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Low-Frequency Ultrasound and Markov Property for Wound Healing Based Management

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ABSTRACT

The global cost of wound care is increasing due to the criticality of hard-to-heal demand. The complexity of chronic wounds makes it difficult to estimate advanced treatment policies. The Wound Healing Foundation recognizes the need for an unbiased consensus on chronic wounds care, according to who heals and who fails to measure progress of heal by constant-12 week. Care assessment is still a topic beyond crucial wound debridement, and there is a growing interest in device-aware interactions with tissue regenerative processes. A temporary spatial dose of low-frequency ultrasound, ISATA = 0,03-3 W/cm2, during debridement, typically between 25-30 kHz, significantly lowers the failure rate of care for hard-to-heal wounds. It is assumed that sonophoresis-induced cavitation can eliminate harmful biofilms as a constant in the heterogeneity of clinical meta-analysis for wave indexing and dosage. It is not yet clear how wave-frequency impacts the phase of tissue regeneration. New assumptions about immunometabolism with a hidden Markov chain address the role of spin operators in regulating the stages of regeneration of any healing wound and their interdependent architecture. The significance of energy exchange in tissues and its relationship with dielectric properties is highlighted in cross- referencing quantum dynamics for biological processes, tissue structuring, and function. In a forward approach to assessing the biophysical effects of low-frequency ultrasound, it is important to evaluate the timing, space, and spacing duty cycle of the wave characteristics for host response cell-tissue delivery over time. Quantum biology suggests that the sonophoresis debridement phase can be effective in promoting regeneration during the healing process, acting as a spin operator. This can be assessed by evaluating the sensitivity index of lower failure rates in wound treatment benchmarks.

Keywords

Low-Frequency Ultrasound Debridement, Treatment time-to-failure, Wound healing time.

Importance

A wound is defined as an anatomical structural lesion with functional discontinuity of normal tissues. Complex signaling networks and biomolecular interactions are involved in host response as a healing process to synthesize matrix and restore components of tissue

structure over time. Failure is a time when it is not healing. Long-term or chronic wounds cause considerable morbidity and require significant health care resources. Treatment remains a puzzle across advanced treatment modalities [1]. The global cost of wound care is increasing due to the criticality of hard-to-heal complexity [2]. Any treatment must consider several casual factors for status along time, in which regular debridement is crucial [3]. In 2022, the Wound Healing Foundation recognized the need for an unbiased consensus on the best treatment according to wound assessment and noninvasive visual correlation (e.g. Bates-Jensen Wound Assessment Tool, Wound Bed score: [4,5] for both healed and wounds that failed to heal within week 12 [6]. Contextually, the Centers for Disease Control and Prevention refined the context by establishing 4 different classes of wound statuses for predicting the likelihood of wound healing time including [7,8]. The adjustment of the debridement cycle to tissues regeneration is still a topic for care assessment. Numerous methods have been reported, and each team has created protocols based on their own experience to reduce wound size over time [9]. However, in this context, the clinical trial meta- analysis shows heterogeneity and bias in pooled random effects between methodologies, taxonomic rank classification, and topology of care [10,11]. Beside the difficulties of standardization, one of the emerging gaps is the quality attributes of physical-aware interactions between medical devices and host response [12]. One of the answers to the healing complexities involves the restoration of the integumentary system from ongoing damage caused by elastic-plastic failure, which involves the physics of matter [13,14]. It is a vital barrier on the area that regulates internal functions and displays its physical structure through its electrical conductivity and physiological ionic distribution, which can be used to control the system itself physiologically. Variations in the electrical properties represent structural changes, and the emulated ionic signals in the tissue that can manipulate the system itself [15-17]. The thermodynamic cycle in any wound area impacts the fluctuation of energy exchange through tissue, which is driven by a well-defined immunometabolism and the overlapping of neuroimmune axis response [18-20]. The conditional bioeffect encompasses the quantum biology approach for regulation governance of tissue molecular dynamics and the dielectric properties [21]. Embracing this field, ultrasound debridement has been extensively studied as a therapeutic agent in chronic wound healing. Low-frequency ultrasound devices, typically between 25-30 kHz (LFU), during debridement has been shown to significantly reduce the failure rate of care within K-12 weeks for hard-to-heal wounds according to clinical evidence [22].

