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Review

The Flow of Life: Convergent Approaches to Understanding Musculoskeletal Health from Molecular- to Meso-Length Scales

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Abstract

In the current perspective and review article, we address the human body as a living ecosystem with collecting watersheds and draining hydrosheds; we integrate our discoveries over the past quarter of a century and pose the critical open research questions to be addressed going forward, with the aim to improve cell, tissue, organ and organismal health. First, we address the flow of fluid through the tissues of the musculoskeletal system, after which we describe the interactions of the fluid, at multiple lengths and time scales, with the molecular to macroscopic non-fluid tissue components, discussing bone and tissues in the context of "living" chromatography and/or electrophoresis columns. Thereafter, we discuss the implications of functional barrier integrity, and the effects of cytokines on active barrier function and molecular transport between organ systems, tissue compartments, and within tissues. In addition, we address the fluid and its flow and the multi-physics implications thereof for the living inhabitants of tissues, i.e., the cells. Finally, we describe the implications of the solid and fluid components and the cellular inhabitants on ecosystem health, where the tissues and organs comprise the organism form interacting ecosystems throughout life and in the context of health and disease. By taking convergent approaches to understanding musculoskeletal, human and environmental health (which themselves are interdependent), we hope to pave new paths of innovation and discovery, to improve the lives of our worlds' inhabitants, from the worlds of our bone and joints and bodies to the interacting ecosystems of our Earth to unknown worlds beyond our current understanding.

Keywords: musculoskeletal health; fluid flow; synovial joint; time scale; length scale; physiological systems; ecosystems; convergent approach

1. Introduction and Historical Context

A quarter of a century ago, the nascent field of "bone fluid flow" emerged and thereafter grew into an ongoing, burgeoning area of research and discovery. Throughout the twenty-five-year period, parallel and combined, multi- time and length scale theoretical (typically computational) and experimental approaches advanced the field, across musculoskeletal tissues and organ systems (e.g., circulatory - lymphatic, vascular, immune, nervous, etc.) [1–21]. The current perspective review article highlights and integrates the resulting discoveries from my laboratory in context of the vibrant research arena; this is not intended to diminish in any way others' significant contributions to the field which are wholeheartedly acknowledged (see **References** and **Acknowledgements**).

The origin and physiological implications of bone fluid flow trace back to a hypothesis first posed by Piekarski and Munro in 1977 [22], that mechanical loading of bone induces fluid flow through the network of periosteocytic interstitial fluid canals (the lacunocanalicular system, LCS), thereby augmenting via convection molecular transport to bone's inhabitant cells. Twenty years ago, empathizing with the resident cells of our bones, we posed the osteocyte-centric research question, "Whither flows the fluid?" [4]. More recently, using molecular tracer tracking methods developed and described in our earliest papers [2–6,23–27], combined with state-of-the-art organ-to-cell-scale cryo- and multimodal imaging methods [28–32], we have begun to answer the "whither" question in context of cellular inhabitants of not only bone but also different tissues comprising synovial joints of the musculoskeletal system. Our recent approaches expand our range of scientific query to the interplay between the cardiovascular and musculoskeletal systems [29,30], as well as interface tissues of the mesoderm, including periosteum, ligament, interosseous membrane, and myofascial tissues [31,32].

The current perspective and review article integrates the resulting discoveries from my laboratory and delineates the critical open research questions to be addressed going forward, with the aim to improve cell, tissue, organ and organismal health in context of the human body as a living ecosystem. To that end, we draw analogies between the ecosystem of the human body and those of environmental ecosystems such as the Amazon River basin [23] and the hydrosheds (analogous to a watershed, with the emphasis on the multiscale fluid flow network rather than the land drainage) of the greater Sydney basin. Insodoing, we use a **convergent** approach to crack a currently intractable challenge; as defined by the U.S. National Academies of Science, "[c]onvergence is an approach to problem solving that

integrates expertise from life sciences with physical [referring to physics, chemistry, materials science, mathematical, and computational] sciences, medicine, and engineering to form comprehensive synthetic frameworks that merge areas of knowledge from multiple fields to address specific challenges. Convergence builds on fundamental progress made within individual disciplines but represents a way of thinking about the process of research and the types of strategies that enable it as emerging scientific and societal challenges cut across disciplinary boundaries in these fields. The concept of convergence ... is thus meant to capture two dimensions: the convergence of the subsets of expertise necessary to address a set of research problems, and the formation of the web of partnerships involved in supporting such scientific investigations and enabling the resulting advances to be translated into new forms of innovation and new products." [33].

2. What Flow?

When one describes the tissues and organs of the body in context of environmental biosystems or household objects such as kitchen sponges, one can better visualize the concept of interstitial fluid flow and load-induced fluid flow. Indeed, ecosystems such as swamps derive their name from the German *Schwamm* or Middle English *Swamm* which itself means "sponge", originally describing an organism with a soft, porous skeleton capable of imbibing and retaining water even long after the organism has died, e.g., when the soft "sponge" skeleton found use as a bathing sponge in Ancient Greece [34].

2.1 Of Musculoskeletal "Swamps"

Bones and cartilage are like swamps that sequester and hold water for entire tissue and organ ecosystems, providing sustenance for inhabitants of entire watersheds through vagaries of the weather and catastrophic events such as bushfires [35]. In contrast to the range and spatial distribution of porosities within, e.g., vertebrate tissues (nm to µm scales, as described in detail in [4]), the water holding pores of the hydroshed swamp "sponge" range from nm to µm, and even to m, if one considers the respective water holding pores of plants, the soil, the rock fissures and crevasses holding the ground water that wells to the surface via springs, and the vast network of streams, creeks, rivers and river basins that make up the hydrosheds supplying watersheds across the globe [23,36].

Fluid flow through the human body and the tissues of the musculoskeletal system exhibits analogies to ecological hydrosheds, with multi length scale pores and conduits and diverse flow patterns described quantitatively by the dimensionless ***Reynolds number*** (***Re***). Defined by the ratio of inertial to viscous forces to characterize flow through pipes, Reynolds number is applied across diverse fields of use to compare flow patterns in different e.g., biosystems, where a high Reynolds number (generally greater than 2200) describes turbulent, i.e., irregular flow path with mixing (e.g., white water rapids), flow and a low Reynolds number (generally below 1100) is described as laminar, i.e., smooth path with minimal mixing (steady slow stream), flow. Inertial forces refer to the intrinsic resistance to acceleration (equal and opposite to accelerating force times the mass of the fluid) and viscous forces refer to the fluid's capacity to resist relative motion between layers of the fluid. In most non-freezing ecological hydrosheds, the water viscosity remains roughly constant, while fluids of the human body can exhibit vastly different viscosities and can also invalidate continuum assumptions, e.g., at small length scales when plasma skimming or reduced rate of red blood cell migration or the formation of a red blood cell free layer occurs in the vicinity of vessel branches (bifurcations) [37,38].

