BioCAE: A New Strategy of Complex Biological Systems for Biofabrication of Tissues and Organs

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Abstract

Biofabrication as an interdisciplinary area is fostering new knowledge and integration of areas like nanotechnology, chemistry, biology, physics, materials science, control systems, among many others, necessary to accomplish the challenge of bioengineering functional complex tissues. The emergence of integrated platforms and systems biology to understand complex biological systems in multiscale levels will enable the prediction and creation of biofabricated biological structures. This systematic analysis (meta-analysis) or integrated platforms for estimating biological process have been named as BioCAE, which will become the key for important steps of the biofabrication processes. Biological Computational Aided Engineering (BioCAE) is a new computational approach to understanding and bioengineer complex tissues (biofabrication) using a combination of different methods as multi-scale modelling, computer simulations, data mining and systems biology. In addition, multi-agent systems (MAS), which are composed of different interacting computing entities called agents, also provide an interesting way to design and implement simulations of biological systems, integrating them with all steps of the BioCAE. MAS as a part of computational science have become a growing area to manipulate and solve complex problems. This paper presents an approach that will allow predicting the development and behavior of different biological processes such as molecular networks, gene interactions, cells, tissues and organs due to its flexibility, beyond to provide a new outlook in the biofabrication of tissues and organs.

Keywords: Biological computational aided engineering (BioCAE); Biofabrication; Information technology; Systems biology; Computer simulations; Multi-agent system

Introduction

Biofabrication as an interdisciplinary area is fostering new knowledge and integration of areas like nanotechnology, chemistry, biology, physics, materials science, control systems, among many others, necessary to accomplish the challenge of bioengineering functional complex tissues. The term biofabrication was widely discussed recently and is broadly used for tissue engineering and additive manufacturing as "the automated generation of biologically functional products with structural organization from living cells, bioactive molecules, biomaterials, cell aggregates such as micro-tissues or hybrid cell-material constructs, through Bioprinting or Bioassembly and subsequent tissue maturation processes" [1]. Undoubtedly, the current biofabrication initiatives are possible because of a set of technologies that are completely supported by information technology (IT), such as imaging, database, bioprinting technique [2], artificial intelligence (AI), software and hardware. These factors make the biofabrication not only a consistent promise but also a reality for the automated production of human tissues and organs.

The bioengineering of functional tissues, functional vascular networks, interfaces, structural hierarchy and complex features is emerging as an unparalleled scientific and technical challenge for the next generation of tissue engineers [3]. However, advances in molecular and cellular biology, over the last decades, have triggered tremendous growth in the availability of experimental data. On the other hand, the computational approaches have allowed the multiparametric analyses of various datasets and biological behaviors. This is, therefore, the first engine to leverage the main goal of bioengineering tissues and organs. It begins with a deep knowledge of the behavior of the cell, mainly their mechanisms to connect molecules and machinery, aiming at activating, sustaining and modulating their functional metabolic networks responsible for the survival, growth, proliferation, differentiation and death [4].

The large-scale high-throughput experimental techniques have greatly increased overall knowledge and understanding of the global organization of complex cross-talks among the different signaling cascades and different cells. Recognizing this complexity, the concept of complex biological systems or systems biology has emerged as a powerful field that requires the ability to mathematics, engineering and information technology domains to analyze, integrate and use data from different databanks for the creation of working models of entire biological systems [5]. The ultimate outcome of this structural and functional organization is the metabolism of the cells, tissues and organs, important in all biofabrication processes. This technology is evolved into a complex system composed of many processes as computer-aided design (CAD), computer aided engineering (CAE) and computer aided manufacturing (CAM) and biological processes, which depends on the combination of different interrelated components as molecules, genes, regulatory networks, cells, organoids and tissues, integrated with computational approaches as design, modeling, simulation and optimization, among others.

Next sessions we expose a new approach, based on Information

Technology that potentially will help to improve understanding, integration and consequently optimizing the output of the biofabrication process.

