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The Necessity of a Theory of Biology for Tissue Engineering: Metabolism-Repair Systems

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Abstract—**Since there is no widely accepted global theory of biology, tissue engineering and bioengineering lack a theoretical understanding of the systems being engineered. By default, tissue engineering operates with a "reductionist" theoretical approach, inherited from traditional engineering of non-living materials. Long term, that approach is inadequate, since it ignores essential aspects of biology. *Metabolism-repair systems* are a theoretical framework which explicitly represents two "functional" aspects of living organisms: self-repair and self-replication. Since repair and replication are central to tissue engineering, we advance metabolism-repair systems as a potential theoretical framework for tissue engineering. We present an overview of the framework, and indicate directions to pursue for extending it to the context of tissue engineering. We focus on biological networks, both metabolic and cellular, as one such direction. The construction of these networks, in turn, depends on biological protocols. Together these concepts may help point the way to a global theory of biology appropriate for tissue engineering.**

Key Words—**Theoretical biology, bioengineering, self-repair and self-replication, metabolism-repair systems**

I. Introduction

Traditional engineering is based on solid theories of how and why things work as they do. Engineering within the domain of biology presents challenges because there is no widely accepted global theory of biology, even though there are standing theories dealing with aspects of biology, such as the Mendelian theory of particulate inheritance. Without a global theoretical framework, bioengineering efforts move forward principally by trial and error on a foundation that biological systems can be treated as machines. However, current efforts in cell and tissue bioengineering can help motivate development of such a theory, and parallel efforts to develop such a theory should prove synergistic to those bioengineering efforts. Bioengineering will benefit by fostering, working within, and contributing to theory.

In this paper, we attempt to initiate such a synergy by exploring the applicability of a proposed global theoretical framework for biology to tissue engineering. That theory is the metabolism-repair systems formalism, initially developed by the theoretical biologist Robert Rosen.

Rosen's work contained a strong criticism of reliance on the Newtonian "reductionist" approach to understanding biological systems. The Newtonian approach assumes that any system can be understood (and furthermore, fabricated) by understanding the physical forces (chemical, mechanical, etc.) acting upon the constituent materials of the system. In other words, any biological system can be "reduced" to its materials and the forces at work on them. Mathematically, this approach translates to the classical formalisms of dynamical systems, differential equations, and input-output systems.[1]

Heuristically, the Newtonian reductionist approach treats living organisms as being analogous to machines [2]. In particular, the problems of engineering living tissue are approached as analogous to those of engineering machines. Bioengineering in general, and tissue engineering in particular, has proceeded thus far largely by trial and error guided by a reductionist approach. This is natural, since that approach is inherited from traditional engineering, i.e., engineering of non-organic, non-living matter.

The nascent field of "systems biology" is based on the realization that the reductionist approach to biology is limited, and that a systems-level, organizational approach must be adopted [3, 4]. Along these lines, we argue that there are organizational and functional aspects of living tissues that tissue engineering must address in a *theoretical* manner if it is to move to the next level and begin the serious business of engineering living systems.

The metabolism-repair framework offers a route for doing so. It augments the reductionist "materials-only" approach by explicitly addressing two "functional" activities essential to living organisms: self-repair and self-replication[2]. Within the metabolism-repair framework, these activities are represented by *functions*. These functional components are included within and regulated by the theoretical representation of the organism itself. Thus, living organisms are explicitly represented as *self-repairing* and *self-replicating*.

We begin by introducing the metabolism-repair framework. Our immediate goal is to begin to translate the concepts of the metabolism-repair formalism to the context of tissue engineering. The metabolism-repair formalism focuses on and is developed within the context of single cell organisms. The theory has not been extended to address the

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[1] For example, the traditional approach to mathematical modeling of morphogenesis "assumes that each biological form is the solution to a difficult calculus problem" [1]. The same article quotes a molecular biologist's experience with this approach: "Physicists are very dogmatic in saying that everything in these systems can be explained with physics. I cannot believe that." The point is then made that organisms are organized mainly by their genes, and *Drosophila* is given as a prime example.

[2] Here, the concept of replication is not limited to replication of the cell but extends to replication of any somewhat modular system, such as a mitochondria or an endocytotic vesicle.

three-dimensional, hierarchical topology essential to most biological domains, including mammals. We indicate a direction for incorporating hierarchical topologies into the metabolism-repair framework, via the concepts of networks and protocols.

II. Background

We begin with a brief exposition of the metabolism-repair framework. We refer the reader to [5], [6], [7], and [8] for further details.