Within tissues of the musculoskeletal system, and within the biosystems of tissue compartments comprising our synovial joints (knees, hips, etc.), most flows, outside of the large nutrient vessels inserting from the cardiovascular system, would be expected to exhibit laminar to creeping ($Re<<1$, viscous forces dominate, and inertial forces are negligible) flow patterns. In tissues of the musculoskeletal system, just as in an ecological swamp, the ratio of convective (flow driven) to diffusive (gradient driven) transport plays an important role in transport of nutrients and wastes and hence ecosystem health. The so defined, dimensionless ***Peclet number*** (***Pe***) measures the relative contribution of convective and diffusive transport within a given control volume (system of interest) and represents the "mass transfer analogue of the Reynolds number" [37–39]. In microscale fluid channels, where often convective transport dominates in the flow direction and diffusive transport dominates in the cross-flow direction (perpendicular to the flow streamlines), the ***Pe*** described quantitatively the balance between the two, which is important to understand the dynamics of ecosystem health, whether within the tissue compartment of the subchondral bone or synovium of the knee joint, for example. Independent, *in vivo* experimental measurement of diffusive and convective transport is impossible at physiological temperatures but can be estimated using state of the art imaging methods (see below, **2.2 Of musculoskeletal "sponges"**).

2.2 Of Musculoskeletal "Sponges"

Bones and cartilage are like sponges, in that they are porous, and both imbibe as well as exude water, but their mechanisms of action differ. Interestingly, some areas of bone exhibit nonintuitive sponge like behavior, due to a unique combination of pore size/distribution and local mechanical stiffness (Fig. 1, Ref. [40,41]) [40]. Namely, we showed experimentally, and probed effects using computational models, to discover and describe how "fortuitous combinations of anisotropic stiffness and permeability coefficients in [the] poroelastic structure [of] bone result in counterintuitive flow", i.e., when the bone "sponge" is sub-

ject to compression (squeeze), bone imbibes fluid, whereas under tension (pull) bone egresses fluid. These "fortuitous combinations" of properties appear to be more prevalent in areas of bone that are less vascularized, providing compensatory mechanisms for molecular transport [40]. Just as ecological hydrosheds exhibit myriad fractal like networks at diverse length scales, bones exhibit both hierarchical and fractal-like vascular transport networks that fully anastomose with the hierarchical fluid porosity networks comprising the lacunocanalicular system (LCS) and bone nano- to microporosity [40–43].

3. Bone and Musculoskeletal Tissues as Living Chromatography and/or Electrophoresis Columns

3.1 Size-Based Molecular Sieving, Analogous to "Living" Chromatography Columns

In addition to their swamp-like (longer length scale of tissue to organ) and sponge-like (length scale of tissues and sub tissue volumes) properties, bone and other tissue compartments of the musculoskeletal system exhibit properties of "living" chromatography columns. Chromatography is a laboratory technique in analytic chemistry designed to separate a mixture into its components, where a fluid mobile phase carries the mixture through a e.g., column or plate carrying a stationary phase; due to differential partitioning between both phases, the mixture constituents separate. Interestingly, flow rate impacts the resolution of e.g., size separation chromatography, where high flow rates shorten the run time but decrease resolution and slow flow rates increase resolution, i.e., prevents peak dispersion, which is the basis of high-pressure liquid chromatography for size separation [44].

Using bone tissue as an example, when biologically and chemically inert, fluorescent-tagged dextran molecules of increasing molecular weight (300–2,000,000 Da) are injected via the tail vein into anaesthetized rats, the differentially sized pores of the bone tissue sieve the molecules according to size [24]. The 300 Da probe penetrates the mineral matrix porosity which impedes permeation of larger tracer molecules. The larger pericellular spaces of the lacunocanalicular system (LCS) permit permeation of larger molecules up to 10 kDa. Without mechanical load-induced convective transport, transport of molecules above 10 kDa is ineffective through the lacunocanalicular space. With mechanical load-induced transport, probes up to 70 kDa penetrate the LCS. Beyond 70 kDa molecular tracers are impeded from bone porosity, irrespective of loading. Hence, "bone acts as a molecular sieve" and "mechanical loading modulates transport of solutes through the pericellular space that links osteocytes deep within the tissue to the blood supply and to osteoblasts and osteoclasts on respective bone forming and resorbing surfaces" [24].

Remarkably, in a study carried out using the same technique albeit in guinea pigs with and without naturally occurring osteoarthritis, and with a bolus injection of **mixed** size fluorescent-tagged molecules via the heart, we demonstrated that the tissues of all compartments of the knee joint exhibit molecular sieving, effectively separating out the bolus of two differently sized (respective green—10 kDa and red—70 kDa) fluorescent tagged dextran tracers [29] within five minutes' circulation time. Using state of the art episcopic cryoimaging, we measured volume (voxels) of red and green tracers which equate to relative tracer concentrations if all imaging parameters are controlled. Using this experimental approach, we observed that aged animals with naturally occurring osteoarthritis exhibited tracer concentrations lower than those of the younger cohort and that the younger cohort exhibited significantly higher concentrations of the 10 kDa (green) compared to the 70 kDa (red) molecular tracer. We were surprised to observe the dearth of fluorescence indicating a lack of tracer permeation in the muscle tissue of either cohort, although muscle fasciae did exhibit bright fluorescence. Tissues of the meniscus, ligament and tendon fluoresced strongly with the 10 kDa (green) tracer but articular cartilage did not. Bone tissue demonstrated colocalization of both the 10 kDa and 70 kDa tracers. The 70 kDa tracer appeared to be excluded from the bounding, interface tissues of periosteum, the growth plate, and cartilage, yet was abundant in the bone marrow compartment. In younger animals, small caliber channels through the articular cartilage fluoresced green with the 10 kDa tracer but not in the older cohort [29]. Based on these studies, the size selective sieving properties of bone and other musculoskeletal tissues change depending on age and health status, respectively disease state.

3.2 Charge, Streaming-Based Molecular Sieving, Similar to Living "Electrophoresis" Columns

Like chromatography, electrophoresis is a technique to separates molecules based on their size; in addition, electrophoresis can separate molecules based on their charge. Electrophoresis uses an electric current rather than fluid flow or pressure to move the molecules through a "column" comprising a gel or matrix [45]. It is typically carried out in an aqueous environment, as the separation mechanism harnesses the difference in migration rates of charged ions, molecules or particles in an electric field. "Most charged species are fairly soluble in aqueous media and thus water is the most obvious solvent for electrophoresis" [45]. Ions, molecules or particles "with a difference in their charge" to size ratio exhibit different migration rates [45].

Saturated (wet) bone tissue represents a model electrophoresis system, if one considers the evidence for streaming potentials with load-induced fluid flow in bone as presented experimentally, respectively computationally three decades ago by Guzelsu and Walsh [46,47], as well as Zeng, Weinbaum and Cowin [48]. Streaming potentials derive from the mechanical force-induced motion of "ion carrying extracellular fluid in the bone matrix" [46], where the

