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Design standards for engineered tissues

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ABSTRACT

Traditional technologies are required to meet specific, quantitative standards of safety and performance. In tissue engineering, similar standards will have to be developed to enable routine clinical use and customized tissue fabrication. In this essay, we discuss a framework of concepts leading towards general design standards for tissue-engineering, focusing in particular on systematic design strategies, control of cell behavior, physiological scaling, fabrication modes and functional evaluation.

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1. Introduction

Engineered technologies such as aircraft, bridges, and microelectronic devices are all designed and manufactured to meet specific, quantitative standards of safety and performance. These more traditional engineering projects are based on a fundamental understanding of the building substrates, such as aluminum, steel, concrete, and gallium arsenide, which are then integrated into the design process. In tissue engineering, similar manufacturing standards have proven elusive, as the field to date has largely focused on feasibility experiments where the mass manufacturing of cells and tissues has not been required. However, as the field advances, the adoption of Good Manufacturing Practices (GMP) will be imperative to satisfy regulatory requirements and enable routine clinical use. This will necessitate a materials characterization of the most difficult building substrate known, the living cell. In the last two decades, a wealth of micro- and nanofabrication tools has become available for creating and customizing cell culture substrates that provide mechanical support and instruct and monitor cell differentiation and survival (Dvir et al., 2011; Gauvin et al., 2012; Hollister, 2005; Kane et al., 1999; Langer and Vacanti, 1993; Lutolf and Hubbell, 2005). Such tools have allowed investigators to mimic cellular environments and test how the cells will respond under various conditions, not unlike the material characterization that precedes any traditional engineering project. These technologies suggest that local control of cell behavior can be exploited to transform cells into predictable building substrates with quantitatively defined performance standards.

Local control of cellular form and function is not a trivial pursuit. Scaling from microenvironments to 3D-tissue, however, remains even more

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challenging with multiscale architecture, mechanics and communication (chemical, electrical, and mechanical) that regulate, in the aggregate, global function. Take, for example, the ongoing quest of tissue-engineering functional heart valve replacements despite of more than 50 years of research and a comprehensive understanding of valve mechanics and morphology (Dasi et al., 2009; Sacks and Yoganathan, 2007). Unlike mechanical and electrical engineering disciplines where components can be isolated and expected to exhibit characteristic material properties independent of context, tissue engineering must account for particularities of a living substrate and its unique behavior within a population. This includes context-dependent gene expression and so-called emergent properties, i.e., novel characteristic exhibited at population level that cannot be easily predicted from individual components, such as self-organization and synergetic effects (Corning, 2002). A purely biomimetic design strategy, i.e. blind copying of the entire system, may not be possible without a fundamental law of cellular behavior and appropriate scaling laws that cover a broad range of spatial and temporal scales (Parker and Ingber, 2007). As an alternative approach, we propose a classical engineering approach adopted most recently to develop design standards in molecular synthetic biology (Andrianantoandro et al., 2006): Decouple the system, i.e. break down global function into smaller structural and functional entities that can be analyzed separately; use abstraction, i.e. organize the system into hierarchies that facilitate analysis and can be combined in novel ways; and implement quality control, i.e. develop definitions of standard biological components and systems.

Quality control is faced with the inherent variability of individual cell behavior due to gene expression noise and context dependence. Further, cell-to-cell and extracellular matrix interactions modulate the impact of individual cellular components within the tissue. Thus, rather than requiring identical cellular building blocks, functional test criteria should be based on statistics of cell populations, the level at which function is generated. The unreliability of individual cell function can be taken into account by establishing ranges of tolerances of population statistics permissive for adequate tissue performance.

Particular opportunities and challenges are presented by the use of embryonic, adult, or induced stem cells for tissue-engineering. Controlled by a complex network of genetic and epigenetic pathways, these cells harbor the potential of both self-renewal and differentiation (Li et al., 2012), promising the advent of autologous implants for repair and restoration of impaired organ function (Jopling et al., 2011), but also bearing the risk of oncogenesis (Zhu et al., 2012). Pluripotent stem cells (iPSCs), for example, have been shown to differ from embryonic stem cells in gene expression, epigenetic landscape, differentiation potential, and mutational load while the functional consequences remain unclear (Bilic and Izpisua Belmonte, 2012; Yamanaka, 2012).

