Conceptualization of Surface-Confined Nano-Assemblies as a Biophysical Battery Circuit during Tissue Rescue: A Bridge to Accessing Genomic Control Mechanisms

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Abstract

The advent of tissue rescue surgical procedures that mimic mammalian wound healing behaviors to facilitate lesion recovery has brought about a renewed interest in biologic surface-confined nano-assemblies that are intrinsic to interfacial venues at which juxtaposed tissue surfaces reside. Used as a trait-targeting substrate, these assemblies are enrolled to direct nanometer level resection precision to create a healthy lesion site devoid of damaged tissue by capacitive balancing the electrochemical voltage potential they generate during treatment with that of alternating current redox magnetohydrodynamic produced engineered irrigants designed to molecularly disaggregate exposed damaged interstitial matrices. As applied to osteoarthritic articular cartilage lesions, this report discusses the interaction dynamics between surface-confined nano-assemblies and alternating current redox magnetohydrodynamics as a biophysical battery circuit serving to bridge access to genomic control mechanisms within a healthy wound bed.

Key Words: cartilage, tissue rescue, proton gradient, AC redox magnetohydrodynamics, battery, gene expression.

Introduction

The disturbance of surface-confined nanoscale assemblies in biologic tissue brought about by nonnative interfacial environments during therapeutic intervention has received very little attention despite the significant role these assemblies play in maintaining tissue integrity against perturbation and pathologic solutes. While much has been written about the interfacial nuances of tissue surfaces for over 125 years [1], the emergence of tissue rescue surgical procedures and associated medical devices (Figures 1-3) has generated a renewed interest in surface-confined assemblies because these assemblies are enrolled to produce a healthy lesion site devoid of damaged tissue as a means to unencumber innate and facilitative wound healing [2-4]. Although becoming increasingly more delineated in various tissue types, surface-confined assemblies remain complex and difficult to study [5], even without imposing iatrogenic disturbances and non-equilibria treatment conditions. Treatment venues that utilize endoscopic surgical access procedures to care for normally juxtaposed tissue surfaces necessarily involve ambient media replacement and mechanical loading alterations, both of which disturb surface-confined assembly behavior despite attempts to simulate *in vivo* conditions.

Endoscopic replacement media such as saline solutions were originally intended to aid surgical visualization as native media do not display either consistent or suitable optical properties [6]. Commensurate with this effort were attempts to limit detrimental effects upon interstitial matrices and resident cells [7-12], followed by the consideration of medical device performance within replacement media [13-16], both without significant deference to surface-confined assembly effects or their reversibility [i]. Media replacement eliminates native fluid lubricants required to accommodate physiologic movement between normally juxtaposed tissue surfaces; consequently, interfacial behaviors associated with hydrodynamic fluid film dissolution-depletion occur so that surface asperities are no longer contained within the thickness of native fluid lubricant pools. Such native fluid film starvation is induced by the lower media viscosity associated with optical improvement and the mechanical unloading that occurs by eliminating the normal contact between tissue surfaces. Because pressure build up in native viscous lubricants is inhibited during endoscopy, interruption of other interfacial regimes like squeeze film, interstitial biphasic, mixed-mode, or versions of elastohydrodynamic fluid film mechanisms can inevitably occur [ii]. These conditions favor the expression of boundary lubrication regimes whereat loading is carried by the surface asperities in a contact area rather than by a fluid film lubricant and at which surface chemistry dominates working properties [19-22]. Because the differential mechanical load that tissue surfaces experience during endoscopy is primarily due to surgical device contact, this situation is ideally suited for the treatment of abnormal surface asperities as relative to boundary conditions. Conversely, the disturbances provoked by fluid film starvation and absent hydrodynamic pressure regimes during endoscopy that express boundary conditions constitutes a tissue vulnerability that has been largely unrecognized as an etiologic factor associated with iatrogenic damage that further impairs wound healing, expands lesion size, and contributes to disease burden [iii].

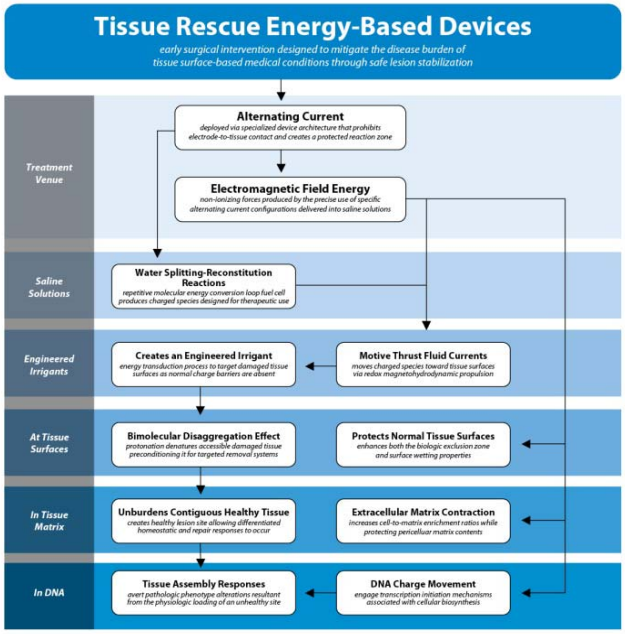

Figure 1: Tissue rescue algorithm. Energy-based medical devices have been designed to create healthy wound sites at tissue surfaces to alleviate various inter-related elements which contribute to disease burden.

Partial-thickness damaged tissue surfaces at locations requiring relative motion characteristically exhibit abnormal surface asperities [24] and the related absence of surface-confined assemblies associated with boundary lubrication regimes [25-30], features that serve as an effective nanoscale trait-targeting substrate for tissue rescue procedures which mimic biologic wound healing behaviors [2-4]. Tissue rescue medical device systems, such as the physiochemical scalpel depicted in Figure 3, deploy alternating current redox magnetohydro-dynamics within media replacement solutions to produce protonating

[i] Damaged tissue removal was an obvious entry-level procedural advance once endoscopic access and visualization was made possible. For articular cartilage, early efforts like powered mechanical shavers and electrosurgical (thermal or plasma) ablation devices were based on imperfect visual-tactile cues rather than upon tissue traits that relate the practitioner's ability to distinguish diseased tissue from normal as correlated to conditions that contribute to disease burden. Tissue rescue treatments are designed to unencumber contiguous healthy tissue function by selectively targeting diseased tissue traits to protect against the iatrogenic collateral damage of over-resection which can further impair contiguous healthy tissue from retaining and displaying differentiated phenotypes necessary for wound healing.