Integrated Platform for Biofabrication

The emergence of platforms and systems biology to understand biological systems in multiscale levels will enable the prediction and the creation of biofabricated biological structures [6]. This systematic analysis (meta-analysis) or integrated platforms for predicting the biological behavior has been named BioCAE (Figure 1) and together with BioCAD and BioCAM will become the key procedures for establishing essential steps of the biofabrication processes.

Biological Computational Aided Engineering (BioCAE) is a new computational approach to understanding and bioengineer complex tissues (biofabrication) using a combination of different methods as multi-scale modeling, computer simulations, data mining and systems biology (Figure 1). In addition, multi-agent systems (MAS), which are composed of different interacting computing entities called agents, also provide an interesting way to design and implement simulations of biological systems [7], integrating them with all steps of the BioCAE. MAS, as a part of computational science, has become a growing area for the manipulation and solving complex problems [8]. This paper, presents a new integrated approach to predict the development and behavior of different biological processes such as molecular networks, intracellular interactions (including genes, mRNAs, microRNAs and proteins), cell–cell interactions and tissues and organs, besides to provide a new landscape in the design of functional organs and tissues for the next step of their production by means of bioprinting processes.

Biological Computational Aided Engineering for Biofabrication (BioCAE)

BioCAE will be an integrated environment where several modules of modeling and simulation are interoperated to understand and predict a suitable and functional organ design (BioCAD) for biofabrication (BioCAM). In other words, today, great efforts and high costs are required to, experimentally, manipulate cells and/or cell agglomerates that will especially necessary for the biofabrication of organs and tissues. Therefore, the use and the development of computational approaches to study complex biological systems in different levels (cells, tissues and organs) in silico are fundamental for the progress of the unique biofabrication field.

The emergence of powerful software platforms to study the biological behaviors in different environments, as BioCAE, depends on data handling/data mining, imaging, computer modeling, computer simulation, integrated computational analysis, MAS and knowledge integration, among many others. One of the main approaches of our proposal is to create computational models that enable users to predict the behaviors of biological systems at multi-scales, thereby helping users to understand the mechanisms involved as well as to predict the impacts that occur during the biofabrication process. It includes a myriad of parameters such as pressures, pH, oxygenation, nutrition, fusion, diffusion, temperature, stresses, velocity and viscosity, among many others that affect biological viability in the survival, growth, proliferation and differentiation.