Let A represent a set of inputs and B a set of outputs. In the initial context of a single cell, A could represent the set of environments in which a cell operates[3], and B the set of cellular metabolic configurations[4] [6].

The metabolism of a cell is then represented by a function

$$f: A \rightarrow B$$

We let $H(A, B)$ denote the set of all physically and contextually realizable maps between A and B (i.e., those maps satisfying the physicochemical constraints of the materials). Then f is an element of the set $H(A, B)$. We suggest that, given a tissue engineering objective, there exists a minimal subset of f about which the bioengineer should be sufficiently knowledgeable so that s/he can make optimum use of that information during engineering decision making.

At this point the framework represents simply the classical "materials-only" input-output relationship. The metabolic activity of a living cell, however, must have the means to sustain itself. This need requires and is implemented, in part, by repair activities. Those processes are represented within the formalism by a repair function P. Such a repair function reconstitutes a METABOLISM[5] from the members of the set outputs, B. Recall that a METABOLISM is an element of $H(A, B)$. Thus, repair is represented by a function

$$P: B \rightarrow H(A, B)$$

Using the notation introduced above, the repair function P is an element of the set of maps $H(B, H(A, B))$. Here also, we suggest that, given a tissue engineering objective, there exists a minimal subset of P about which the bioengineer should be sufficiently knowledgeable so that s/he can make optimum use of that information during engineering decision making.

The repair function P may be interpreted simply as a representation of the processes employed by the cell to sustain itself as components of its metabolic machinery degrade and need repair. Similarly, however, the repair processes themselves degrade. Rather than invoking an additional entity to repair the repair function, which would quite obviously lead to an infinite sequence of repairers, Rosen introduced REPLICATION[6] into the framework.

In biology, replication processes allow the cell to replace its repair machinery with a new version. In the metabolism-repair formalism, REPLICATION is a function which takes as input an existing METABOLISM and outputs a new repair map. Thus, REPLICATION is represented by a function

$$R: H(A, B) \rightarrow H(B, H(A, B))$$

Where does the replication function come from? Rosen's central result was to show that replication arises from the system of metabolism and repair itself. By examining these mappings in the context of Category Theory [9], he showed that, under certain conditions, the replication map R could be identified with an element of the set B. Hence replication does not need to be engineered from outside the system, and the system of metabolism, repair and replication is closed. It is in this sense that the metabolism-repair formalism represents a theory of self-replicating and self-repairing systems.

Here yet again, we suggest that, given a tissue engineering objective, there exists a minimal subset of R about which the bioengineer should be sufficiently knowledgeable so that s/he can make optimum use of that information during engineering decision making.

III. Methods

Rosen took a strong ontological stance regarding the "functional" components of REPLICATION and repair in the metabolism-repair framework. He viewed them not as just mathematical constructs, but as representing real and essential aspects of living organisms. We can then ask: if, indeed, biological counterparts for the mathematical mappings do exist, then what are they and where are they?

We propose that the concept of *networks* may lead to the biological locations of the functional repair and replication components. At the level of the single cell, repair and replication may reside within the metabolic network. This is addressed in the treatments of metabolism-repair systems in [7] and [8], so we do not repeat those observations here. We note, however, that recent analyses of metabolic networks have indicated that, more than the materials that make them up, it may be the structures of the networks that are conserved by evolution [10]. This in itself begins to hint at the importance of "relational" (versus strictly "material") aspects of biology, which Rosen saw the metabolism-repair framework as addressing [8].

We believe these ideas may be applied toward the task of scaling up the concepts of metabolism-repair systems to address multicellular tissues. Metabolic networks contain an implied intracellular topological component behind replication and repair in the single cell case. Similarly, cellular networks may be an essential dynamic topological component behind replication and repair in the multicellular case. In order for multicellular tissues to have functional repair and replication components, the local repair and replication components of the constituent cells must be

[3] These will include "raw materials" that are taken in from outside the cell plus recycled materials.

[4] These will include gene products and the cellular components composed of those products.

[5] The definition and use of this term is new. To distinguish it from traditional usage we use small caps.

[6] As with METABOLISM, the definition and use of this term is new. To distinguish it from traditional usage we use small caps.

integrated into global repair and replication components for the organism as a whole. We conjecture that this integration is determined by the cellular network's dynamic topology. Reference [5] contains a sketch of some ideas in this direction, with a brief discussion of cellular metabolism-repair networks. These are mentioned as a direction of future study, with great potential for insight into areas relevant to tissue engineering, such as cellular differentiation. It is a direction that, to our knowledge, has yet to be pursued.