[ii] Replacement media pressurization within a constrained endoscopic cavity can produce significant hydrostatic forces; and in certain settings, residual lubricant entrapment may occur [17-18]. Further, the role of hydrodynamic fluid film regimes during endoscopy for porous tissue surfaces like articular cartilage remains to be fully clarified [19-20], including the effects porosity may exert upon wettability.

[iii] Because early endoscopic device systems were designed only for palliative tissue resection, iatrogenic collateral damage remained a consequence of procedural expediency, which in turn allowed less demanding and cheaper engineering designs to persist for articular cartilage treatment. For example, optimized thermal and plasma ablation devices were unable to eliminate volumetric or functional over-resection and caused residual tissue necrosis in the range of 250 µm additive to tissue resection margins. Consequently, surface-confined assemblies (~450 nm) and subsurface healing phenotypes located within the Superficial Zone (~200 µm) were effectively eliminated during treatment [23]. Surface-confined assembly preservation has become a differentiating feature between palliative resection and tissue rescue wound healing procedures.

engineered irrigants designed to disaggregate exposed damaged interstitial matrices through molecular cleavage planes not protected from that irrigant by surface-confined assemblies [2-4, 23, 31, 32]. This targeted molecular disaggregation prepares damaged tissue for mechanical removal by surgically blunt shear forces produced by the device edge to create a healthy lesion site devoid of damaged tissue. Because boundary conditions display a kinetic friction coefficient that is invariant relative to factors that influence formation of a fluid film, such as sliding velocity and axial load, the mechanical implement design for articular cartilage limits its function to low contact speed and pressure loading to yield a kinetic friction coefficient safe for exposed boundary lubrication regimes [23, 33-35]. Since increased surface asperities suppress the formation of surface-confined assemblies by decreasing interstitial matrix surface hydrophobicity [30], a condition that impairs wound healing behaviors [2-4], re-establishing surfaces devoid of damaged tissue decreases surface roughness so that surface hydrophobicity [36] is increased to a more normal level (i.e. for articular cartilage, a contact angle approximating 105^0) supportive of and associated with the capacity to build and maintain surface-confined assemblies.

To illustrate the emerging nexus involving nanoscale biostructures with nanofluidic technology for regenerative medicine [37, 38], this report discusses the trait-targeting dynamics during saline solution media replacement treatment conditions between surface-confined nanoscale assemblies and alternating current redox magnetohydrodynamic tissue rescue procedures as deployed for commonly encountered articular cartilage lesions exhibiting increased surface asperities. As each creates and maintains an electrochemical voltage potential during treatment, tissue rescue is conceptualized as a biophysical battery circuit that deploys capacitive balancing as a trait-targeting mechanism.

Tissue Surface-Confined Assemblies and Endoscopic Boundary Conditions

Tissue surfaces display a complex tribochemical interfacial system that integrates phase-state transitions between ambient media and differentiated interstitial matrices. Tissue surface-confined assemblies are germ cell independent systems rooted in a foundation of self-assembling amphiphilic bioaggregates which emerge *in situ* to manage tissue boundaries intrinsic to interfacial venues at which juxtaposed tissue surfaces reside. This system enables solubilization of solid tissue surfaces by transforming the hydrophobic surface of normal interstitial tissue matrices toward a hydrophilic character. To mitigate the high surface hydrophobicity of articular cartilage interstitial matrices (due to very low cell-to-matrix ratios) and their rheologic chemomechanical loading requirements, these assemblies are considered to consist of multiple oligolamellar hydrophilic bimolecular layers ranging between 6-10 nm each and conceptualized as a large three-dimensional reverse micelle approximating 450 nm in thickness [30, 39-40]. These layers absorb and hold water within their charged core in the manner of hydrophilic lamina with a strong laterally bonded network exhibiting both lipid mobility and viscous resistance. The amphiphilic components are integrated onto solid-liquid surfaces as surfactants in order to modify the interfacial wetting behavior and free energy of hydrophobic interstitial matrices, allowing boundary water to spread into a surface biofilm state rendering the surface more hydrophilic. As the water content of this layer fluctuates during perturbation, amphiphilic components migrate to reduce surface tension and avoid hydrophobic adhesion. Surface-confined assemblies function to protect underlying interstitial matrices from physiochemical perturbation [2, 4, 23, 27-31, 39-43] and like other surfactants are often non-uniform in thickness, discontinuous, or can deposit in an island form dictated by surface geometry and interfacial energy conditions. Because they have been shown to replenish by self-assembly mechanisms through surface loading at healthy tissue matrix sites [44] or through native lubricant component delivery [45], surface-confined assembly mechanisms suggest a tissue homeostatic and repair role that is related to their stability and durability as evident in other tissue types. By serving as an occasional sacrificial layer that is subsequently reconstituted as a means to help mitigate certain perturbation events, the ability to restore tissue surface properties after removing the bioburden of damage tissue that suppresses surface-confined assembly formation and maintenance remains an important wound healing approach [2-4, 46-48].

