry, 2011; Meny et al., 2013). Clearly, a more cost-effective solution needs to be implemented in order to shift toward artificial blood supply (Rodrigues et al., 2011).

We propose a platform for on-demand artificial blood production, wherein umbilical cord HSCs are cultured in a biomimetic, cost-effective, 3D bioreactor, expanded and differentiated into red blood cells by careful signaling to externally control the same process of blood production that is diseased in leukemia (green panels, Fig. 1).

3.1. In vitro: *A novel 3D bioreactor for* ex-vivo *culture of healthy and diseased blood*

Blood cell production takes place in the bone marrow (BM), a highly porous three dimensional organ of great complexity, where hematopoietic stem cells (HSCs) reside. HSCs in the BM receive appropriate signals to proliferate and specialize toward functional cellular units of the immune and oxygen-carrying systems (Quesenberry and Colvin, 2001). These signals consist of both chemical (nutrients, oxygen and growth factors, which are signaling proteins that provide extracellular stimuli to the cells) and mechanical (adhesion, cell–cell contact) stimuli unique to the 3D microenvironment (Panoskaltsis et al., 2005). However, most current research is still performed in 2D culture systems, wherein the mechanical stimuli received by the cells are nonnative and thus the cellular proliferation is reduced. This limitation is typically overcome by increasing chemical stimulation from the expensive, specialized growth factor proteins (Timmins and Nielsen, 2009). Taking into consideration the BM microenvironment architecture, we describe, in the sequel, development of two 3D *in vitro* platforms which serve as an *in vitro* bone marrow mimicry allowing the expansion of normal and diseased blood.

A 3D micro-bioreactor was developed by Mortera-Blanco et al. (2010, 2011), consisting of highly porous Polyurethane (PU, pore size approximately 100 μm), of dimensions $5 \times 5 \times 5$ mm, as shown in Fig. 2, which allows perfusion of nutrients and oxygen within the