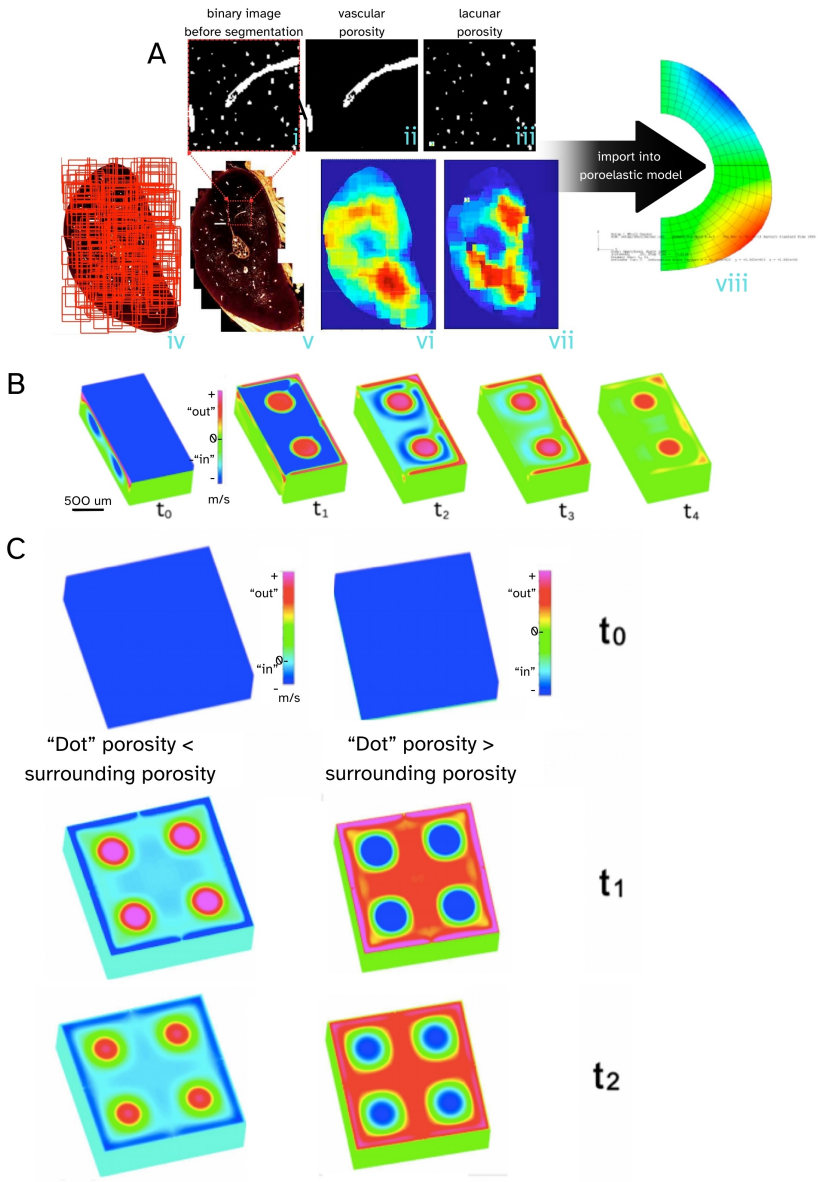

Fig. 1. Bone, the "smart sponge". Tracking high resolution spatial distribution of bone pores, including vascular porosity and lacunar porosity in the rat ulna cross section, together with poroelastic finite element modeling (FEM) and computational fluid dynamics (CFD) simulations, reveals counterintuitive flow (imbibement under compression and exudation under tension, opposite to that of a typical kitchen sponge) under specific pore distributions. (A) Thousands of high-resolution confocal images (iv) are stitched together to create a single high resolution image of the ulna cross section showing both vascular and lacunar pores (v). The black and white (binary) images (i) are separated into the respective porosities, including lacunar (ii) and vascular (iii), with density heat maps depicting their respective spatial distributions (vi, vii - warm colors indicate higher densities). Poroelastic FEM gave first predictions of counterintuitive behavior, with flow going into the bone under compression unlike typical sponge behavior, where squeezing a sponge squeezes the fluid out. (B,C) Using CFD we created a modular model system, akin to a miniature (500 micron on edge) computer keyboard key with four dots extending through the volume, on a computer keyboard, to model a tiny section of bone. (B) In cut through images, the depth of the "key" can be visualized. (C) Depending on whether the "dot" porosity was smaller (left column) or respectively greater (right column) than the porosity of the surrounding material, compressing the key resulted in either exudation at the dots and imbibement at the surrounding surface, respectively imbibement at the dots and exudation at the surrounding surface. Pressing on the key (compression) commenced at t_0 and flow was followed along sequential steps, t_1, t_2, t_3, etc. Outward (+) flows are red and pink, and inward (-) flows are turquoise and blue. Reproduced and adapted with permission from M.L.K.Tate [40,41].

slope of the "streaming potential versus pressure [force/area of application]" "...[relate] to the electrokinetic (zeta) potential" and is linear in the low-pressure region. Furthermore, similar trends have been reported in comparing "estimated zeta potentials from streaming potentials with existing data obtained by particle electrophoresis..." [46].

In follow on experiments Walsh and Guzelsu [47] probed the unique contributions of the inorganic, exposed mineralized matrix and the organic, protein lined channels of the vascular system to the calculated zeta potentials from intact streaming potentials and postulated that the organic vessel lining "limits potential-determining ions' access to the mineralized matrix". At the time of Walsh and Guzelsu's studies (1990–1991) [46,47], my lab had not yet demonstrated that collagen lines the canalicular channels as well [49], which would further limit potential-determining ions' access to the mineralized matrix, placing the dominant mechanism for streaming potential development onto the flow of fluid through the nano- and microporosity of bone itself.

Finally, Walsh and Guzelsu [50] examined effects of osmotic gradient induced flows (in the absence of mechanical loading) on streaming potentials in saturated bone exposed to high ionic strength (0.75) NaCl solutions, observing "flow-dependent streaming potentials in the absence of mechanical deformation", indicative of how changes in the ionic concentration of the fluid phase of bone resulting from e.g., trauma and/or health conditions, may also impact flow through bone and physiology of the cellular inhabitants of bone tissue.

4. Effects of Cytokines on Functional Barrier Integrity

Early studies (early 2000s) from my group in collaboration with Schaffler and Nasser [51], where we developed a fatigue fracture model in the forelimb of the rat [51], showed a systemic increase in the small molecular weight (615 Da) fluorescent intravital tracer, Procion Red, permeability, indicated by increased tracer fluorescence in the fractured ulna as well as the uninjured contralateral ulna of the control side compared to healthy, uninjured control ulnae [52]. At the time we postulated that immunomodulatory cytokines, released in response to the localized fracture, exerted a systemic effect on bone tissue permeability.

In the subsequent years, research groups determined across a variety of tissues, from brain to lung, that cytokines, secreted by cells of the immune system in response to inflammatory events as diverse as flu or trauma, modulate molecular transport and molecular barrier function across tissue interfaces. In 2013 in collaboration with Docheva and Richter *et al*. [53], we demonstrated for the first time that human periosteum, the outer bounding membrane of bone, expresses zonula occludens 1 (ZO-1), "a tight junction membrane protein conferring epithelial barrier membrane properties" to periosteum. The implication of this functional barrier membrane property covering all nonarticular surfaces of bones was significant, as it provided a putative molecular mechanism [54], together with Sharpey's fibers "velcro-ing" periosteum to bone [55,56], to "zip-lock" and "unzip" in a controlled manner the barrier function on the outer surface of bone, via immunomodulatory control.

Fifteen years after our initial observation of systemic permeability changes with trauma (2001) [51,52], we tested the hypothesis "that two common cytokines, with multifaceted roles in the etiology of osteoarthritis as well as immune state in general, modulate the barrier function properties of joint tissue interfaces". We delivered fluorescent tagged 70 kDa dextran tracers in a single bolus with one of two immunomodulatory cytokines, transforming growth factor-β (TGF-β or tumor necrosis factor-α (TNF-α), via intracardial injection [30], simulating the effect of an acute spike in "cytokines on molecular transport within and across tissue interfaces of the circulatory and musculoskeletal systems" of aged guinea pigs with naturally occurring osteoarthritis. We observed that within five minutes' circulation time, the acute doubling of circulating cytokines "significantly disrupted barrier function between the circulatory and musculoskeletal systems, with barrier function essentially abrogated in the TNF-α group" [30]. By measuring fluorescence in the entire volume of the joint and its tissue compartments, we observed that tracer concentration was significantly decreased in the TGF-β- and TNF-α-compared to the control-group. These studies "implicate[d] inflammatory cytokines as gatekeepers for molecular passage within and between tissue compartments of our joints" [30]. While we focused on the anti-inflammatory and pro-inflammatory cytokines TGF-β and TNF-α due to their putative roles in controlling tight junction permeability and hence molecular transport dynamics between interfacing tissues of the circulatory and other organ systems, this approach could yield mechanistic insights into many other cytokines, including, in the case of osteoarthritis, the proinflammatory cytokine Interleukin-1 β (IL-1β) [57], cytokines inhibiting these pro-inflammatory cytokines [58], as well as anti-inflammatory cytokines IL-4, insulin-like growth factor (IGF), IL-10 and TGF-β [59,60].