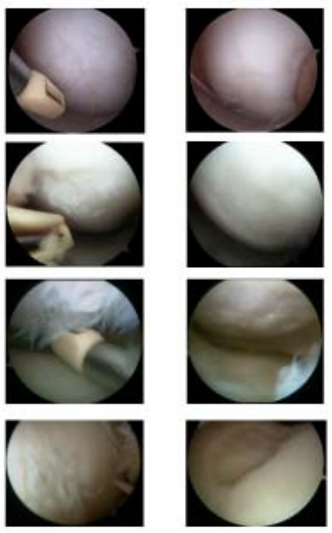

Figure 2: Tissue rescue for the articular cartilage lesions associated with osteoarthritis. Intraoperative digital photographs of pre-treatment (left) and post-treatment (right) lesions with various grades of knee femoral condyle articular cartilage damage advancing from top to bottom. Damaged articular cartilage is characterized by deteriorating surface-layered properties, like collagen fibril disruption and orientation changes, weak collagen-to-proteoglycan bonds, proteoglycan and lipid depletion, aberrant water content, and decreased fixed charge density that can be altered by physiochemical loading to a state amenable to gentle shear debridement. Proton gradient irrigants deliver their electrochemical potential as a chemical denaturing stress to exposed damaged interstitial matrices comprised of two main classes of macromolecules, proteoglycans and fibrous proteins; and, at physiologic pH, charged sulfate and carboxyl groups create a negative charge density in the range of 0.04 to 0.2 $mEq\,mL^{-1}$. Protein solubility is minimal at their isoelectric point because equal charges allow formation of intermolecular bonds which assist aggregation between proteins by managing hydration shells. During proton gradient chemical denaturation processes, by inducing local charge variations through irrigant charge injection, macromolecules lose negative and gain positive charge. As positive charge increases, aggregation becomes compromised; and, in areas of large same charge density, resultant intramolecular repulsion causes unfolding. As unfolding becomes more extensive, hydrophobic segments become exposed through hydrogen bond, disulfide bond, salt bridge, and non-polar hydrophobic disruption which lead to chain separation by unmasking buried water (i.e. altering the position of the water molecule) and other molecular groups thereby causing irreversible disaggregation. This conformational folding and bonding changes through alterations in macromolecular net surface charge density results in protonating biopolymer disaggregation occurring at molecular cleavage planes of secondary, tertiary, and quaternary structures that preconditions damaged tissue for gentle mechanical debridement. At damaged tissue sites amenable to tissue rescue, morphological tissue grades exist such that deteriorating surface-layered properties ultimately transition to more normal interstitial matrix configurations. Because the denaturing stress needs only to be strong enough to precondition accessible damaged surface matrices, this tissue grade spectrum serves to render ineffective an engineered irrigant designed for denaturation of damaged tissue as it interacts with normal tissue at the base of the lesion. In this manner, the depth-effect boundary is controlled by the protic solvent strength relative to normal tissue matrix character such that the scale of normal fixed negative charge densities becomes a loading barrier that protects healthy tissue by rendering the proton load inconsequential. This technique allows fine tuning the scale of proton load delivered relative to the technique of mechanical debridement based upon tissue characteristics that can be assessed during treatment whereby healthy tissue exhibits a large fixed charge density that cannot be altered to a level amenable to gentle mechanical debridement by the magnitude of proton gradient deployed. Note the resultant decrease in surface roughness which increases surface hydrophobicity to a level that can allow surface-confined assemblies to re-form and be maintained. Images courtesy of Jack Farr, MD; Brian McKeon, MD; and Craig Rosen, MD.

Because pH [iv] can affect the wettability, frictional coefficient, swelling, contact angle hysteresis, and interfacial energy associated with surface-confined assembly behavior, intrinsic amphiprotic properties allow active acid-base equilibria maintenance and stabilization of ambient charged species [30, 40, 41]. In so doing, surface-confined assemblies function as a charge barrier [25, 30, 40, 41] that can modulate osmotic drive energy [49, 50] and interstitial biphasic fluid movement during perturbation [51, 52], ultimately serving as a link between tribological and mechanical regimes during physiologic conditions [5]. This charge barrier, because of its amphiprotic properties, has been shown to be protective of underlying interstitial matrices during the physiochemical loading, such as ambient protonation potentials, delivered by tissue rescue surgical procedures [2-4, 23, 30, 40, 41]. In these settings when polar replacement media like saline solutions are utilized to express boundary conditions so as to delineate abnormal

[iv] Consider the robust charge barrier of the gastric mucosa which exhibits similar surface-confined assembly behavior. Because pH is a useful *in situ* measure of electrochemical voltage potential, it can be monitored by practitioners in order to titrate the delivery of protic solvents during treatment [2, 23, 31, 32].

surface asperities, surface-confined assemblies induce formation of an additional longer-range charge barrier mechanism with energy storage properties. As an attribute of water residing adjacent to hydrophilic biosurfaces, an ordered-water molecular zone contiguous to surface-confined assemblies forms within which thermal and density gradients do not blend freely [1, 50, 53-55]. This zone forms rapidly to a thickness of 100-300 μm [v], excludes solutes like salts, and is mechanically less mobile due to its crystalline-like architecture. This zone demonstrates electrochemical voltage potentials between 100-200 mV such that the zone is negatively charged and balanced by a region of increased proton concentration within the contiguous bulk water solution. This charge separation proton gradient is a non-thermal process that occurs by absorbing incident interfacial energy to augment the natural water dissociation processes [55-56]. Because surface-confined assemblies create a hydrophilic surface upon which this proton gradient veneer is formed, this zone supplies a source of stored interfacial energy as a protonation potential during saline media replacement.

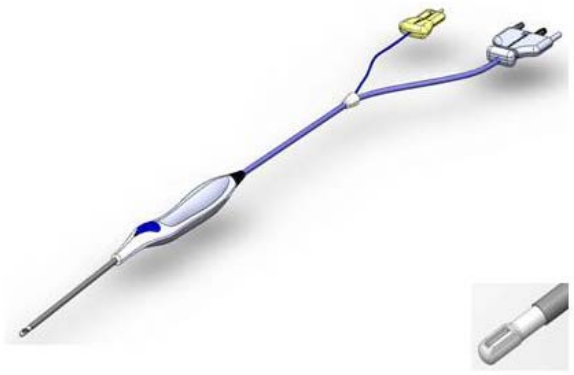

Figure 3: The physiochemical scalpel designed to achieve nanometer resection precision, increased cell-to-matrix enrichment ratios, and induction of tissue assembly transcriptional responses in tissue subadjacent to the wound bed (Ceruleau®, NuOrtho Surgical, Inc.; Fall River, MA). The inset depicts the tip architecture that facilitates the use of alternating current redox magnetohydrodynamics.

Alternating Current Redox Magnetohydrodynamics of Tissue Rescue

The technique of alternating current redox magnetohydro-dynamics involves positioning localized alternating current circuits in saline solutions containing electroactive species to move electrons between device electrodes utilizing electron donor and acceptor carriers within host media replacement fluid [2, 4, 31]. This electron transport produces fuel cell like reversible redox reaction pairs associated with charged specie intermediaries formed above baseline solution dissociation rates upon which the attendant alternating current non-ionizing electromagnetic field quanta influence the reaction dynamics. These influences include charged fluid acceleration that creates magnetohydrodynamic propulsive thrust currents adapted for medical therapeutics as irrigants. These "irrigants within water" are comprised of regional structure altered molecular water [32] exhibiting differential charged specie separation that results in a sequestered energy source contained within the irrigant that is useful for surgical work.