Therefore, safety criteria might have to be based on individual cell characteristics, highlighting the need for standardized procedures and quality control customized for each building material.

In the following, we will discuss a framework of concepts leading towards general design standards for tissue-engineering.

2. Systematic approach: design, build, test

Prerequisite to developing design standards is adopting the traditional engineering algorithm which iterates analysis and design of key structure–function relationships, assembly of quality-controlled prototypes, and performance testing using quantitative benchmarks.

Our long standing interest in the heart led us to ask if there are common design principles in all muscular pumps, and if they would be revealed by reverse engineering one and reconstructing it with parts from another. In a proof-of-concept study, we recently reported the reverse engineering of a *Aurelia aurita* jellyfish in the form of a biohybrid life form consisting of a synthetic polymer thin film and precisely engineered rat cardiac tissue (Nawroth et al., 2012). This model system was chosen because of the jellyfish's simple and easily accessible anatomy that, paired with well-defined propulsion and feeding functions (Dabiri et al., 2005), facilitated analysis, design, assembly and testing of structure–function relationships at multiple scales using quantitative metrics. In particular, behavioral and structural studies of the native jellyfish revealed key functional entities underlying swimming and feeding performance, such as stroke kinematics and spatiotemporal synchrony of contraction, which in turn are based on structural entities ranging from myofibril organization to body geometry (Fig. 1, top half).

Subsequently, quality-controlled engineered compounds were combined to meet structural and functional benchmarks of the native entities. Computational and empirical analysis revealed weaknesses of the design and guided design optimization (Fig. 1, bottom half).

Linking structure to function represents the greatest challenge in biology. In the jellyfish example, tissue and behavioral complexity were sufficiently modest to model straightforward structure–function relationships and constrain the design choices according to rational criteria. Creation of more complex systems, where functional entities and structure–function relationships are less well-defined, may benefit from complementary approaches such as an initial sensitivity analysis, which indicates important design parameters, and directed evolution, which screens random design variations according to functional selection criteria, such that working solutions "emerge" without necessitating initial full mechanistic insight (Andrianantoandro et al., 2006; Esvelt et al., 2011). Importantly, biomimetic function ensuing from any of these strategies does not necessitate biomimetic materials at all levels of organization; rather, we propose that functional convergence of dissimilar starting materials can be reached if key structure–function relationships are reproduced. For these ends, it is imperative to understand and control morphology and the response profiles of the engineered tissue's building blocks, cells, extracellular matrix components and cellular networks.

3. Tissue design: exploit dynamic cell responses and emergent properties

Cells and extracellular matrix components are the building blocks of all tissues. Matching a tissue's list of component parks, is necessary, but not sufficient, to potentiate function; function is conferred by spatiotemporal organization and interaction of cells and their environment (Tsang et al., 2009).

Microenvironmental cues such as matrix rigidity and the boundary conditions imposed on the cells drive the organization and function of cells and tissues (Grosberg et al., 2011). Substrate elasticity, for example, has been reported to contribute to mesenchymal stem cells commitment to neurogenic, myogenic or osteogenic phenotype (Engler et al., 2006). Further, changes in substrate elasticity can trigger remodeling in differentiated cells, such as the pathological adaptation of cardiomyocytes to fibrosis-associated matrix stiffening which alters cell-to-cell adhesions and ultimately impairs contractile function (McCain et al., 2012). Another example for microenvironmental cues are the systemic soluble factors accounting for age-associated decline of both myogenesis and neurogenesis in mice, such that progenitor cells from young animals exposed to blood serum from older animals assume the proliferation and regenerative capacities associated with aged systems, and vice versa (Conboy et al., 2005; Villeda et al., 2011). Other cues that influence cell behavior include spatiotemporal dynamics of extracellular matrix (ECM) components, signaling molecules, substrate topography and biomechanical forces (Keung et al., 2010; Sheehy et al., 2012). All of these agents present opportunities to turn cells into predictable building substrates and standardized components of tissues. Accordingly, various release and presentation schemes have been developed to incorporate chemical and physical cues into scaffolds, forming so-called microniches that trigger specific cell responses (Place et al., 2009). In the tissue-engineered jellyfish, muscle morphogenesis was controlled