5. Whither the Flow, From the Cell's Perspective in Health and Disease?

In health, the interstitial fluid flow cycle sustains the inhabitant cells of the respective tissue compartments of the e.g., synovial joint ecosystem by ensuring nutrient and waste transport. Any changes resulting in less efficient transport of either nutrients or waste would be expected to impact adversely on the cellular inhabitants of the respective ecosystems, as we measured using classical experimental fluid mechanics methods in scaled-up, 3D-printed volumetric renderings of actual LCS image stacks from healthy and diseases subjects [61] (Fig. 2, Ref. [23,62–65]). This

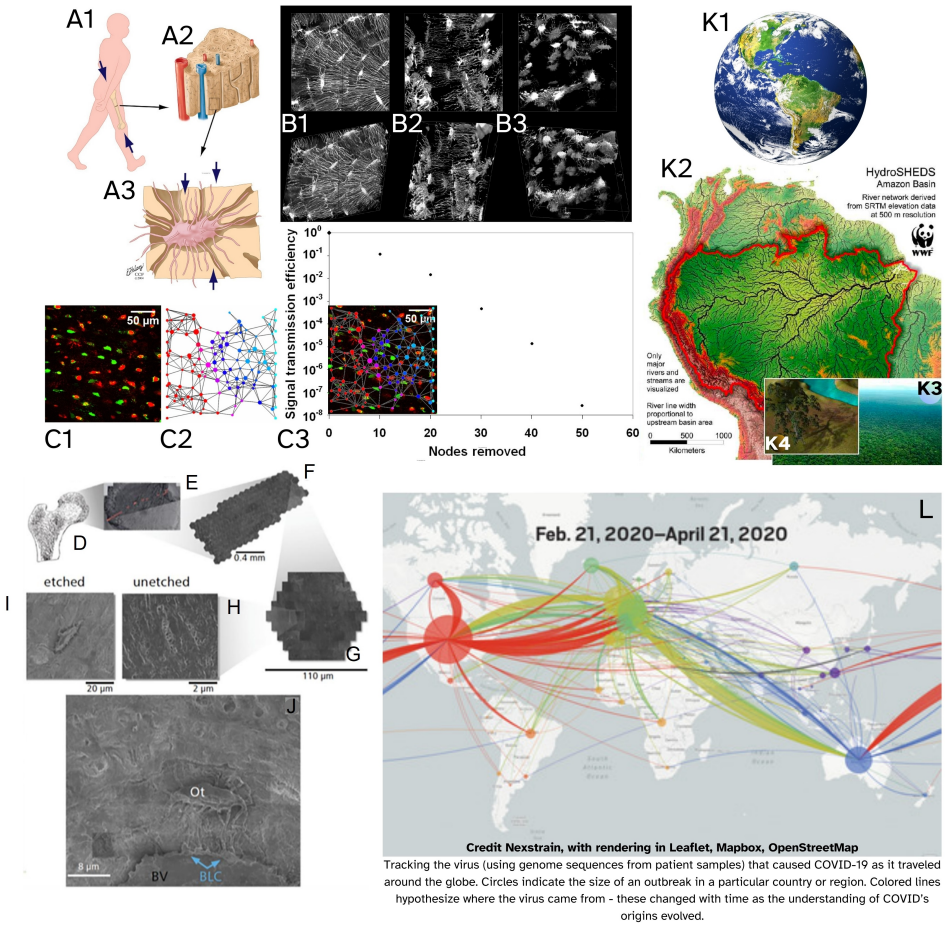

Fig. 2. Cross scale approaches and cross domain synergies aid in predicting and managing emergence of diseases in diverse ecosystems of e.g., the human body and the Earth. Approaching diverse organ systems of the human body as interacting biosystems, with relevant hydro- and watersheds, and using geospatial and epidemiological approaches, offers unique utility to understand disease outbreaks and management in individual patients and populations of patients. New, ultra-high (time and length scale) resolution imaging modalities will in the future enable the identification and, thereafter, the prediction of disease emergence. This in turn is expected to enable a new era of healthcare where diseases are treated at earliest stages of emergence, before significant tissue degeneration occurs, ultimately paving a path for prevention. (A1–A3) Impact of physiological loading of the tissues of the musculoskeletal system on molecular traffic to/from inhabitant cells, (A1) e.g., the stiff, saturated "sponge" of bone tissue (A2), results in interstitial fluid flow through the lacunocanalicular system (A3) in which osteocytes are anchored. (B1–B3) High resolution volumetric microscopy of the osteocytic network demonstrates changes relevant to the cellular and pericellular networks of the living inhabitants of bone, (B1) in health, and disease, e.g., (B2) early osteoporosis, (B3) advanced osteoporosis. (C1–C3) Osteocyte network connectivity and its impact on molecular traffic, i.e., signal transmission efficiency (e.g., nutrient transfer) through the network: (C1) Red-green viability assay (ethidium bromide) indicates viable (green) and nonviable (red) osteocytes *in situ* in slice of bone tissue. (C2) The original cell network (C1) is recreated to probe effect of node removal from network on signal transmission through the network (C3). This provides a means to probe diverse effects of disease and trauma on signal transmission, both forward (prospective) and backward (retrospective) in time. (D–J) Advances in imaging have enabled google-maps navigation and study of human hip joints resected in the normal course of hip replacement surgery, with the capacity to zoom in from the entire hip to single cells and collagen fibrils inhabiting the joint. The technique allows for unprecedented length scale resolution but not yet temporal resolution of disease processes. Fig. 2 (A–J) is reproduced and adapted with permission from M.L.K.Tate [62–64]. (K1–K4) This convergent approach integrates advanced microscopy with geospatial, computational and machine learning (AI) approaches to enable a new era of epidemiology within the worlds of individual's tissues, populations of individuals, and environmental health which is interdependent on human health. (K1) The Earth's ecosystems include e.g., the Amazon River Basin (K2) including forest populations (K3) comprised of individual trees (K4). Adapted and used with permission [23]. (L) The geonavigational approach described in (D–J) was applied to track the outbreak and spread of COVID during the pandemic. Adapted and used with permission [65].

circles back to Piekarski and Munro's original hypothesis of 1977 [22], where they postulated but could not yet prove that mechanical loading of osteons, with their concentric arrangement of lamellae, would promote convective transport as a means to augment less efficient diffusional molecular transport through the LCS in the mineralized matrix of bone, thereby sustaining the cells (osteocytes) firmly "rooted" (non-motile) within the bone matrix. In context of the historical development of this research area, it is interesting to note that Biot first developed the theory of poroelasticity, since applied to fields of use as diverse as soil mechanics and hydrology to biological tissues, in 1941 [66]! Around the same time of Piekarski and Munro's original postulate in 1977 [22], Carter and Hayes [67] published the first in a series of papers treating bone as a two-phase porous structure to probe its behavior under compression and Lakes and Katz [68] reported on the viscoelastic properties of wet cortical bone.