Many papers highlight the importance of computational multi-scale methods in systems biology [9-13] and recently, in the biofabrication [14]. The biological systems are made up of many spatial and temporal scales. These diverse levels coupling intra and interscale interactions make a biological system extremely complex, requiring advanced mathematical and computational models for the integration of the different scales [15,16]. There is a range of multi-scale modelling methods that could potentially be employed in systems biology [17-22] and consequently in the biofabrication of tissues and organs.
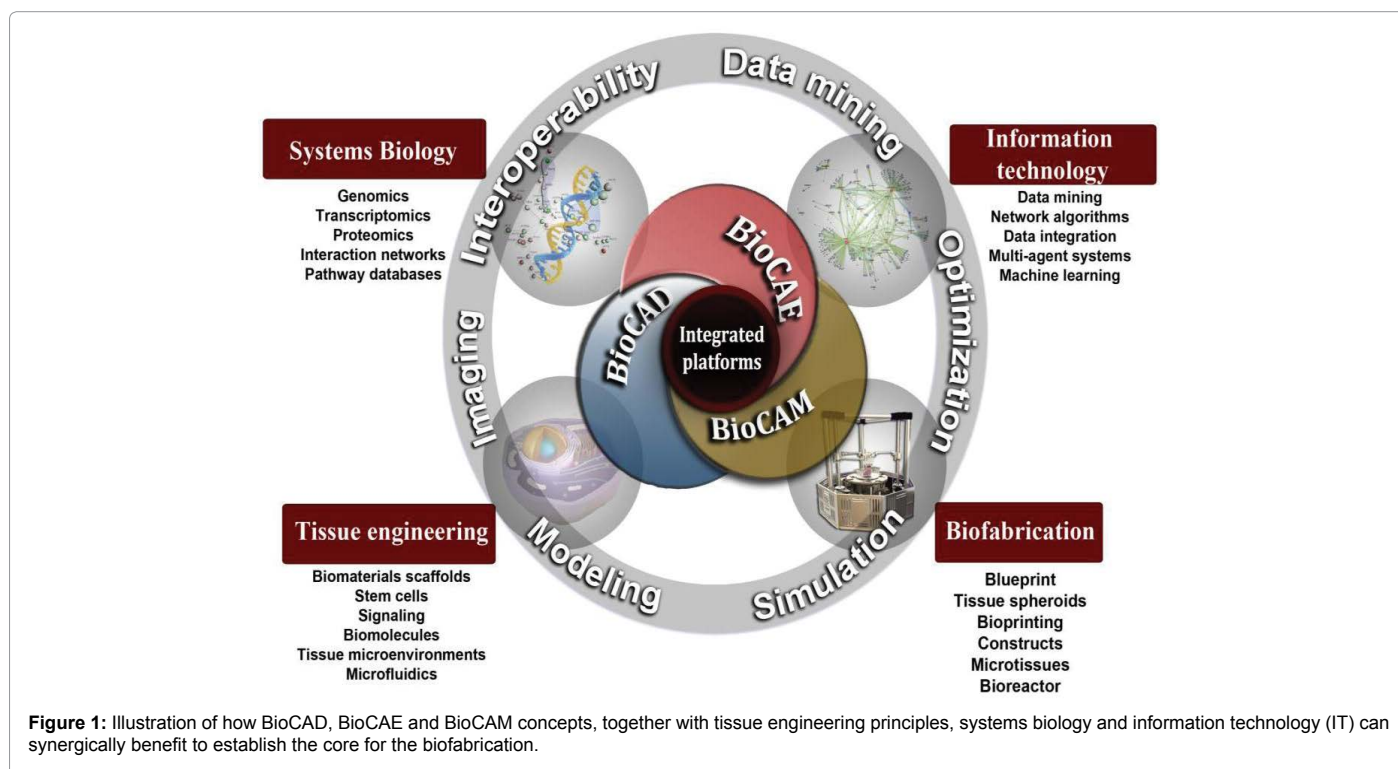

Figure 1: Illustration of how BioCAD, BioCAE and BioCAM concepts, together with tissue engineering principles, systems biology and information technology (IT) can synergically benefit to establish the core for the biofabrication.

Then, in the next section, we will describe some multi-scale approaches and/or software which may be part of the BioCAE and that are playing or will play important roles in multi-scale problems in systems biology and tissues biofabricated, thereby preventing a large amount of trial and error experiments in laboratories.

From Molecules, Cells and Tissues towards Organ

The aim of multi-scale modelling is to represent, predict and understand the behaviour of complex systems across, not only in a wide spatial scale (molecules, genes, mRNAs, proteins, metabolic networks, cells, organoids, tissues and organs) as shown in Figure 2, but also in temporal scale (seconds (s), minutes (min), hours (h), days, weeks, months, years). Despite the significant growth of this field of knowledge, there is a need to develop frameworks for the interoperability among different simulation software. In this context, it is possible to find that several toolkits, databases, pipelines, methods, integrated frameworks and platforms have been developed for this purpose [23]. On the other hand, the major drawback of these approaches is the high computational requirements, particularly for higher eukaryotes, where even a single organ is composed of a large number of cells. Many approaches share mathematical models, especially when using integrated platforms or software are used. Accordingly, various methods are presented below, which were developed for the study of complex biological systems that can be adapted to compose the BioCAE concept.

For a better understanding, the following three sections describe a multilevel approach, from molecules to organs that will be integrated with relevant information and models using the BioCAE framework proposal.