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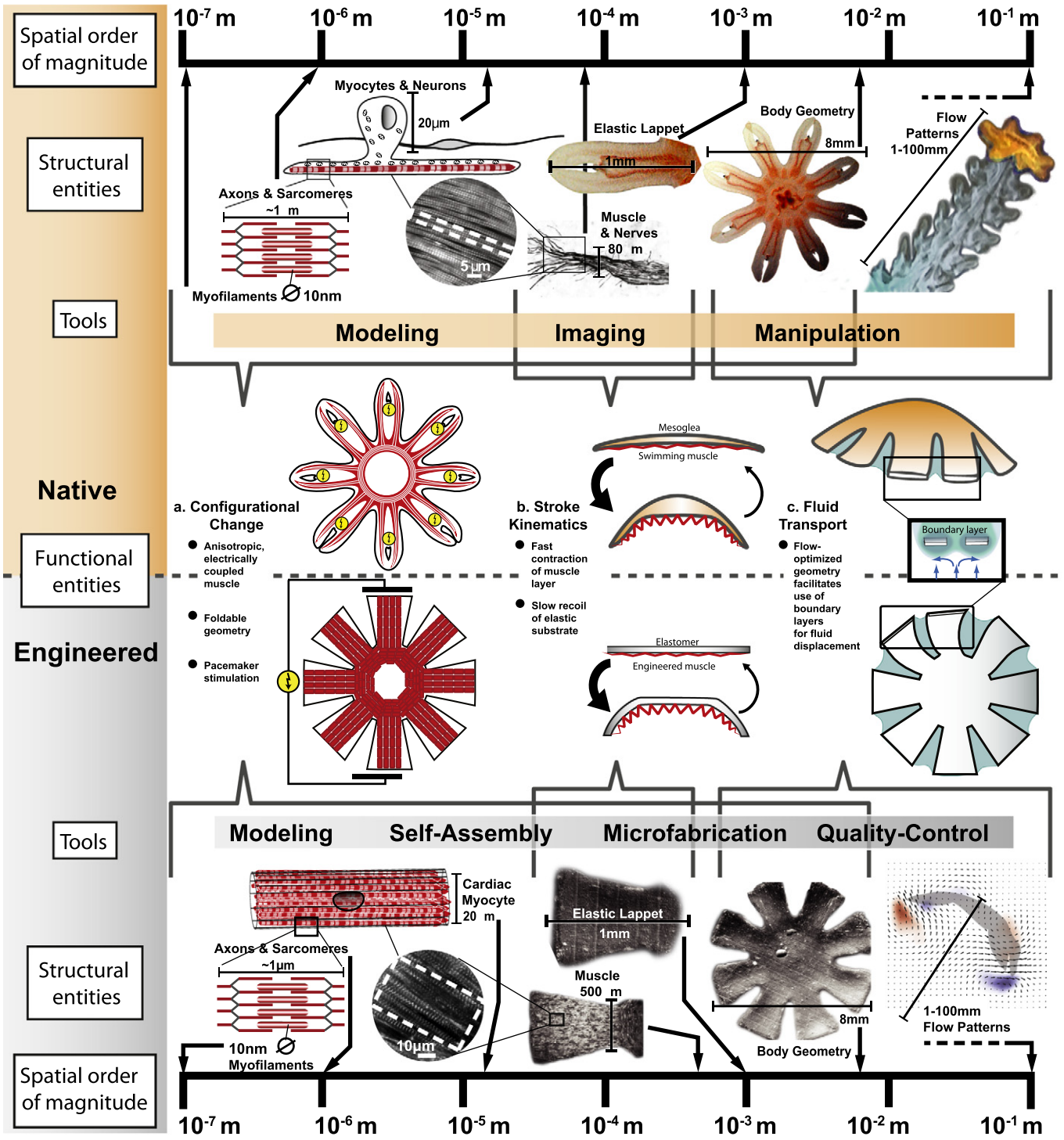