The essential nature of fluid flow to tissue health extends not only throughout the life cycle of organisms but also plays a requisite role at the earliest stages of life, i.e., in the patterning of the embryo and the emergence of complex, multiscale flow networks through development of the cardiovascular system and musculoskeletal system [69,70]. As an example, the etiology of hypoplastic left heart syndrome, "a life-threatening congenital heart disease" in which left heart structures fail to develop correctly or completely, relates to disturbances in blood flow within the developing heart [71]. Mineralization of the bone templates (*Anlagen*) *in utero* is itself modulated by mechanical loading of the poroelastic cartilaginous *Anlage* [72–74], though the degree to which flow fields *per se* modulate the process has not yet been fully described. Even the transport of calcium, predominantly from the mother via the placenta through the fetal circulation to the skeleton is flow dependent [75] and in a relatively closed loop until birth; "the fetal kidneys filter the blood and excrete mineral into urine, which in turn makes up much of the volume of amniotic fluid, [which] is swallowed, and its mineral content can be absorbed by the fetal intestines, thereby restoring it to the circulation" ([75], see [76–79] for further descriptions of blood flow in bone patho-/physiology). Indeed the flow of fluid is essential across lifeforms and length and time scales; the "flow of life" is just as important for nascency of coral reefs [80] and ancient mountain ranges [81,82] as it is for human beings and for the diverse biological organisms supported through Earth's own hydrosheds.

At some point in the life cycle of the organism, the balance of sustainability and health tips and degradation processes outpace growth and repair processes. This tipping point is a natural consequence of the collective effects of acute trauma, fatigue damage (wear and tear, under the threshold for acute failure, over many cycles) throughout life, lifestyle (diet, exercise) and age-related tissue degeneration which manifests in middle age, across all tissues of the human body. In addition, common musculoskeletal (osteoarthritis – for a detailed, recent review of transport related data related to the osteoarthritic joint, refer to [83], osteoporosis, osteomalacia) as well as other organ system-wide diseases, such as diabetes and cardiovascular disease, manifest not only with immunomodulatory changes but also with physical and chemical and flow pattern changes to both the "water- and hydroshed networks" of organisms, organs and tissues (Table 1, Ref. [23,84,85]). Such changes become evident, e.g., through denudation of native forests, where air and water flow patterns are changed and exert significant impacts on individual trees as well as the entire ecosystem; e.g., physical changes in boundary conditions via logging which exposes trees to higher gusts, increasing the potential for branch breakage and uprooting [23]. Spillage of chemicals and/or use of pesticides may affect viability of plants and organisms in exposed areas, changing the viability of the ecosystem not only in directly affected regions but potentially with far-flung effects given the interdependence of species within the ecosystem habitat [86].

Such physical changes range from changes in lacunar and canalicular size and shape, changes in network connectivity, to changes in mineralization and associated microporosity of the matrix and/or increased cross linking of organic matrix molecules. Associated changes to bone and musculoskeletal tissue compartment fluid biochemistry and/or ionic properties are less well described in context of flow and transport.

6. Future Directions, Critical Open Questions and Need for New Technologies

We are in an exciting era of science, where physical and algorithmic computing power has the potential, when used responsibly, to push other technological developments, such as in imaging, pharmaceuticals, theranostics, wearables, next generation implants *cum* bionics, exercise and physiotherapy as health adjuvants (like tooth brushing), to new heights with associated anticipated benefits for human and environmental health. Given increasing scarcity of R&D resources it will be important to both set priorities as well as to use convergent, interdisciplinary and multiscale approaches to ask and decipher the hardest, most compelling research questions that will also have impacts across disciplines, maximizing benefit for human and environmental health, e.g.,

- Understanding (bio)mineralization with development of integrated chemical engineering models of bone transport and balances across kingdoms and length-/timescales of life, from coccoliths to corals to bones to mountains [75,80–82,87];

- Deciphering synergies and parallels between sponge and tissue development, given that sponges are the earliest ancestors of most genuses and sponge evolution may give clues to processes relevant to human health, from endochondral ossification to age-related degeneration;

Table 1. Some examples of changes in multiscale system - organ – tissue – cell - subcell structure with aging and disease likely to change flow and transport to and from cellular inhabitants, and within their networks, with ecosystem hydroshed and watershed and botanical analogies at the respective system/meso and micro/nano length scales.

System - subcell	Effect on Flow, Transport	Example Disease States | *Ecosystem Analogies*
1 Cardiovascular		
System	Δ blood pressure, chemistry	Cardiomyopathy, congestive heart failure | *Changing systemic weather conditions or human interventions reducing wind, water tables*
Meso	Δ vascular networks, flow patterns, rates	Edema, dehydration | *Flooding, drought*
Micro	Occlusions, local damage Δ flow patterns, rates Δ transport efficiency	Atherosclerosis, aneurysms, phlebitis | *Damming, land slips, sediment pollution* Peripheral vascular disease | *Xylem vessel occlusion, insect (e.g., borer) damage* Tissue necrosis, gangrene | *Xylem and root tissue disease: root rot, branch dieback*
Nano	Opening, closing of cell-cell adhesions Δ flow patterns, rates	Closing tight junctions in blood-brain-barrier promotes edema after infarct or stroke [84] | *Closing or occlusion of plasmodesmata prevents exchange of cytoplasm between plant cells* [85]
2 Immune		Diverse, *e.g.*, Autoimmune conditions, most diseases and trauma involve inflammation
System	Systemic cytokine release, which modulates cytokines and tight junction permeability	*Destruction of hydrosheds by humans and/or natural disasters, insect infestation, effects of pesticides; denuding of forest changes boudary conditions and hydrosheds, with trickle down changes at smaller length scales (e.g., plasmodesmata), affecting health and immune function of individual trees* [85]
Meso		
Micro	Δ barrier function Δ flow patterns, rates Δ transport efficiency Δ fluid and solute balance	
Nano	Δ tight junction permeability	
3 EM protein aggregation (Nano)		Diabetes, neurodegenerative conditions (*e.g.* tau proteins in dementia) |
Note: Effects at NANO-MICROSCALE scale up to matrix and tissue scale (MESOSCALE)	Protein aggregation, crosslinking modulates mechanical properties of matrix/associated tissues, including vascular networks, Δ matrix permeability, network connectivity Diminishment of network connectivity between cells => associated decrease in information (molecular, cell signaling, etc.) transfer efficiency (see Fig. 2)	*MICRO to MESOSCALE - changes in algal and fungal populations, insect populations, scaling up to plant and animal populations* *MESOSCALE = Over/undergrowth of rainforest canopy (e.g. invasive vines overgrowing native plant species) – lack of balance of plant life due to pollution (pesticides), ageing of ecosystem or lack of renewal due to internal/external factors, deforestation/forest denudation/development (disruption to natural flow paths of air and water* [23]) *Changes in network connectivity, e.g. of syncytial plants and their communities*

1 and 2 take a systems-centric perspective on effect of changes to specific organ systems, and 3 takes a disease-centric view, up-scaling the nano-scale effect of age-related degenerative diseases, *e.g.,* EM protein aggregation (dementia, diabetes), across systems. Botanical analogies are in italics.

