Journal of Theoretical Biology ■ (■■■■) ■■■–■■■

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Letter to Editor

Dynamic reciprocity revisited

HIGHLIGHTS

- In this letter, an amendment to the concept of dynamic reciprocity is proposed.
- Flow and transport, along with the ECM, play a primary role in dynamic reciprocity.
- Cells can alter transport, without involving the ECM, through the use of cilia.
- Ciliary flow plays a key role in morphogenesis.
- Simulating dynamic reciprocity is crucial to developing biological substitutes *ex vivo*.

ARTICLE INFO

Keywords:
Cell
Cilia
Extracellular matrix
Flow-fields
Morphogenesis
Transport phenomena

ABSTRACT

The cellular microenvironment – which includes the cells, extracellular matrix (ECM), and local transport processes – affects the cell which in turn responds by synthetic or degradative processes causing the composition and the structure of ECM, and the local transport processes, to change which in a coupled manner influence the cell, and so forth.

1. Letter

Benedict de Spinoza (1632–1677) in his correspondence with Henry Oldenburg, the first secretary of the Royal Society, opined the existence of dynamic interdependence between various elements within the body. Articulating in a Newtonian style, quite typical of that era, he wrote, "All natural bodies can and ought to be considered in the same way as we have here considered the blood, for all bodies are surrounded by others, and are mutually determined to exist and operate in a fixed and definite proportion, while the relations between motion and rest in the sum total of them, that is, in the whole universe, remain unchanged (Spinoza and Elwes, 1883)." The year was 1663, and the basic unit of life – the cell – was hitherto undiscovered.

The gist of Benedict de Spinoza's afore-quoted expression found its true cellular context in the early nineteenth century when Christian Heinrich Pander, a German Biologist, hypothesised dependence of tissue development on a dynamic interplay between cells and their surrounding microenvironment (Pander, 1817; Wessel, 2010). Pander's speculation was finally confirmed in 1928 when developmental biologists observed certain regions of hydra and amphibian embryos directing the adjacent group of cells to specific tissue fates (Spemann, 1918; Spemann and Mangold, 1924). This mutually instructional relationship between cells and their immediate environment was conceptualised, in 1982, as *dynamic reciprocity*: a phrase coined by Bornstein et al. (1982). That same year, Bissell et al. (1982) proposed a model, which suggested that the ECM affects gene expression *via* transmembrane receptors that interact with the cytoskeleton to alter the patterns of gene expression. According to Bissell et al. (1982), this interdependence "appears to evolve continually". As such, "the ECM affects the cell which in turn responds by synthetic and degradative processes causing the composition and the structure of ECM to change which in turn influences the cell and so forth" (Bissell et al., 1982). The discovery and characterisation of integrins validated this model (Schultz et al., 2011). The inability of cells to form functional structures when cultured as monolayers or on two-dimensional substrates (with certain exceptions) also testified to the importance of the cells' microenvironment to tissue development. The dependence of tissue micro-architecture on the ECM-forming ability of cells further validated this principle (Hansen and Bissell, 2000; Nelson and Bissell, 2006). The principle as well as its current definition, however, limited the microenvironment to the extra-cellular matrix (ECM), or the 'solid' phase, surrounding the cells alone.

Folkman reported the dependence of histogenesis on mass transport requirements of the growing structure back in the 1970s (Folkman and Hochberg, 1973). Of course, the growing number of cells would inevitably lead to an increase in metabolic demands of the system, which would subsequently necessitate the need for better perfusion conditions; but the increase in transport requirements is not solely a result of the increase in number of cells. A colony of cells may deposit ECM, which is bound to alter the local permeability, in value and (an)isotropy, and in turn affect transport occurring in that area. As adequate perfusion, and thereby transport conditions, are necessary for cells to proliferate, these

http://dx.doi.org/10.1016/j.jtbi.2015.01.016
0022-5193/

conditions shape how a system of cells develops in a culture (or inside the body). The proliferating cells, on the other hand, by both aggregating (into a monolayer and then growing in the third-dimension) as well as, consequently, depositing (or degrading) matrix, alter the transport characteristics of their immediate environment and, thus, shape the transport processes that operate in their vicinity, and possibly overall. While the definition proposed in the original article explained this eventuality, it, nevertheless, restricted the role of flow and transport to being secondary artefacts of the interplay between cells and their ECM, ignoring altogether their informational contribution to morphogenesis. The implication being that (i) flow and transport cannot by themselves regulate cellular growth and proliferation and (ii) cells are wholly reliant on the ECM to alter flow and transport around them: conclusions that offer limited explanation to account for the following set of observations.

More recently, in the late 1990s, Bejan introduced the constructal law (Bejan and Lorente, 2011), which implicates flow as a major player in design and structural evolution. The concept finds direct relevance in the multiple operations of biological systems, which dynamically rely on flow and transport to govern their spatiotemporal development. This is evident from the impact blood flow (Bishop and Lindahl, 1999; Chen et al., 2012) and interstitial flow (Griffith and Swartz, 2006; Ng et al., 2005) have on the overall tissue development and behaviour, and, eventually, the flow itself (Chen et al., 2012). In fact, the role of blood flow in regulating cerebral vasculature (Chen et al., 2012) and the response of the cardiovascular system to changes in haemodynamics (such as increase in blood pressure and flow/shear, mechanotransduced by the smooth muscle cells and the endothelium) in tissue remodelling (Bishop and Lindahl, 1999; Watton et al., 2011; Weinbaum et al., 2003) underscore the importance of flow to the spatiotemporal evolution of biological systems. Similarly, normal development of heart valves (Hove et al., 2003), blood vessels (Buschmann et al., 2010; Corti et al., 2011), and glomerulus (Serluca et al., 2002) have been observed to be contingent on haemodynamic shear; as is the formation of functional haematopoietic stem cells in embryonic blood vessels and *in vitro* cultures (Adamo et al., 2009; Pardanaud and Eichmann, 2009). Another topical example (reviewed in great depth elsewhere Peiffer et al., 2013) of the contribution of flow and transport in dynamic reciprocity is the impact of haemodynamic shear on the trans-endothelial transport of low-density lipoproteins, which is considered to initiate atherosclerotic plaque formation, eventually influencing blood flow (Olgac et al., 2008; Vincent et al., 2009).