Alternating current electron movement produces a repetitive molecular energy conversion loop fuel cell in saline solutions involving salt bridge catalyzed splitting and reconstitution of the water molecule [2, 4, 31, 32]. The thermochemical redox reaction pair can be represented as

$$\alpha H_2O_{(l)} + \beta XCL \xleftrightarrow{\text{energy}} (\alpha-\beta)H_{2(g)} + \frac{(\alpha-\beta)}{2}O_{2(g)} + \beta HCl_{(aq)} + \beta XOH_{(aq)} \quad (1)$$

$$(\gamma-\delta)H_{2(g)} + \frac{(\gamma-\delta)}{2}O_{2(g)} + \delta HCl_{(aq)} + \delta XOH_{(aq)} \xleftrightarrow{\text{energy}} \gamma H_2O_{(l)} + \delta XCl_{(s)} + \Delta \quad (2)$$

with the variables α, β, γ, and δ as the molar quantities that satisfy the oxidation reduction requirements for the overall reaction set and Δ as the available heat and/or electrical energy. Attendant non-ionizing electromagnetic field quanta influence this redox reaction pair to move reactant and product charged species formed above baseline solution dissociation rates away from the device electrodes and directionalized by a plenum. As regional proton concentration differentials increase above normal solution dissociation rates due to the magnetohydrodynamic pumping mechanism, an electrochemical proton gradient develops from the resultant charge separation, creating an irrigant with energy storage properties similar to that created by surface-confined assemblies during saline media replacement [2-4]. This energy source is maintained during device activation and delivered to tissue surfaces as a protonation potential below the isoelectric point of exposed damage interstitial matrices. The protonation potential is delivered in the form of a protic solvent that balances proton delivery with sensible thermal contributions typical of acute wound healing exudates [2-4, 31, 32]. In so doing, the irrigant battery energy is consumed by the exposed negative charge density of damaged interstitial matrices leading to molecular disaggregation useful for eliminating damaged interstitial matrix tissue.

Theory and Conceptualization

Direct Current Model of Tissue Rescue

Proton gradients are a common biologic mechanism utilized to generate electrochemical potential in order to convert and store energy. Regardless of their generation mechanism, by depicting proton gradients as electrochemical cells, their electrical polarity can be represented as a unidirectional flow of electric charge suitable for direct current modeling. For example, biologic membrane-based proton gradients such as in mitochondria and chloroplasts can be depicted as $-\,\|\,+$ because these gradients require a physical membrane structure to maintain charge separation after charge movement. Likewise, $\|\,-\,+$ can represent a proton gradient that forms adjacent to hydrophilic tissue surfaces such as that generated by surface-confined assemblies during saline media replacement; and, $-\,+$ can represent protonating irrigant gradients that form within solutions without physical structures to maintain charge separation such as those generated by alternating current redox magnetohydrodynamics [2-4, 31, 32]. In each instance, and although generated by different mechanisms, these proton gradients serve as energy conversion systems generated from electron transport between charge carriers to create protonation potentials. Consequently, each proton gradient electrochemical cell is capable of direct current discharge of its protonation potential which can be represented in a battery circuit.

Because surface-confined assemblies form and maintain a proton gradient veneer when confronted with saline solution media replacement, and because boundary conditions are dominated by chemistry, alternating current redox magnetohydrodynamics was chosen for tissue rescue because a similar proton gradient can be design formulated within the same saline solution and delivered *in situ* as a trait targeting mechanism for areas of abnormal surface asperities associated with absent surface-confined assemblies. Accordingly, trait-targeting energy can be modeled as a direct current supercircuit represented by instantaneous voltage energy transfers using the water molecule as an energy transducer. During tissue rescue, a proton gradient is formed that is delivered to tissue surfaces, much like a portable battery, and discharged as a protonation potential. Because the intermolecular hydrogen bond stretching frequencies of water demonstrate a proton based femto- to pico-second oscillation period [57], electron movements associated with alternating current polarity changes are less rapid so that water protons in the irrigant experience direct current forces ($10^{12\text{-}15}$ Hz oscillation rate versus $10^{5\text{-}6}$ Hz circuit frequencies) during device activation. Accordingly, irrigant batteries generated through motive proton delivery gradients can be reduced to a direct current energy storage model capable of direct current discharge during contact with a specific therapeutic target [2, 4, 32]. Viewed historically, these intramolecular dynamics are analogous to a full-wave bridge electrolytic rectifier that converts an alternating current into a direct current except that redox magnetohydrodynamics produce a steady direct current electrochemical voltage potential from the rectified alternating current supply without using a smoothing reservoir capacitor, capacitor-input filter, or voltage regulator. During tissue rescue, the irrigant battery interacts with the tissue battery generated by surface-confined assemblies.

Normal Tissue Surface Properties in Electrical Terms

Normal tissue surface-confined assemblies create a hydrophilic substrate upon which a proton gradient veneer forms during saline solution media replacement. In this setting, an electrochemical circuit can be conceptualized as a direct current model of retained

[v] Even with the mechanical turbulence of vigorous stirring, such as that which occurs during endoscopy, this zone is not eliminated but has been shown to decrease in size [53].

voltage potential with intact surface-confined assemblies serving as an insulator substrate while the electrochemical gradient battery is charged by proton veneer formation mechanisms described above. Viewed *in toto* for a specific surface-confined assembly geographic island with distinct margins, a single continuous electrochemical cell can be conceptualized as participating in a battery circuit as depicted in Figure 4 and which retains a protonation potential capable of discharge.

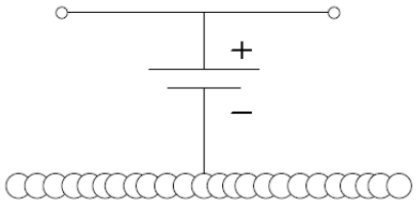

Figure 4: Electrochemical circuit diagram of a biophysical battery formed by saline solution media replacement at normal tissue surfaces displaying intact surface-confined assemblies. Serving as a hydrophilic substrate and replacement media irrigant insulator, these assemblies induce the formation of reversible tissue surface interfacial batteries as a manifestation of interfacial energy management activities to protect underlying interstitial matrices. For the purposes of illustration, surface confined assemblies are depicted as overlapping polar head groups representative of amphiphilic molecules.