- Tying changes in network connectivity/permeability/signal transmission at the smallest length scale, e.g., tight junctions, to tissue and organ level molecular permeability, transport, and signaling underpinning healthy ecosystems and/or disease emergence [62,63,87].

Using convergent approaches such as those implemented for environmental protection and sustenance, one can envision a future with a more integrated understanding of musculoskeletal health in context of systemic wellness, and management of injury or disease using multifaceted approaches, from

- physical therapy and rehabilitation to

- implementation of wearables and implants *cum* bionics for augmented performance and continuous enhancement of cellular healing, to

- targeted cytokine control of functional barrier interfaces to modulate permeability direction and magnitude, with the aim to

- achieve guided transport of nutriceuticals or bioactive molecules to sites of healing and/or tissue neogenesis.

7. Conclusion

Interestingly, the recent albeit painstaking discovery of "dark oxygen" presents a compelling example of the power of convergent thinking, where lack of convergent thinking likely slowed the process of discovery, even though curiosity and persistence ultimately prevailed. Namely, it has long been assumed that all oxygen derives from photosynthesis, by plants and algae, with far reaching implications for the origin of biological life on Earth [88]. "Dark oxygen" refers to oxygen found in depths of the ocean (4000 m depth) where no sunlight can penetrate. Reported by Smith *et al*. [88] recently, "anomalous oxygen readings" in the depths of their ocean exploration site were originally thought to be attributed to defective sensors; over subsequent years of exploration, Sweetman and his team discovered that electrolysis, i.e., the separation of (sea)water into oxygen and hydrogen, via an electrical current, appears to occur naturally on the sea floor in the presence of rare metals called "polymetallic nodules". Ironically, these metals have caught the attention of the mining industry for their battery-like properties.

Whether this groundbreaking discovery could have been made sooner through intentional convergent approaches cannot be tested, but the application of convergent research practices may provide an additional tool for transdisciplinary research teams to make new discoveries "hidden at the interface" between scientific and technological disciplines. The U.S. National Science Foundation describes convergence research as a "means of solving vexing research problems, especially those focusing on societal needs, ...driven by a specific and compelling problem [regardless of whether posed via "deep scientific questions or pressing societal needs"... [with a] deep integration across disciplines...intentionally bring[ing] together intellectually diverse researchers to develop effective ways of communicating across disciplines, ...[causing] their knowledge, theories, methods, data and research communities [to] intermingle" [89].

By taking convergent approaches to understand musculoskeletal, human and environmental health (which themselves are interdependent) we hope to pave new paths of innovation and discovery, to improve the lives of our worlds' inhabitants, from the worlds of our bone and joints and bodies to the interacting ecosystems of our Earth to unknown worlds beyond our current understanding.

Abbreviations

LCS, Lacuno Canalicular System; Re, Reynolds number; Pe, Peclet number; Da, Dalton; kDa, kilo Dalton; TGF, Transforming Growth Factor; TNF, Tumor Necrosis Factor; ZO-1, Zonula Occludens 1.

Author Contributions

The single author (MLKT) was responsible for the conception and writing and revision of the entire manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest with respect to the review. For full disclosure, Prof Knothe Tate serves as a science and technology advisory on a number of corporate and academic advisory boards, as an editor or member of the editorial board on a number of biomedical journals, and she has financial interests in start-up companies she founded; none of these activities intersects directly with the subject of the current scientific perspective which is fundamental in nature.

References

[1] Knothe Tate ML, Niederer P, Tepic S, Perren SM. Study of convective transport in compact bone as a modulating factor in bone structure and regeneration. In 10th Conference of the European Society of Biomechanics. Leuven, Belgium. 1996.

[2] Knothe Tate ML, Niederer P, Knothe U. In vivo tracer transport through the lacunocanalicular system of rat bone in an environment devoid of mechanical loading. Bone. 1998; 22: 107–117.

[3] Knothe Tate ML, Knothe U, Niederer P. Experimental elucidation of mechanical load-induced fluid flow and its potential role in bone metabolism and functional adaptation. The American Journal of the Medical Sciences. 1998; 316: 189–195.

[4] Knothe Tate ML. "Whither flows the fluid in bone?" An osteocyte's perspective. Journal of Biomechanics. 2003; 36: 1409–1424.

[5] Knothe Tate ML, Niederer P, Tepic S, Perren SM. The role of convective transport in bone physiology and functional adaptation. In 2nd Combined Meeting of the Orthopaedic Research Societies of U.S.A. Japan, Canada and Europe. 1995.

[6] Tate M L K, Niederer P. A theoretical FE-based model developed to predict the relative contribution of convective and diffusive transport mechanisms for the maintenance of local equilibria within cortical bone. ASME International Mechanical Engineering Congress and Exposition. American Society of Mechanical Engineers. 1998; 15984: 133–142.

[7] Montgomery RJ, Sutker BD, Bronk JT, Smith SR, Kelly PJ. Interstitial fluid flow in cortical bone. Microvascular Research. 1988; 35: 295–307.

[8] Keanini RG, Roer RD, Dillaman RM. A theoretical model of circulatory interstitial fluid flow and species transport within porous cortical bone. Journal of Biomechanics. 1995; 28: 901–914.

[9] Hillsley MV, Frangos JA. Bone tissue engineering: the role of interstitial fluid flow. Biotechnology and Bioengineering. 1994; 43: 573–581.

[10] Turner CH. Mechanotransduction in bone: the possible role of interstitital fluid flow. Biorheology. 1995; 32: 186.

[11] Tate MLK. Preface: Special Issue on Bone Fluid Flow: Organ to Cell, Lab Bench to Bedside, On Earth and In Space. Annals of Biomedical Engineering. 2005; 33: 1–2.

[12] Qin YX, Kaplan T, Saldanha A, Rubin C. Fluid pressure gradients, arising from oscillations in intramedullary pressure, is correlated with the formation of bone and inhibition of intracortical porosity. Journal of Biomechanics. 2003; 36: 1427–1437.

[13] McCarthy ID. Fluid shifts due to microgravity and their effects on bone: a review of current knowledge. Annals of Biomedical Engineering. 2005; 33: 95–103.

[14] Fritton SP, Weinbaum S. Fluid and Solute Transport in Bone: Flow-Induced Mechanotransduction. Annual Review of Fluid Mechanics. 2009; 41: 347–374.

[15] Price C, Zhou X, Li W, Wang L. Real-time measurement of solute transport within the lacunar-canalicular system of mechanically loaded bone: direct evidence for load-induced fluid flow. Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research. 2011; 26: 277–285.

[16] Li J, Rose E, Frances D, Sun Y, You L. Effect of oscillating fluid flow stimulation on osteocyte mRNA expression. Journal of Biomechanics. 2012; 45: 247–251.