Cell Modelling Level: From Molecules to Cells

Because of the intrinsic nature of biological systems and their processes (sequences, genes, proteins, signaling networks, regulatory networks and metabolic networks), the unequivocal identification of a molecule or sequence in a specific process is nontrivial. In contrast, the vast amount of experimental data and high throughput analyses (genomics, transcriptomics, miRNomics and proteomics) has identified a myriad of key factors (genes, RNAs, microRNAs, proteins and pathways). With this in mind, tissue bioengineers and other researchers who wish to biofabricate tissues and organs should understand firstly how molecular-scale mechanisms lead to complex functional structures at the scale of tissues, organs and organisms.

The characterization of intracellular pathways and their behaviour are the original focus of systems biology and it has a long history of work and achievement in the development and in the use of mathematical models of cellular signalling, metabolic control and MAS to set up simulations for molecular and cellular biology [10]. Equally important are the graphical diagrams of biological processes, which are useful for visual presentation, mainly for biologists. In terms of
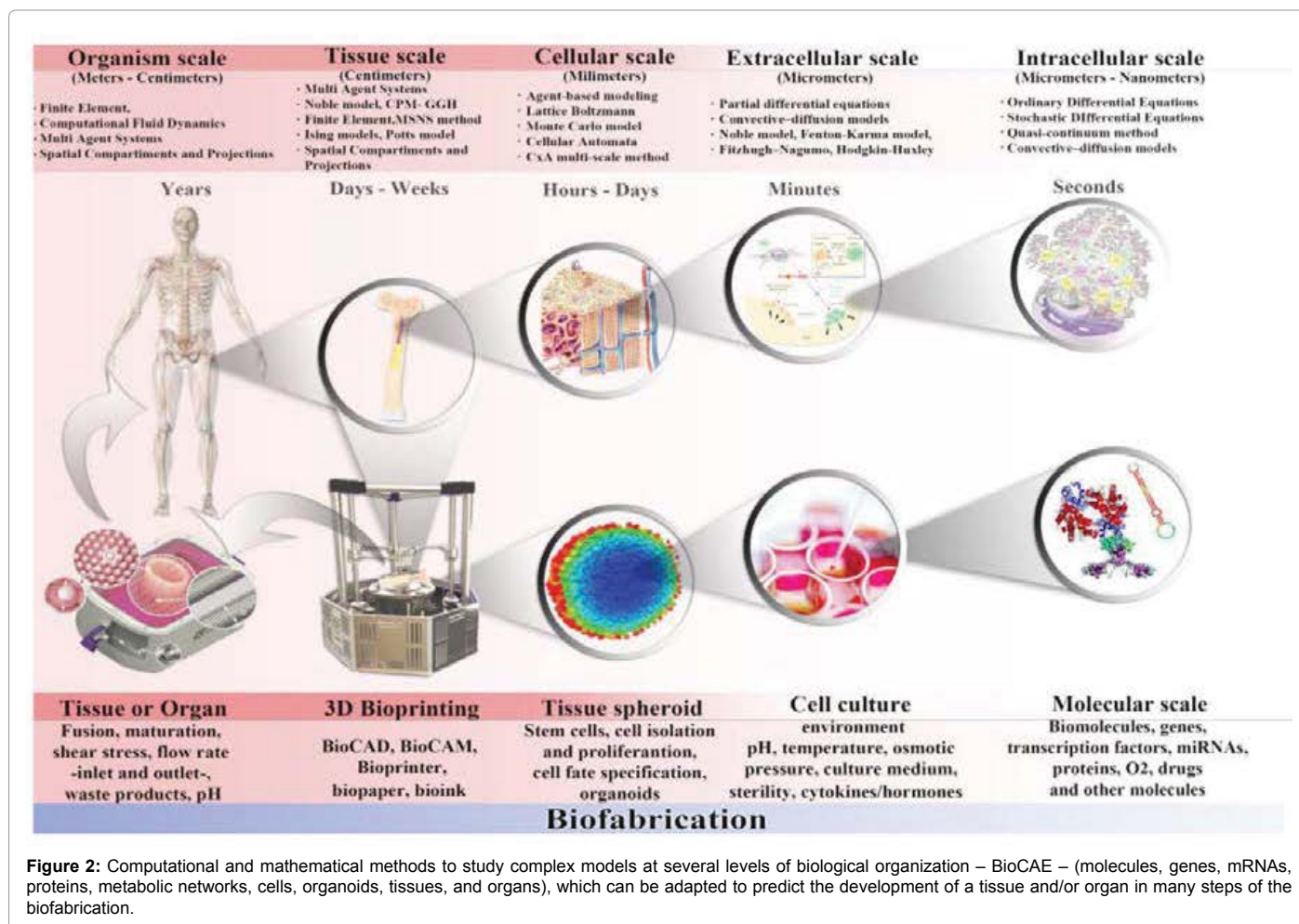