Damaged Tissue Surface Properties in Electrical Terms

Because damaged tissue surfaces lack surface-confined assemblies and therefore the formation of a proton gradient veneer, the exposed interstitial matrix constitutes an abnormal hydrophobic region that presents its negative charge density to the treatment venue. As depicted in Figure 5, this exposed negative charge density separates surface-confined assembly islands through edge contact angle hysteresis with the damaged tissue surfaces acting as an electrical ground. This ground leads to discharge of adjacent tissue surface electrochemical cells as a protonating force upon the negatively charged exposed tissue. This protonation potential discharge facilitates molecular disaggregation of damaged interstitial matrices that already exhibit deteriorating surface-layered shear properties of collagen fibril disruption and orientation changes, weak collagen-to-proteoglycan bonds, proteoglycan and lipid depletion, aberrant water content, and decreased fixed charge density. This disaggregation leads to a decrease in surface roughness that can lead to an increase in surface hydrophobicity toward a level capable of building and maintaining surface-confined assemblies necessary to facilitate increased wettability, more normal chemomechanotransductive environments for subadjacent tissue, and unburdened tissue homeostatic and repair mechanisms. This biopolymer disaggregation process mimics the brining effects on damaged tissue of acute wound healing exudates [58-60].

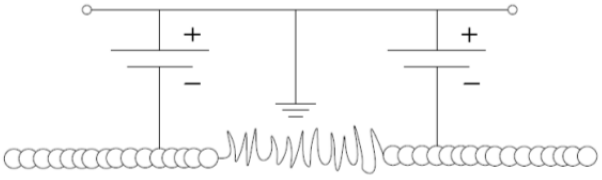

Figure 5: Electrochemical circuit diagram depicting biophysical battery discharge induced by adjacent damaged tissue surfaces during saline solution media replacement. Damaged tissue surfaces constitute a hydrophobic breach in surface confined assemblies that inhibits the formation of a proton gradient veneer associated with hydrophilic biosurfaces. Acting as an electrical ground because of its negative charge density, exposed damaged interstitial matrices are subject to the protonation potential associated with adjacent surface-confined assemblies during saline media replacement. This protonation of exposed damaged interstitial matrices can partly explain the clinical benefit of arthroscopic saline solution lavage historically observed in certain settings. For purposes of illustration, damaged interstitial matrices are depicted as a line scribe rendering of surface fibrillation.

Tissue Rescue in Electrical Terms

At damaged tissue sites that exhibit a level of surface roughness which cannot be disaggregated by the protonating discharge of adjacent surface-confined assembly batteries alone during saline media replacement, tissue rescue procedures as depicted in Figure 6 deliver an engineered irrigant protonation potential that is capacitance balanced and with reverse polarity to that generated by surface-confined assemblies at normal tissue surfaces. The technique of capacitance balancing between the irrigant and tissue surface batteries is used so that varied capacitance between the two energy sources does not lead to significant discharge of either during treatment. By designing the irrigant battery with a capacitance similar to the tissue surface battery, the reverse polarity delivery is a safe targeting force because the engineered irrigant is very portable within saline media replacement venues. The magnetohydrodynamic propulsive force easily interrupts the interfacial discharge of adjacent tissue surface protonation potentials as depicted in Figure 5 and concentrates a larger protonation potential at the exposed negative charge density of the damaged interstitial matrices [2, 4, 32]. This therapeutic process mimics the protic solvent generated by enhanced azurophilic degranulation of polymorphonuclear neutrophil granulocytes during the early phases of acute wound healing [2-4].

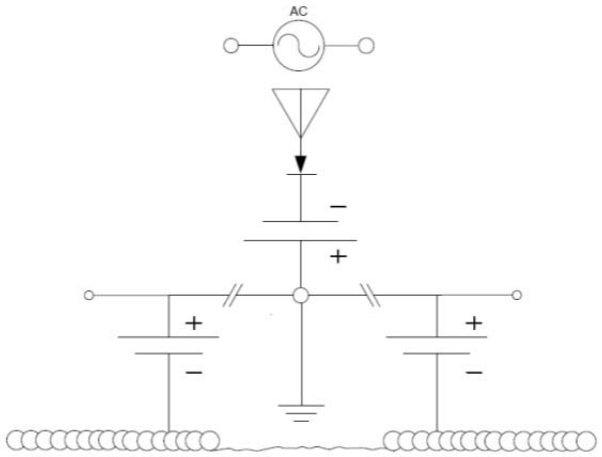

Figure 6: Electrochemical circuit diagram representing the trait-targeting effects of tissue rescue alternating current redox magnetohydrodynamics. The irrigant battery diagram is shown as forming through a rectified signal whereby capacitive balancing in reverse polarity during saline media replacement disrupts adjacent tissue surface interfacial battery discharge at hydrophobic sites lacking surface-confined assemblies. This trait targeting mechanism augments the molecular disaggregation process by increasing the protonation potential delivered over time to damaged interstitial matrices. Targeted disaggregation allows damaged tissue to be removed as it exhibits a decreased negative charged density magnitude, among other features, relative to normal. The wound bed periphery is protected from the design formulated protonation potential by the normal interstitial matrix negative charge density magnitude so that the energy transduction process of protonation couple conformational dynamics relative to accompanying thermal contributions can be titrated by the practitioner.