[17] Sansalone V, Kaiser J, Naili S, Lemaire T. Interstitial fluid flow

within bone canaliculi and electro-chemo-mechanical features of the canalicular milieu: a multi-parametric sensitivity analysis. Biomechanics and Modeling in Mechanobiology. 2013; 12: 533–553.
[18] Verbruggen SW, Vaughan TJ, McNamara LM. Fluid flow in the osteocyte mechanical environment: a fluid-structure interaction approach. Biomechanics and Modeling in Mechanobiology. 2014; 13: 85–97.
[19] Meslier QA, DiMauro N, Somanchi P, Nano S, Shefelbine SJ. Manipulating load-induced fluid flow in vivo to promote bone adaptation. Bone. 2022; 165: 116547.
[20] Zhu L, Barber J, Zigon R, Na S, Yokota H. Modeling and simulation of interstitial fluid flow around an osteocyte in a lacunocanalicular network. Physics of Fluids. 2022; 34: 041906.
[21] Nile M, Folwaczny M, Wichelhaus A, Baumert U, Janjic Rankovic M. Fluid flow shear stress and tissue remodeling-an orthodontic perspective: evidence synthesis and differential gene expression network analysis. Frontiers in Bioengineering and Biotechnology. 2023; 11: 1256825.
[22] Piekarski K, Munro M. Transport mechanism operating between blood supply and osteocytes in long bones. Nature. 1977; 269: 80–82.
[23] Knothe Tate ML, Falls T, Mishra S, Atit R. Engineering an ecosystem: taking cues from nature's paradigm to build tissue in the lab and the body. Fields Institute for Mathematics in Biology monograph series on New Perspectives in Mathematical Biology. 2010; 57: 113–134.
[24] Tami AE, Schaffler MB, Knothe Tate ML. Probing the tissue to subcellular level structure underlying bone's molecular sieving function. Biorheology. 2003; 40: 577–590.
[25] Knothe Tate ML. Mixing mechanisms and net solute transport in bone. Annals of Biomedical Engineering. 2001; 29: 810–811; author reply 812–816.
[26] Knothe Tate ML, Steck R, Forwood MR, Niederer P. In vivo demonstration of load-induced fluid flow in the rat tibia and its potential implications for processes associated with functional adaptation. The Journal of Experimental Biology. 2000; 203: 2737–2745.
[27] Knothe Tate ML, Knothe U. An ex vivo model to study transport processes and fluid flow in loaded bone. Journal of Biomechanics. 2000; 33: 247–254.
[28] Ngo L, Knothe Tate ML. Multi-modal sample preparation and imaging protocol for nano-to-mesoscopic mapping of cellular inhabitants in diverse tissue compartments, across organ systems. Protocol Exchange. 2023. (preprint)
[29] Ngo L, Knothe LE, Knothe Tate ML. Knee Joint Tissues Effectively Separate Mixed Sized Molecules Delivered in a Single Bolus to the Heart. Scientific Reports. 2018; 8: 10254.
[30] Ngo L, Knothe Tate ML. A spike in circulating cytokines TNF-α and TGF-β alters barrier function between vascular and musculoskeletal tissues. Scientific Reports. 2023; 13: 9119.
[31] Anastopolous S, Ngo L, Ng J, Putra V, Knothe Tate ML. Interface Tissues of the Mesoderm: Periosteum, Ligament, Interosseous Membrane, & Myofascial Tissues, an Inspiration for Next Generation Medical Textiles. Current Opinion in Biomedical Engineering. 2024; 31: 100543.
[32] Knothe Tate ML, Tami AE, Netrebko P, Milz S, Docheva D. Multiscale computational and experimental approaches to elucidate bone and ligament mechanobiology using the ulna-radius-interosseous membrane construct as a model system. Technology and Health Care: Official Journal of the European Society for Engineering and Medicine. 2012; 20: 363–378.
[33] Convergence: Facilitating Transdisciplinary Integration of Life Sciences, Physical Sciences, Engineering, and Beyond. 2014. Available at: https://new.nsf.gov/funding/learn/research-types/learn-about-convergence-research (Accessed: 15 August 2024).
[34] Homer. The Odyssey. W. Heinemann: London, GP Putnam's Sons: New York. 1919.
[35] Olivia McDonald. American Wetlands Month: 5 Reasons to Love Wetlands. 2021. Available at: https://wmap.blogs.delaware.gov/2021/05/17/american-wetlands-month-5-reasons-to-love-wetlands/ (Accessed: 21 December 2023).
[36] WWF. HydroSHEDS. https://www.worldwildlife.org/pages/hydrosheds (Accessed: 21 December 2023).
[37] Niederer PF, Knothe Tate ML, Steck R, Boesiger P. Some remarks on intravascular and extravascular transport and flow dynamics. International Journal of Cardiovascular Medicine and Science. 2000; 3: 21–31.
[38] Niederer PF. Mathematical foundations of biomechanics. Critical Reviews in Biomedical Engineering. 2010; 38: 533–577.
[39] Chabra R, Shankar V. Transport Processes in Microfluidic Applications. In Coulson and Richardson's Chemical Engineering (7th edn) (pp. 529–546). Butterworth-Heinemann: Oxford. 2018.
[40] Knothe Tate ML, Steck R, Anderson EJ. Bone as an inspiration for a novel class of mechanoactive materials. Biomaterials. 2009; 30: 133–140.
[41] Sidler HJ, Duvenage J, Anderson EJ, Ng J, Hageman DJ, Knothe Tate ML. Prospective Design, Rapid Prototyping, and Testing of Smart Dressings, Drug Delivery Patches, and Replacement Body Parts Using Microscopy Aided Design and ManufacturE (MADAME). Frontiers in Medicine. 2018; 5: 348.
[42] Knothe Tate M.L, Steck R, Tami A, Sidler H-J. Computational Modeling of Extravascular Fluid Flow in Bone. In Computational Methods in Biomechanics (pp. 307–328). Springer: Berlin. 2010/2011.
[43] Sidler H, Steck R, Knothe Tate ML. Site-Specific Porosity and Its Impact on Load-Induced Fluid Movement in Cortical Bone. In ASME Summer Bioengineering Conference. 2005.
[44] Rajendran A. Chromatographic separations. In Coulson and Richardson's Chemical Engineering (6th edn) (pp. 657–684). 2023.
[45] Hansen SH, Bjørnsdottir I, Tjørnelund J. Nonaqueous Capillary Electrophoresis. In Encyclopedia of Separation Science | Electrophoresis. Reference Module in Chemistry, Molecular Sciences and Chemical Engineering (pp. 1293–1300). Elsevier: Amsterdam. 2000.
[46] Guzelsu N, Walsh WR. Streaming potential of intact wet bone. Journal of Biomechanics. 1990; 23: 673–685.
[47] Walsh WR, Guzelsu N. Electrokinetic behavior of intact wet bone: compartmental model. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 1991; 9: 683–692.
[48] Zeng Y, Cowin SC, Weinbaum S. A fiber matrix model for fluid flow and streaming potentials in the canaliculi of an osteon. Annals of Biomedical Engineering. 1994; 22: 280–292.
[49] Reilly GC, Knapp HF, Stemmer A, Niederer P, Knothe Tate ML. Investigation of the morphology of the lacunocanalicular system of cortical bone using atomic force microscopy. Annals of Biomedical Engineering. 2001; 29: 1074–1081.
[50] Walsh WR, Guzelsu N. Ion concentration effects on bone streaming potentials and zeta potentials. Biomaterials. 1993; 14: 331–336.
[51] Tami AE, Nasser P, Schaffler MB, Knothe Tate ML. Noninvasive fatigue fracture model of the rat ulna. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 2003; 21: 1018–1024.
[52] Tami A, Schaffler MB, Knothe Tate ML. Cellular and tissue-level permeability are increased in fractured and in contralateral control bones. In ASME Summer Bioengineering Conference, 2001. 2001.