A longer-term program is to extend the metabolism-repair framework to an even wider variety of biological contexts. One avenue for doing so may be to focus on the concept of *functional units*. The clearest example of a biological functional unit is the single cell. Subcellular organelles may also be identified as functional units. Most relevant to tissue engineering, of course, are multicellular functional units that make up organs, and ultimately organs themselves. In this sense, tissue engineering is involved in the reconstruction of multicellular functional units outside of their original context *in vivo*. Hence, tissue engineering could benefit from a *theory* of functional units. The metabolism-repair framework may be the basis of such a theory. The concept of a functional unit is an intuitive one, but it lacks a precise definition. Since the capacities for self-repair and self-replication seem like they are central to functional units, it may be that metabolism-repair systems are a formalism for describing functional units.

Finally, we discuss some potential connections between the ideas discussed above and another recently developed abstraction of biological systems: protocols. Csete and Doyle, in describing aspects of engineering theories that can be applied to complex biological systems [11], focus on the importance of what they call protocols. They define protocols as rules that arise repeatedly in systems as interfaces between "modules." As examples of biological protocols, they cite a list of diverse abstractions: gene regulation, signal transduction pathways, cell-mediated activation, and many others.

Any engineered system cannot ignore the relevant protocols. Hence, bioengineering efforts must discover the biological protocols essential to the systems being engineered. This in itself is another important point for consideration by the tissue engineering community.

With respect to the ideas of biological networks mentioned above, however, Csete and Doyle note that the protocols are central to understanding and engineering biological systems in part because they facilitate evolution. Protocols allow existing systems to be cobbled together, thus allowing the evolutionary construction of novel systems. Csete and Doyle call this process "evolutionary tinkering," and argue that it is essential to the robustness and modularity of biological systems.

From this, it is possible to see roles for protocols in biological networks. It has been widely observed that biological networks are robust and highly modular (scale-free). Indeed, it has been noted that these aspects of biological networks can be attributed to the fact that they arise from evolutionary tinkering [12]. Thus, protocols may in fact be the mechanisms that allow the evolutionary construction of biological networks.

Returning finally to the repair and replication, we have conjectured that these functions may be located within certain biological networks, whether metabolic or cellular. This indicates that biological protocols play a central role in constructing these functions. We may go further and speculate that replication and repair are themselves protocols of a sort, but that they are "meta-protocols." They are the protocols essential to life, and all other protocols are the ingredients that give rise to replication and repair, via the construction of appropriate networks.

Our premise is that in order to make progress on engineering living tissues, we need a theory of biology. However, in order to make progress in building such a theory, we conversely need ways to test ideas. Computational modeling and simulation methods may be the best available bridge between theory (of metabolism-repair systems, for example) and practice (of bioengineering) [13]. The theoretical frameworks described above are abstract and far removed from the biological reality. For example, to test hypotheses about aspects of the theory, we first need ideas that posit form and location of the repair and replication maps. We can begin to make progress in this direction by developing modeling and simulation techniques where the model components map to the biological system in a natural way, yet also encode aspects of the theoretical framework.

We believe that the envisioned modeling and simulation techniques will have more in common with *in vitro* model systems than with traditional modeling and simulation methods, in that they will need to be dynamic, flexible, adaptable, and thus capable of capturing multiple aspects of the biological system. They should also be capable of automatic model revision and extension when the simulation system is presented with new data. The Functional Unit Representation Method (FURM) is a step in that direction in that it encompasses many of the concepts discussed above [14]. As its name indicates, FURM focuses on modeling at the level of biological functional units, and initial applications of FURM have represented biological networks. In the future, FURM may serve as a method of discovering and testing biological protocols *in silico*, and eventually may incorporate prototypes of the repair and replication maps of the metabolism-repair framework.

IV. Conclusion

Over 30 years ago, Robert Rosen recognized the applicability of his work to fields such as tissue engineering: "We may envisage the construction of artificial engineering systems manifesting organizational characteristics of biological organisms. Such attempts have been pursued for a long time, especially in the area of artificial intelligence, the design of artificial biological organs, and so forth, but never in a completely systematic manner" [8].

Tissue engineering has been pursuing such attempts at an ever-accelerating pace. But without a theory of living organisms in place, it will continue to do so in an unsystematic manner. Rosen's metabolism-repair systems, by treating in a theoretical manner the essential biological processes of self-repair and self-replication, may be a path to a theory of biology useful for tissue engineering.

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