Fig. 1. Breakdown of jellyfish swimming and feeding into structural and functional entities at various scales, and translation to engineered materials. Top half (yellow): Illustration of *spatial orders of magnitudes* spanned by the *structural entities* in native jellyfish that underlie swimming and feeding function, ranging from nanoscale contractile fibers to macroscale flow patterns. Research *tools* including computational modeling, imaging approaches and experimental manipulation reveal how structural entities combine and interact to form three key *functional entities* relevant for swimming and feeding: a, specific conformational change of bell shape controlled by lobed body geometry, muscle anisotropy and synchronized electrical pacing signal. b, asymmetric stroke kinematics depending on fast muscle contraction and slow elastic recoil of the lappet substrate, and c, geometry-dependent exploit of viscous boundary layers for diverting oncoming flow (blue arrows) from gap spaces, thus facilitating efficient fluid displacement during contraction. Bottom half (gray): In order to recapitulate the key *functional entities* underlying jellyfish function, *tools* such as computational modeling, self-assembly, microfabrication, and quality-control are used to design and build engineered *structural entities* across multiple *spatial orders of magnitudes*, including contractile fiber organization at micrometer scale, lappet geometry at millimeter scale, and flow patterns at centimeter scale.

through micropatterning of fibronectin and suitable substrate stiffness (Feinberg et al., 2007).

Ensembles of cells, however, generate and sense mechanical, electrical and physiological properties not captured on the level of the microniche. Reentry, for example, the most common cause of cardiac arrhythmias, is an emergent property of the heart where combinations of conduction velocity, refractory periods, and tissue geometry can potentiate circular activation pathways (Lusis and Weiss, 2010). The elastic recoil of lung tissue

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results from the multiscale organization of its cellular and matrix constituents and cannot be understood from the properties of individual components (Suki and Bates, 2011). Changes in cell motility can generate self-organization into patterned tissues (Chen et al., 2012), and cell polarity underlies spontaneous tube formation (Bryant and Mostov, 2008). Conversely, tissue geometry and dimensions influence cell shape and force distributions within the cells, including distension of the cell nucleus which affects gene expression and differentiation (Ruiz and Chen, 2008). In addition, cell ensembles can normalize the effects of stochastic gene expression, mutations, cell death and other sources that render single cells behavior unpredictable (Andrianantoandro et al., 2006; Elowitz et al., 2002). If understood and harnessed, such emergent properties need not be a nuisance but facilitate building functional tissues. In the tissue-engineered jellyfish, for example, understanding the chain of effects linking myocyte shape, sarcomere alignment, electrical conduction and global force generation based on both empirical and computational studies (Alford et al., 2010; Bursac et al., 2002; Grosberg et al., 2011; Shim et al., 2012) provided clear guidelines for the design of the swimming muscle (Nawroth et al., 2012). Managing emergent properties, however, is not the only challenge when altering tissue dimensions; its complement is to preserve properties at various scales and conditions.

4. Physiological scaling: integrate allometric and dimensional analysis

Preserving function in a tissue at altered scales or at different external conditions requires understanding how physiological function varies with spatiotemporal and environmental parameters. Allometric analysis generates quantitative expressions of how physiology scales with body dimensions but often stop short of providing mechanistic insights. One example is Kleiber's law (Kleiber, 1932) which concludes from empiric data that the metabolic rate of an animal scales to the 3/4 power of its mass. Although this relation has been shown to hold for a surprising range of organisms, its mechanistic basis remains unresolved, possibly because of the expectation that it should apply to single cells and elephants alike (Agutter and Tuszynski, 2011), thereby limiting its use for systematic design studies. Greater promise for exposing biological structure–function relationships lies in focusing on functionally related systems with comparable constraints, and pairing a systematic search for allometric laws in physiological data with dimensional analysis as performed in engineering and physical sciences. Dimensional analysis is a rigorous mathematical approach to identifying basic physical quantities, such as length, time and mass, and their interdependences relevant to explaining the functional characteristics of a system. Maintaining these relations when changing design parameters preserves kinematic and dynamic behavior, a concept called similitude, which allows, for example, for modeling the drag of cars based on data from miniature-sized models.