Discussion

Tissue rescue, the technique of unburdening biologic homeostatic and repair responses to avert pathologic phenotype shifts, is an important early surgical intervention advance toward mitigating disease burden. At sites where normally juxtaposed tissue surfaces require relative motion, surface-confined nanoscale assemblies form *in situ* as functional integrators to manage the hydrophobic interfacial character and differentiated behavior of interstitial matrices. Once surface areas become damaged and exhibit abnormal asperities exceeding the capacity of intrinsic homeostatic and repair mechanisms, surface hydrophobicity decreases to a state upon which surface-confined assemblies cannot form or be maintained [25-30]; a condition of interfacial dysfunction leading to altered chemomechanotransductive environments for and provocation toward further pathologic phenotypic shifts in subadjacent tissue [61-63]. The bioburden that such damaged tissue represents is related to its clearance potential; and, in settings of limited or acquired clearance deficiency, wound bed preparation remains an important therapeutic endeavor. For this reason, trait-targeting interventions have been designed to afford practitioners the ability to create a healthy wound bed when intrinsic homeostatic and repair capacities may be overwhelmed. By mimicking the important mammalian wound healing behavior of distinguishing between normal and damaged tissue surfaces based upon the presence or absence of surface-confined assemblies [2-4, 23, 31, 32], the removal of damaged tissue associated with abnormal surface asperities decreases surface roughness so that surface hydrophobicity can be increased to more normal levels, producing conditions favorable to surface-confined assembly nucleation, reformation, growth, and maintained lesion site coverage [30, 36, 40]. By creating a healthy wound bed unencumbered by damaged tissue [64-65], the re-establishment of interfacial regimes

upon return to native environments post-treatment [44, 45, 51, 66] can restore conditions supportive of differentiated function, including intrinsic homeostatic and repair capacities, in subadjacent tissue.

The bioburden clearance potential for many damaged interstitial matrix surfaces is augmented by the formation of acute wound healing exudates when intrinsic homeostatic and repair capacities are not adequate. These exudates precondition damaged tissue toward a state amenable for removal by mechanisms like phagocytosis [64, 67]. This preconditioning is brought about by protic solvents, such as those generated through azurophilic degranulation of polymorphonuclear granulocytes during the acute phases of wound healing, that are primarily responsible for biopolymer disaggregation of damaged tissue present in a wound bed. Because the rheologic requirements of normally juxtaposed tissue surfaces can create challenges for establishing acute wound healing exudates and localization of associated cellular complements, this clearance potential limitation above intrinsic homeostatic and repair mechanisms has been advanced as one reason why some differentiated tissue surfaces have been linked with a reputation for poor healing capacity [2-4]. Alternating current redox magnetohydrodynamic technology has been adapted for surgical applications to address this clearance deficiency by imitating the protic solvent component of acute wound healing exudates to produce biopolymer disaggregation of exposed damaged tissue not protected by surface-confined assemblies [vi]. By adapting alternating current redox magnetohydrodynamics, the advantages of protic solvents can be delivered as engineered irrigants without the disadvantages of full enzyme system deployment typically associated with azurophilic degranulation such as myeloperoxidase and nicotinaminde adenine dinucleotide phosphate oxidase systems [68-71].

By using various saline media replacement formulations during endoscopic procedures to express boundary conditions at normal sites, surface-confined assemblies display tribological and mechanical working properties governed by interfacial chemistry [19-22] and a kinetic friction coefficient invariant to perturbations effecting fluid film formation [33-35, 72], respectively. Capacitance balanced engineered irrigants controllably deliver protonation potentials appropriate for boundary condition interfacial chemistry in order to precondition damaged tissue for removal. The energy transduction processes of protonation coupled conformational dynamics has been shown to achieve nanometer resection precision through a guest chemical denaturation process below the isoelectric point of exposed damaged interstitial tissue matrices [2-4, 23, 31, 32]. This energy transduction process utilizes low stability protonating agents involved in exothermic tissue homeostasis and repair mechanisms through disproportionation redox reactions like those produced by the respiratory burst myeloperoxidase system activated by azurophilic degranulation of polymorphonuclear neutrophil granulocytes during the acute phases of wound healing [67, 73-79]. Rather than relying upon local phagocytic-like processes as in acute wound healing behaviors, once preconditioned, damaged tissue is removed by physical implements of the device system appropriate for treatment interfacial mechanical conditions through shear debridement and flushed away by the saline media solution. Preconditioning and removal of damaged tissue in this manner has been a successful acute wound healing biomimic to produce a healthy wound bed and assist differentiated biosynthetic tissue assembly activities in subadjacent tissue [23, 80-82].

Although the deterioration of hydrophobicity associated with surface roughness can be responsible for the absence of surface-confined assemblies at damaged sites, changes in interfacial energy and composition of synovial fluid likely play important complementary roles. As a manifestation of interfacial dysfunction, the inability of surface-confined assemblies to build on damaged tissue surfaces may relate to pressure-to-surface area dependent gas-gap alterations [36], exposed interstitial matrix negative charge density effecting hydrogen bond alterations in interfacial water [50, 54], or cavitation erosion associated with wear particles [83] not captured by innate removal mechanisms. As discussed in this report, and as in other tissue types for which irrigants affect surface roughness [84], the protonation potentials generated by saline media replacement that self-target exposed interstitial matrices by adjacent interfacial energy discharge have been observed clinically during endoscopy at articular cartilage surfaces for many decades. The simple observation that surface fibrillation characteristics change with different replacement media provides an important clue to the clearance potential that can be augmented by engineered irrigants through targeted biopolymer disaggregation. This disaggregation of exposed fibrillated tissue bathed in saline solutions accentuates the distinction between normal and abnormal surfaces and the resultant preconditioning remains a very plausible mechanism [4] explaining the clinical improvements observed with arthroscopic lavage [85-86]. Increased protonation potentials likewise have been demonstrable within synovial fluid alterations that occur commensurate with disease [72, 87-89]; altered synovial fluid composition in these instances manifests as a large endogenous wound exudate delivering increased protonation potentials when damaged tissue removal is required. By preconditioning damaged surface tissue to facilitate removal, disaggregated debris by increased synovial fluid protonation potentials can be delivered to the long-known mechanisms of synoviocyte phagocytosis [90-91].

Osteoarthritis results in whole joint-organ disease persuaded by articular cartilage integrity failure. Because damaged cartilage serves as a biologic and mechanical irritant that causes symptoms and advances disease, treatment efforts designed for its removal remain an intuitive and important focus intended to maintain articular cartilage integrity and alleviate disease burden. Older technologies enabling palliative tissue resection have been deemed inappropriate for wound healing because of unavoidable volumetric and functional over-resection that simply expanded lesion size, eliminated structurally stratified healing phenotypes, provoked disease progression, and left a residual damaged tissue surface in no way suitable for the nucleation, reformation, growth, or maintenance of surface-confined assemblies [4, 23]. Concerns that such palliative approaches provoke disease progression have understandably led to reconsideration as to whether these treatments provide any benefit toward wound site bioburden control even when used only to achieve short-term symptomatic relief [24]. While articular cartilage has shown many of the wound healing behaviors associated with homeostatic and repair activity at its surfaces [92-106], it is unable to remove macroscopic damaged tissue from its surface in any meaningful way. This clearance deficiency is largely due to the unique avascular structural transport properties and synovial environment of articular cartilage, both of which alter typical inflammatory processes and the ability to localize effective wound healing exudates [105-106] aside from altered synovial fluid composition when viewed as a form of wound exudate [4]. Because an effective clearance process is important during the acute phases of wound healing [108-112], this deficiency has frustrated the efforts to create a healthy lesion site widely considered important for both primary and secondary intention articular cartilage wound healing [4, 24, 113-117].