As another example, of gaseous flow and transport, the etiological role of pathological airflow in causing anatomical alterations (Gungor and Turkkahraman, 2009; Hartsook, 1946; Ricketts, 1968) has been extensively documented. Furthermore, an excellent example of the dynamic relationship between gaseous flow/transport and tissue morphology is that of airway remodelling (Bergeron et al., 2009) initiated due to the introduction of allergenic/non-allergenic particulates within airways: a set of symptoms which often manifest themselves as asthma (Kay, 2000; Lukacs, 2001; Pascual and Peters, 2005; Vonk and Boezen, 2006) or chronic obstructive pulmonary disorder (Decramer et al., 2012; Fattahi et al., 2013). These particulates cause the airway cells to respond by increasing the airway wall thickness and minimising its lumen (Bergeron et al., 2009; Pascual and Peters, 2005), thereby reducing the airflow that may have been responsible in exposing the airway to these particulates in the first place. Finally, it must be emphasised that while cells can alter transport and flow indirectly through, as Bissell et al. (1982) discussed in their original article, the ECM, they can also do so directly – and rather dramatically – through the use of cellular components (for example, active cilia Chen et al., 2011; Nonaka et al., 1998). The impact of ciliary flow on morphogenesis is illustrated by the documented role of cilia-mediated flow in the formation of inner ear and otolith (Colantonio et al., 2009), cardiac morphogenesis (Slough et al., 2008), and migration of neuroblasts following cerebrospinal fluid flow regulated by the beating of ependymal cilia (Sawamoto et al., 2006). Dynamic Reciprocity, as introduced originally, overlooked this primary and direct impact of flow/transport on biological dynamism and informs the reader little about the role of such transport-remodelling interactions.

One can sympathise with the omission of flow, and the corresponding transport processes in the original definition, for it is easy to omit the vital role played by transport processes in the evolution of biological systems, in the absence of suitable experimental methodologies that can visualise flowfields and gradients. These, even today, remain mostly inaccessible to direct observation in experiment (certainly in the presence of cells anyway), and can only be simulated computationally. However, the level of complexity associated with dynamic reciprocity, particularly due to (i) the set of multiple, non-linear, complex interactions between cells and their microenvironment (Kaul and Ventikos, 2013), and especially with (ii) the inclusion of flow and the resulting local transport processes, makes it quite difficult to be captured by most numerical models. Current computational approaches and formulations, generally either continuous or discrete, struggle to account for both (i) and (ii). The classical models of the continuum variety, due to the underlying homogeneity condition, treat the entire biomass (cells, matrix, etc.) as a continuum, thereby ignoring the microscopic, heterogeneous details of biological systems. However, unlike biological systems, continua are not dynamic and they do not alter their material properties over time (Semple et al., 2005)—though various formulations incorporating such variations have been proposed. The continuum approach, basically, fails to offer a realistic ontology to capture biological interaction(s). Furthermore, a population-based approach to model cellular behaviour, instead of providing clarity, end up implicating "random or 'unseen' mechanisms" as responsible for the underlying mechanics "especially when small number of input cells are used" (Viswanathan and Zandstra, 2003). However, the *continuum* assumption makes the approach most suited to simulate the bulk aspects of a biological system (such as hydrodynamics, transport, reaction of species, etc.). Discrete models, on the other hand, typically divide a system into discrete entities that are capable of responding to local information based on a rule-set attributed to them at each discrete time-step. As such they consider the relevant microscopic details of the systems they are being employed to simulate. However, they are not recommended to study bulk phenomena due to the high computational overhead—a direct result of their considering the microscopic details of the system. To illustrate this point, consider, for example, the diffusion of an arbitrary solute in 1 μL of water. Solving the relevant equations will take the continuum approach a matter of hours (if not minutes); however, the discrete approach considering all the particles in the system (*i.e.* water and the solute) will take days (if not weeks) to compute the same process.[3] Hybrid models, which incorporate both continuous and discrete features, succeed in capturing both cellular and environmental aspects of a biological system, though only to an extent. This is due to the fact that current hybrid approaches have been limited in capturing the appropriate data-structures (continuous, discrete, binary, spatial) operating in biological systems, explaining the scarcity of models that can capture dynamic reciprocity in appropriate resolution.

Nevertheless, for reasons discussed above, the contribution of flow and transport processes towards dynamic reciprocity cannot be neglected, and must also be quantitatively pursued. Yet, this

[3] A volume of 1 μL water contains 10^{19} molecules of water.

Please cite this article as: Kaul, H., Ventikos, Y., Dynamic reciprocity revisited. J. Theor. Biol. (2015), http://dx.doi.org/10.1016/j.jtbi.2015.01.016