[53] Evans SF, Docheva D, Bernecker A, Colnot C, Richter RP, Knothe Tate ML. Solid-supported lipid bilayers to drive stem cell fate and tissue architecture using periosteum derived progenitor cells. Biomaterials. 2013; 34: 1878–1887.
[54] Anderson JM. Molecular structure of tight junctions and their role in epithelial transport. News in Physiological Sciences: an International Journal of Physiology Produced Jointly by the International Union of Physiological Sciences and the American Physiological Society. 2001; 16: 126–130.
[55] Evans SF, Parent JB, Lasko CE, Zhen X, Knothe UR, Lemaire T, *et al*. Periosteum, bone's "smart" bounding membrane, exhibits direction-dependent permeability. Journal of Bone and Mineral Research: the Official Journal of the American Society for Bone and Mineral Research. 2013; 28: 608–617.
[56] Evans SF, Chang H, Knothe Tate ML. Elucidating multiscale periosteal mechanobiology: a key to unlocking the smart properties and regenerative capacity of the periosteum? Tissue Engineering. Part B, Reviews. 2013; 19: 147–159.
[57] Wang T, He C. Pro-inflammatory cytokines: The link between obesity and osteoarthritis. Cytokine & Growth Factor Reviews. 2018; 44: 38–50.
[58] Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nature Reviews. Rheumatology. 2011; 7: 33–42.
[59] Nguyen LT, Sharma AR, Chakraborty C, Saibaba B, Ahn ME, Lee SS. Review of Prospects of Biological Fluid Biomarkers in Osteoarthritis. International Journal of Molecular Sciences. 2017; 18: 601.
[60] Mabey T, Honsawek S, Tanavalee A, Yuktanandana P, Wilairatana V, Poovorawan Y. Plasma and synovial fluid inflammatory cytokine profiles in primary knee osteoarthritis. Biomarkers: Biochemical Indicators of Exposure, Response, and Susceptibility to Chemicals. 2016; 21: 639–644.
[61] Anderson EJ, Kreuzer SM, Small O, Knothe Tate ML. Pairing computational and scaled physical models to determine permeability as a measure of communication in micro- and nanoscale pericellular spaces. Microfluidics and Nanofluidics. 2007; 4: 193–204.
[62] Knothe Tate ML, Srikantha A, Wojek C, Zeidler D. Connectomics of Bone to Brain-Probing Physical Renderings of Cellular Experience. Frontiers in Physiology. 2021; 12: 647603.
[63] Hageman D, Pereira AF, Zeidler D, Knothe UR, Gardner L, Knothe Tate ML. Cellular Epidemiology of Human Disease using Biogeographic and Google Maps Approaches - Towards Definition of Cell Network Indices for Rapid Diagnostics. Annals of Biomedical Engineering. 2016; 44: 3732–3734.
[64] Knothe Tate ML, Zeidler D, Pereira AF, Hageman D, Garbowski T, Mishra S, *et al*. Organ-to-Cell-Scale Health Assessment Using Geographical Information System Approaches with Multibeam Scanning Electron Microscopy. Advanced Healthcare Materials. 2016; 5: 1581–1587.
[65] Nextstrain. Availabele at: https://nextstrain.org/ (Accessed: 10 March 2021).
[66] Biot MA. General Theory of Three-Dimensional Consolidation. Journal of Applied Physics. 1941; 12: 155–164.
[67] Carter DR, Hayes WC. The compressive behavior of bone as a two-phase porous structure. The Journal of Bone and Joint Surgery. American Volume. 1977; 59: 954–962.
[68] Lakes RS, Katz JL. Viscoelastic properties of wet cortical bone–II. Relaxation mechanisms. Journal of Biomechanics. 1979; 12: 679–687.
[69] Knothe Tate ML, Falls TD, McBride SH, Atit R, Knothe UR. Mechanical modulation of osteochondroprogenitor cell fate. The International Journal of Biochemistry & Cell Biology. 2008; 40: 2720–2738.
[70] Filipowska J, Tomaszewski KA, Niedźwiedzki Ł, Walocha JA, Niedźwiedzki T. The role of vasculature in bone development, regeneration and proper systemic functioning. Angiogenesis. 2017; 20: 291–302.
[71] Rahman A, Chaturvedi RR, Sled JG. Flow-Mediated Factors in the Pathogenesis of Hypoplastic Left Heart Syndrome. Journal of Cardiovascular Development and Disease. 2022; 9: 154.
[72] Wong M, Carter DR. Mechanical stress and morphogenetic endochondral ossification of the sternum. The Journal of Bone and Joint Surgery. American Volume. 1988; 70: 992–1000.
[73] Tanck E, Blankevoort L, Haaijman A, Burger EH, Huiskes R. Influence of muscular activity on local mineralization patterns in metatarsals of the embryonic mouse. Journal of Orthopaedic Research: Official Publication of the Orthopaedic Research Society. 2000; 18: 613–619.
[74] Nowlan NC, Murphy P, Prendergast PJ. Mechanobiology of embryonic limb development. Annals of the New York Academy of Sciences. 2007; 1101: 389–411.
[75] Kovacs CS. Bone development and mineral homeostasis in the fetus and neonate: roles of the calciotropic and phosphotropic hormones. Physiological Reviews. 2014; 94: 1143–1218.
[76] McCarthy I. The physiology of bone blood flow: a review. The Journal of Bone and Joint Surgery. American Volume. 2006; 88: 4–9.
[77] Tomlinson RE, Silva MJ. Skeletal Blood Flow in Bone Repair and Maintenance. Bone Research. 2013; 1: 311–322.
[78] Marenzana M, Arnett TR. The Key Role of the Blood Supply to Bone. Bone Research. 2013; 1: 203–215.
[79] Hughes L, Centner C. Idiosyncratic bone responses to blood flow restriction exercise: new insights and future directions. Journal of Applied Physiology (Bethesda, Md.: 1985). 2024; 136: 283–297.
[80] Tambutté E, Tambutté S, Zoccola D. Biomineralisation in reef-building corals: from molecular mechanisms to environmental control. Comptes Rendus Palevol. 2004; 3: 453–467.
[81] Kim J, Kimura Y, Puchala B, Yamazaki T, Becker U, Sun W. Dissolution enables dolomite crystal growth near ambient conditions. Science (New York, N.Y.). 2023; 382: 915–920.
[82] Bressan D. The Birth of the Dolomites - Beautiful Mountains born out of the Sea. Scientific American. 2012.
[83] Ngo L, Knothe Tate ML. Osteoarthritis: New Strategies for Transport and Drug Delivery Across Length Scales. ACS Biomaterials Science & Engineering. 2020; 6: 6009–6020.
[84] Winkler L, Blasig R, Breitkreuz-Korff O, Berndt P, Dithmer S, Helms HC, *et al*. Tight junctions in the blood-brain barrier promote edema formation and infarct size in stroke - Ambivalent effects of sealing proteins. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2021; 41: 132–145.
[85] Lee JY, Lu H. Plasmodesmata: the battleground against intruders. Trends in Plant Science. 2011; 16: 201–210.
[86] National Research Council (US) Committee on Research Opportunities in Biology. Ecology and Ecosystems. Opportunities in Biology. National Academies Press (US): Washington (DC). 1989.
[87] Kahil K, Weiner S, Addadi L, Gal A. Ion Pathways in Biomineralization: Perspectives on Uptake, Transport, and Deposition of Calcium, Carbonate, and Phosphate. Journal of the American Chemical Society. 2021; 143: 21100–21112.
[88] Smith AJ, De Jonge DS, Hahn T, Schroedl P, Silverstein M, Andrade C, *et al*. Evidence of dark oxygen production at the abyssal seafloor. Nature Geoscience. 2024; 17: 737–739.
[89] U.S. National Science Foundation. Available at: https://new.nsf.gov/funding/learn/research-types/learn-about-convergence-research (Accessed: 15 August 2024).