Similar to the fundamental cancer observation that abnormal cell growth kinetics could serve as a therapeutic trait-targeting substrate to preserve healthy tissue and enable substantial disease burden mitigation, surface-confined nanoscale assemblies are likewise providing this opportunity for conditions like osteoarthritis [80]. Although homeostatic and repair capacities may be decreased in areas surrounding diseased articular cartilage as in other tissue types, partial thickness lesions by definition contain viable cells and residual tissue function [24, 82] so that creating conditions favorable to the responsive capacity of subadjacent tissue allows that tissue the opportunity to mount unencumbered differentiated homeostatic and repair responses. For juxtaposed tissue surfaces requiring relative motion such as articular cartilage, a therapeutic focus upon partial-thickness lesion wound healing by secondary intention will likely augment recent approaches studying primary intention wound healing as applicable to full thickness lesions [113-114, 116, 118]; understanding interfacial behavior [119] during treatment [120-122] [vii] can better enable tissue surface host-to-implant integration and reconstruction of suitable surface wear properties. Secondary intention wound healing approaches, while typically dependent upon exudative processes, seek preserved subadjacent tissue because of tissue loss that occurs with damage. While assisting the limited or acquired clearance deficiency, alternating current

[vi] Exposed damaged tissue, often characterized as surface fibrillation due to its collagen content, exhibits deteriorating surface-layered shear properties of collagen fibril disruption and orientation changes, weak collagen-to-proteoglycan bonds, proteoglycan and lipid depletion, aberrant water content, and decreased fixed charge density that is a suitable biopolymer disaggregation target for protic solvents not strong enough to overcome the normal subadjacent tissue makeup at the wound bed periphery [2-4, 23, 31, 32]. In this manner, the physiochemical scalpel can produce a healthy wound bed without altering cell viability or residual differentiated function.

[vii] For example, by time averaging the Lorentz force, an applied therapeutic electromagnetic field generated by a tissue rescue device can be described by the equation $F = Q\,(E + v \times B) \times L \int_0^{2\pi} \sin \omega t \sin(\omega t + \emptyset)\, d\emptyset$, with L as the distance between the device electrodes.

redox magnetohydrodynamics has been shown to achieve other important secondary intention wound healing effects in addition to tissue surface engineering, including wound bed contraction that increases cell/matrix enrichment ratios [123] [viii] and induction of tissue assembly responses accessing genomic control mechanisms [80-82] [ix], useful to provocate post-treatment wounding healing as interfacial properties are re-established toward a better bearing surface.

Because engineered irrigants interact with tissue surfaces to enable trait-targeted resection precision, healthy tissue around the lesion site is spared allowing exploration into the therapeutic potential of homeostatic and repair activities in contiguous differentiated tissue. At short distances below the tissue surface, non-ionizing electromagnetic field quanta may access genomic control mechanism based upon charge movement. Although electrons are involved in or related to all biochemical processes and have a very high charge/mass ratio, electrons do not exist as an isolated discrete entity in most biologic tissue settings, but are bound to various charge carriers or contained within atoms or molecules and transferred between reductant and oxidant species. Unlike proteins that are generally electrical resistors, the observed electrical conductance behavior of DNA, with and without its counter-ion-water structure *in vivo*, indicates that intermolecular charge transfer is enhanced due to its unique stacked base pair aromatic rings and overlapping electron π orbitals which exhibit electron lattice interaction. One dimensional charge transfer has been shown to occur by coherent charge tunneling and diffusive thermal hopping via electron and cationic hole transport between the low redox potential G-C base pairs [124-126]. Charge transport efficiency is influenced by both differential redox potentials between base pairs and charge localization in and around DNA whereby charging effects both electrostatic repulsion and associated hydration energies. Similar to the chemical-induced biopolymer disaggregation initiated by engineered irrigants, non-thermal electronic induced DNA duplex destabilization can be used to initiate rapid biosynthetic transcription related to base pair opening dynamics [81, 127-129] at electromagnetic-specific promoter domains, like the low electronegative sequence nCTCTn [127]. During the deployment of electromagnetic field quanta during tissue rescue, electrons can be displaced in hydrated DNA that cause transient charging of small groups of base pairs [81, 127] that have been shown to induce transient transcriptional upregulation of matrix and chaperone genes indicative of tissue assembly [82]. The relationship between DNA conductivity, non-ionizing electromagnetic field quanta charge movement, base pair opening dynamics, and biosynthetic matrix synthesis has led to the tissue rescue technique of charge injection and subsequent charge migration through DNA. As a form of oxidation doping, this technique is based upon natural processes that manage both normal oxygen metabolites in and electromagnetic field conditions of cells that have an important role in cell signaling and homeostasis. DNA charge transfer mechanisms are designed as a sensing mechanism to perceive and integrate changes in cellular environmental such as oxidative stress levels by facilitating charge migration toward segments with the lowest sequence specific redox potential [130]. Such fluctuations in environmental conditions are anticipated with well-developed and conserved cellular responses like molecular chaperone production. Because aspects of DNA conductivity can be considered an oxidation mitigation mechanism to non-ionizing electromagnetic field quanta by facilitating charge movement toward low redox potential sequence-specific base pairs, the observed biosynthetic upregulation may represent normal non-injury induced tissue assembly behavior that occurs in response to the typically fluctuating electromagnetic environment in which eukaryotic cells reside. For low level non-ionizing energy fluctuations, tissue responds to the altered electrostatic and hydration energies and resultant base pair openings in DNA by normal homeostatic and repair mechanisms. Although not all cell types respond to such electromagnetic field quanta, the specific gene clusters relevant for tissue rescue include tissue assembly clusters that tend to demonstrate a transient acceleration of differentiation at the expense of proliferation [131-132]. Because this charging process exhibits hydration dependency, water as a charge carrier, specifically its hydrogen bond flicker, may provide a direct current model for DNA charge transfer, charging, and subsequent charge migration that leads to the homeostatic re-balancing of matrix production.