Figure 2: Computational and mathematical methods to study complex models at several levels of biological organization – BioCAE – (molecules, genes, mRNAs, proteins, metabolic networks, cells, organoids, tissues, and organs), which can be adapted to predict the development of a tissue and/or organ in many steps of the biofabrication.

software, a different representation format is needed for quantifying a model for simulation and analysis. This representation can use a standard language called Systems Biology Markup Language (SBML) [24]. SBML is a machine-readable format for representing models and it is suitable for representing models commonly found in research on a number of topics, including cell signalling pathways, metabolic pathways, biochemical reactions, gene regulation and many others [25].

Another possibility to comprehend these phenomena would be by means of specialized frameworks, for example, the CompuCell3D (CC3D), which is multi-model software that simulates interactions of a gene regulatory network with cellular mechanisms, cell adhesion, haptotaxis and chemotaxis, among others. The three main background components of CC3D are a Cellular Potts Model (CPM), a Reaction–Diffusion (RD) module and a combined ODE/state model of genetic regulatory networks and differentiation [26].

The crucial step to the computational modeling is to cast the model into a standardized, computable format that can be analyzed rigorously using simulations and mathematical methods, whereas the different representations of models are useful for different purposes. For this reason, many research groups have developed approaches for studying biological processes related to the intracellular and extracellular environment, as secretion, absorption, diffusion of chemicals with the environment, cell proliferation, cell differentiation, adhesion, cell movement and cell internal dynamics. Below are described some of these models found in the literature:

i) Chemical diffusion: the process of molecule secretion and absorption as facilitated diffusion. The literature lacks information about the transport mechanisms of such molecules as genes, transcription factors microRNAs, proteins and about the rate of diffusion. However, the following approaches can be used to study these processes: Quasi-continuum (GC), Quantum Mechanics-Molecular Mechanics (QM-MM), Computational Fluid Dynamic (CFD), Equation-free Multi-scale (EFM), Kinetic Monte Carlo (KMC), Lattice Boltzmann (LB) and Molecular Dynamics Codes (MDC).

ii) Regulatory network: the replication, transcription, translation from the perspective of DNA and RNA begin with the binding at the gene promoter of one or more transcription factors. However, these intrinsic regulations might also be repressed by transcription factors and microRNAs [27]. This activation/inhibition is stochastic and highly depends on the concentration of molecules and sequences. Therefore, the probability of molecular mechanisms is a sum of positive and negative contributions from the concentration of enhancers and silencers, respectively [28]. Logical models (Boolean models, Probabilistic models and Bayesian Models) and Continuous Models (Linear Model and Differential equation based model) are the mathematical and statistical methods most commonly found in the regulatory networks prediction platforms [29].

iii) Migration and adhesion: The model of cell movement and adhesion considers the chemotaxis phenomenon, which is known to be responsible for cell sorting during morphogenesis and this model component is inspired by a previous work that considers chemotaxis as an important actor for the creation of self-organized structures [30,31]. The latest models proposed in the literature to describe different events in cellular adhesion and migration are based on Cellular Automata (CA) and Cellular Potts Models [32,33].

iv) Mitosis: cell division is fast and synchronous until cleavage, then slows down and becomes asynchronous. The rate of division is constant in the first hours of cell development and then decreases until a low value [34]. Mogilner et al. showed some related models with mitosis, among them, stochastic and transient microtubes - motor assemblies to drive steady, accurate movements during the process [35].