In the case of the synthetic jellyfish, dimensional analysis and computational modeling revealed how to achieve native propulsion efficiency by adapting the body geometry to account for the differences in fluid dynamics between seawater at 15 °C and culture medium at 37 °C (Nawroth et al., 2012). In a classic study, Murray (1926) was able to explain the branching pattern of cardiovascular systems by showing that they minimize the costs of flow generation and material use, a law that also proved applicable to the geometric similarity of various tubular fluid transport systems in animals and plants (LaBarbera, 1990; Murray, 1926). In a more recent example, applying dimensional analysis to morphological and behavioral data of aquatic invertebrates revealed how access to nutrients and consequently the metabolic rate scale with flow parameters and body geometry (Patterson, 1992).

Combining dimensional scaling laws with control of structure–function relationships at the level of cells and cellular networks provides the basis for the design of engineered tissues. The subsequent task is to develop fabrication strategies that can implement the design based on engineered materials and fabrication methods.

5. Fabrication scaling and limits: exploit technology and self-organization of cells

A particular challenge for tissue-engineering is the reproduction of anisotropy that characterizes biological systems at various scales and is crucial to conferring functional characteristics, e.g. cell polarity, extracellular fiber orientation and preferential electrical conductivity. Which parts of this organization should be created by micro- and nanofabrication? Which parts can develop from physical and chemical processes (e.g. diffusion gradients, self-assembly, and degradation)? And which parts are best left to the self-organizing powers of cells, an extreme example of which is given by the maze-solving abilities of the slime mold (Nakagaki et al., 2000)?

Attempts to engineer interfacial tissues, which are particularly rich in anisotropy, exemplify the advantages of combining all of the above approaches and including cellular self-organization as part of the fabrication process. Tissue interfaces include bonds of mechanically dissimilar materials such as ligament-to-bone and cartilage-to-bone transitions where anisotropic structural properties gradually vary from one tissue to another and thereby reduce the risk of rupture. Such transition zones can be generated by self-organization of cellular phenotypes along gradients of soluble factors or physical properties. For example, differentially activating bone-specific gene expression using a gradient of transcription factors resulted in a mineralization gradient that mimicked the mechanics and microstructure of native ligament-to-bone interfaces (Phillips et al., 2008). Also, as discussed earlier, stem cell differentiation is induced by substrate elasticity, often resulting in cell types that reinforce the mechanic characteristics of their environment, such as bone formation on stiff substrates (Engler et al., 2006). This response can be exploited for generating gradients in cell populations and tissue types (Seidi et al., 2011). In the case of the tissue-engineered jellyfish, photolithography was used for generating features at cellular resolution (ECM patterns with 20 μm line width), and cellular self-organization was exploited for the alignment of subcellular entities (e.g. myofibrils and gap junctions).

Importantly, fabricated tissues must meet structural benchmarks defined during the design process. Otherwise, no insight can be gained from evaluating the functional performance of the construct. It is equally important to choose well-defined criteria for system-level performance tests.

6. Evaluate performance: use of traditional and novel physiological metrics at system level

Systematic evaluation and optimization of tissue design requires common performance benchmarks for engineered and native systems, the parameter space of which is illustrated in Fig. 2. As case in point, the synthetic jellyfish was evaluated based on quantitative measures of flow field dynamics and feeding/swimming performance established in native medusae (Dabiri et al., 2005). However, whereas assessing cellular function by means of gene expression, protein synthesis and ionic fluxes has become standard practice across biological sciences, the functional evaluation of organs or organisms is rarely reported outside the fields of comparative biomechanics and medicine (e.g. Romanes, 1898).