Since surface matrix cells display significant phenotypic plasticity and high anabolic capacity, improving their environment by targeted damaged tissue resection is an effective means to stabilize contiguous differentiated phenotype(s), even if that includes interrupting early phenotypic adaptations-alterations to disease. As reversibility for some lesions may require a phenotypic shift (or redifferentiation) such as that induced by physiologic loading a healthier site, the capability to transiently upregulate focal biosynthetic activity reflective of differentiated tissue assembly repair mechanisms remains an important early post-treatment therapeutic desire [x]. Inducing *in situ*, targeted, appropriate, and differentiated biosynthetic cellular function within contiguous tissue subadjacent to diseased locales, thereby recruiting local cells to aid lesion recovery, requires the ability to access genomic control mechanisms that govern tissue assembly and display promoter domain-segment threshold responsiveness slightly above micro-environmental perturbation noise. Otherwise, the relative strength of perturbation assaults upon tissue could lead to senescence, apoptosis, or unregulated cells growth kinetics in normal cells or in those less able to mitigate the stress. Appropriately tuned non-ionizing electromagnetic field quanta remain a uniquely suited biosynthetic signaling pathway. A good measure of inherent tissue assembly behavior is the transcriptional upregulation of molecular chaperone genes associated with matrix production. For example, inducible-form HSPA1A transcription is a useful biomarker of differentiated matrix biosynthesis in response to a wide variety of stimuli as different promoter domains may be associated with different perturbation stimuli [127]. Thermal stimuli direct cellular biosynthetic responses marked by HSPA1A once tissue temperatures reaches 39^0 C [135], the temperature at which type II collagen begins to denature [136]. As type II collagen is a major constituent of the extracellular matrix, these direct cellular chaperone response linked to matrix assembly only occurs once a damage threshold is reached. On the other hand, non-ionizing electromagnetic field quanta can also directly stimulate transcriptional upregulation of HSPA1A via its own promoter domain different than that of thermal stimuli. This direct transcriptional mechanism exhibits a non-damage-related threshold responsiveness. Such a stimulus utilizes stress induced duplex destabilization mechanisms that nature has evolved during harsh conditions and has been perfected over time by eukaryotic cells. Utilizing charge transfer mechanism in DNA designed to mitigate local redox fluctuations, *in vivo* transcription initiation technology based upon charge/mass ratio dependent acceleration utilizes low level fluctuations in redox potentials as the lowest perturbation above background noise which can be easily mitigated by the cell and are associated with matrix biosynthetic

[viii] Although the exothermic character of protonation may contribute to surface reorganization, within healthy tissue around a lesion site that is not affected by irrigant loading itself, electromagnetic field quanta can impart energy transfer. Covalently bonded biopolymers constrain the movement of charged species as proteins are generally electrical resistors that do not linearly conduct current because their valence electrons are generally locked into individual bonds (some exceptions are sp^2 hybridized covalent bonds and conjugated p-orbitals). Because charge mobility, migration, and transport are limited through the molecule, dielectric heating can occur in response to non-ionizing electromagnetic field quanta that attempt to move charge. For tissue rescue frequencies, this is typically measured by specific absorption rates based upon tissue density and electrical conductivity manifesting as thermal effects that increase the incident venue temperature above thermal noise. Because collagen provides the framework for interstitial matrices, collagen type profiles can control matrix volume through specific thermal contraction responses. For instance, tissue matrices with predominant type VI collagen, like those associated with pericellular regions, are resilient to contractile alterations, protecting cells; whereas volume contraction can occur more readily in extracellular regions comprised of predominantly type II collagen. This interstitial matrix contraction differential based upon collagen type profiles has been shown to preferentially contract the extracellular matrix rather than the pericellular matrix leading to a tissue supportive increase in cell-to-matrix enrichment ratios. These alterations are useful for tissue surface based medical conditions that primarily manifest as matrix failure due to the inability of widely spaced cellular components to maintain geographic integrity against perturbation.

[ix] In the Standard Model of particle physics, photons are the gauge bosons, or force carriers, of electromagnetism. While photons as field quanta can be considered to lack rest mass, charge, spontaneous decay, or probabilistic behavior, their momentum, alternatively represented as pressure by applying Poynting vectors, is determined by frequency (or wavelength); and, hence is relative to the electromagnetic energy incident upon matter. Photon energy can be depicted by $E = \frac{hc}{\lambda}$, where h is Plank's constant, c is the speed of light, and λ is the wavelength. Commonly utilized tissue rescue electromagnetic frequencies range between 100 kHz and 1 MHz which approximates $4.14e^{(-10)-(-9)}$ eV or $4.0e^{(-8)-(-7)}$ kJ/mol per photon, respectively. In the instance of applying 25W of power at these frequencies, equating to 0.025 kJ/sec, photons are delivered at $62.5e^{3-4}$ mol/sec. This electromagnetic energy is non-ionizing as it does not produce field quanta energetic enough to break chemical bonds, alter strong chemical reactions, or overcome atom-molecule electron binding energies present within incident venues; rather, the energy can excite, rotate, vibrate, or move an electron or alter valence configurations without producing charged ions.

[x] The matrix constituents of surfaced-based tissues exhibit slow turnover rates making the ability to trait-target diseased tissue for resection to avoid iatrogenic over-resection an important goal. For example, the half-life of aggrecan core protein ranges from 3-24 years [133], with the glycosaminoglycan components of aggrecan being synthesized more readily under low-turnover conditions, displaying more rapid matrix turnover in the pericellular regions. Proteoglycans are essential for protecting the collagen network, which itself has a half-life of more than 100 years [134] if not subjected to inappropriate degradation.

responses. When therapeutic surgical interventions are being designed for biologic tissues, an interaction (agitation) sweet spot exists at both the cellular and matrix level between micro-environmental perturbation noise and the irreversible damage of matrix disaggregation and cellular necrosis. It is for this reason that it may be an easier task to treat partial-thickness defects rather than full-thickness as the former allow better access to *in situ* fully integrated and blended gene complex global control mechanisms not based upon achieving injury as in thermal treatments.

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