Tissue Modelling Level: From Cells to Tissues

Tissue-scale models explain how local interactions within and between cells lead to complex biological patterning where some methods have already been mentioned before. However, the two main approaches to tissue modeling are continuum models, which use cell-density fields and partial differential equations (PDEs) to model cell interactions without explicit representations of cells and MAS, which represent individual cells and interactions explicitly [17]. Furthermore, the most promising family of mathematical models in tissue simulation is those based on the Ising model, the Potts model and the CPM-GGH model. The frameworks TSIM˚ (http://www.tsimsoftware.com), Morpheus (https://imc.zih.tu-dresden.de/wiki/morpheus/doku.php?id=start), Simmune modeler (https://www.niaid.nih.gov/research/simmune-project), CellSys (http://ms.izbi.uni-leipzig.de/index.php/software/cellsys2010) and CC3D (http://www.compucell3d.org/) are some solutions that use this family of models.

Organs Modelling Level: From Tissues to Organs

A biological organ is a group of tissues joined in structure unit to perform a specific function or functions (e.g. heart, brain, kidney, lungs, etc.). Various processes at the tissue, cellular, sub-cellular and

Model	Strategy	References
Modelling and simulation of diffusion process in tissue spheroids	CFD	[14]
Agent-based virtual tissue simulations	CC3D	[17]
Cell compressibility, motility and contact inhibition on the growth of tumor cell clusters	CC3D	[18]
Multiscale modeling of the early CD8 T cell immune response in lymph nodes	CC3D	[19]
Multi-scale knowledge on cardiac development	CC3D	[20]
The cell behavior ontology	CC3D	[21]
Cell differentiation in the transition to multicellularity	CC3D	[22]
Dynamics of cell aggregates fusion	CC3D	[36]
A multi-cell model of tumor evolution	CC3D	[37]
Virtual tissues	MAS	[38]
Disruption of blood vessel development	CC3D	[39]
Tumor growth and angiogenesis	CC3D	[40]
Agent-oriented *in silico* liver (ILS)	MAS	[41]
Model of thrombus development	MAS (TS)	[42]
Three-dimensional multi-scale tumor model	MAS	[43]
A multi-scale model of dendritic cell education and trafficking in the lung	CM	[44]
Multi-scale model of follicular development	CM	[45]
Multi-scale *in silico* leukocytes model	MAS	[46]
Multi-scale model of organogenesis	CM	[47]
Limitations of spheroids under inappropriate conditions	FE	[48]
Finite element modelling of the viscoelastic human cranial cavity	FE	[49]

CM: Continuum Model; SH: Spatially Hierarchical; TS: Temporally Separated; CC3D: CompuCell 3D; CP: Cellular Potts; FE: Finite element; CFD: Computational Fluid Dynamics; MAS: Multi-Agent System

Table 1: Summary of models of the biological system and the strategies used.

lower levels occur at multiple time scales influencing the behavior of the organ. Multi-scale models are usually based on the continuum modeling and/or MAS approaches which can be decomposed into N single-scale mathematical models and several physical processes. Various works have already been done which apply many multi-scale methods in several biological systems [14,17-22,36-49]: a good review is proposed in Table 1.

Conclusion

Systems biology aims at describing and understands the complex biological systems and ultimately to develop predictive models of human disease, meanwhile, our long-term goal is to develop a new strategy using the information technology to model, simulate and predict behaviours of a biological system for biofabrication of tissues and organs. Computational models can be used to explicitly represent a set of entities with a complex internal behaviour, which interacts with the others and with the environment generating an emergent behaviour representing the system dynamics; under those circumstances, many fields of knowledge will obtain essentials biological insights.

The BioCAE approach intends to integrate the various modeling levels by means of relevant information among them. This accomplishment requires integration of knowledge from diverse biological components, data and methods that span several spatial and temporal scales into models of the system as a whole, though an important difficulty in multi-scale modeling is their high computational costs and integration. Therefore, the development of functional tissues and organs will only be possible with the emergence of a BioCAE framework that will take advantage of the huge amount of available models.

Acknowledgement

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