Whole-organ studies can generate comprehensive functional data unattainable from cell cultures and other reduced experimental platforms. The Langendorff preparation, for example, an classical mammalian heart preparation, enables the study of contractile function, heart rate, vascular tone and cardiac metabolism over the course of several hours, (Bell et al., 2011; Skrzypiec-Spring et al., 2007; Wiechert et al., 2003). Complementary to preserving traditional physiology assays is the development of novel functional metrics that facilitate evaluating biological

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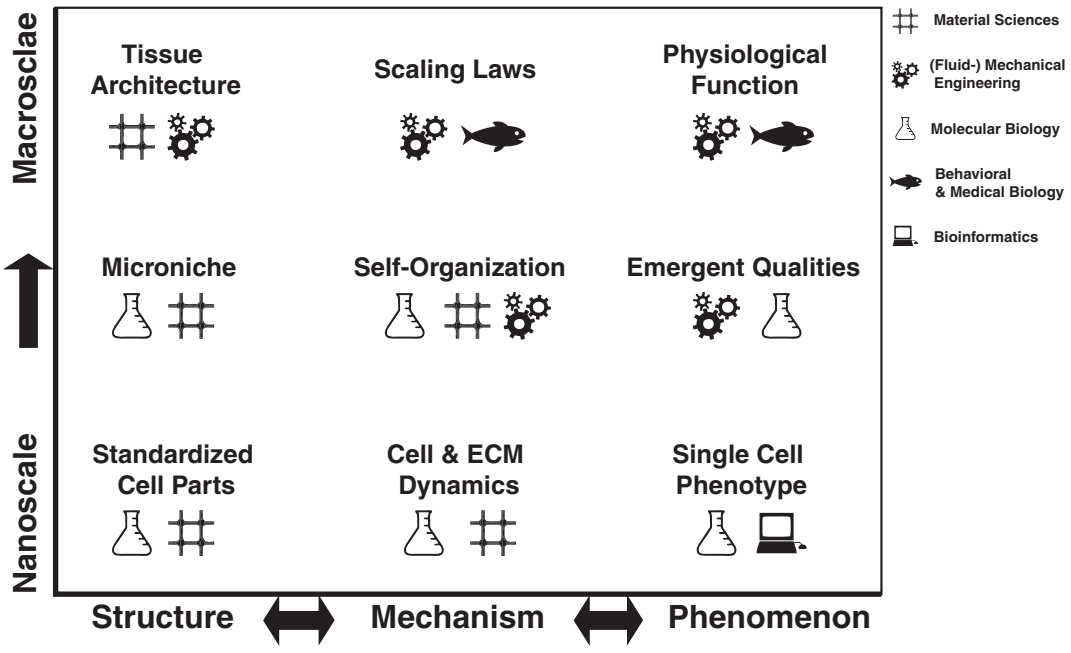

Fig. 2. Simplified design–build–test landscape for tissue engineering. Employing the design–build–test algorithm to engineer tissues and develop design standards involves the analysis, recapitulation and testing of materials, mechanisms and phenomena (abscissa) across multiple orders of magnitude (ordinate axis), a task that requires expertise and interaction of various scientific and engineering disciplines (examples indicated with icons).

and engineered structures at system-level. A recently described universal index of efficiency in fluid transport via vortex formation, for example, applies to heart output, squid propulsion and piston pumps alike and gave rise to a non-invasive assay for assessing cardiac function and disease progression based on echocardiographical data (Dabiri, 2009; Gharib et al., 2006). Beyond its diagnostic function, the efficiency index is also a promising candidate for evaluating tissue-engineered heart repairs and substitutions.

7. Discussion and conclusions

Developing design standards for engineered tissues will not only advance the creation of artificial organs and novel biological tools but also improve in vitro disease models currently limited to 2D cell cultures (Hutmacher, 2010). As outlined in this article, it requires implementing the classical engineering algorithm (design, build, and test) based on mechanistic understanding of the tissue's building substrates, dimensional scaling laws, multi-modal fabrication strategies and system-level performance metrics. Importantly, quality control should be part of tissue engineering, and in many cases, this will include both multiscale histology and organ-level physiological performance.

Implementing the design–build–test algorithm will rely on both empirical and computational tools; the latter will be of particular benefit to design studies, dimensional scaling analysis and fabrication optimization. The greatest challenge, however, will be to provide scientists with the background and training needed to comfortably navigate the biodesign algorithm's landscape spanned by various scientific and engineering disciplines (aka medicine-to-informatics axis), multiple spatial orders of magnitude (aka nanoscale-to-macroscale axis), and complementary modes of analysis (aka structure-to-phenomenon axis).

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