Issue of Concern

LFU medical devices for generating bioeffects and determining safety are based on the intensity of sonophoresis, which is the topology of duty cycle in a total of six cross-sectional areas in units of watts [W] per square centimeter [23]. FDA mechanical index (MI) requirement is used to indicate the proportional bioeffect benefit in humans [24,25]. The display screen displays the real-time MI rate, which is equivalent to the expenditure of energy passing through the area in one second for a certain density of molecules. This is based on acoustic theory for generating sonophoresis in tissues medium with appropriate intensity, pressure, and frequency by a contact or non-contact handpiece vibration. LFU is determined as a United States uses customary units of 20-120 kHz with a range of 0.05-1.0 power density W/cm^2 as a low power and "*very*" low frequency. However, only small fractions of the nominal energy are released and delivered to the deep-seated tissue layers, which contrasts with the derived output acoustic power. The combined voltage equation and modulating index (i.e., frequency deviation constant, signal amplitude, and maximum frequency deviation) are the main parameters for demodulation (i.e., maximum peak-to-peak voltage of amplitude modulation wave and minimum) of emission forces, but tissue impact can only be inferred for its primary and secondary areas based on their timeline response. The LFU machinery's labels with the allowed standardized measurement, however, do not fulfill the key characteristics for timing shifts the benefit. In end-to-end analysis, further consideration remains to be given to LFU endpieces and vector waves aggregate in the timing of space- spacing time between wound and host response [26].

Observation

LFU propagation in biological tissue is essentially a non-linear process, with linearity for intensity secondary phenomena as a gate for observation [27]. The finite-sample majority and plurality rules results in microstreaming and cavitation effects in interstitial fluid medium for controlling and remove harmful biofilms with bacterial load. The background of biophysical principles of contact-probe piezo- electrically mechano-transduction force is focused on low power temporospatial intensities of ISATA = 0.03-3 W/cm^2 in a vector field. Typically, it is considered that the ultrasound beam is focused at one point, so selectively target lie between the ultrasonic transducer and the target tissue. Under this umbrella a variety of methods (i.e., contact, or non-contact probe) have been investigated, with different delivery of absorption bands. In human tissues, the LFU interfacial Maxwell-Wagner effect of mechanical energy flux density of about 0.25 ml./mm^3, can generate bioelectric signaling in the network biology environment. It is emerging that the biophysical effect changes the network biology and neuromodula- tion of immunity of wound multi-cell (tissue) response [28,29].

The Organ-on-a-Chip Model

Organ-on-chip model systems recapitulate key biological processes and responses to mechanical stimulation in exhibited by cells, tissues, and organs *in vivo* [30]. While the nature of the biomechanical signal is important, the cellular response is also heavily dependent on the duration, magnitude, and frequency of the active biomechanical cue. Biomechanical cues are often extrinsic to the cell and can take passive or active forms. Substratum stiffness, geometric confinement, or topographic cues are all passive biomechanical stimuli. Active stimuli include tissue tensile stretch and compression, shear stress, interstitial fluid flow, and hydrostatic pressure. Bio signal generation is a biopotential propagation in tissues anisotropy and represents the macro physiological system for the organization of space-time mechanical properties of tissues over

time (e.g., a Young's modulus). The adaptative form is determined by two- way biocommunication workflow for the relaxation-time of tissues (i.e., Boltzmann equation). Tissues response is conditional to varying dielectric properties matching tissue conductivity [31]. The mechanism is closely related to the return to an undisturbed molecular motion, as path of the conduction electrons and the average distance of undisturbed motion between collisions. The linear relationship is determined by the perturbation timeline of the mechanosensitive force, which has a proportional size and is accompanied by casual variables such as compressive rigidness, shear, and direct stress to the tissues tensile strength when used to regenerative brake resistance. Biopotential as a corollary of it falls in the dielectric permittivity properties, which is crucial for time-varying ionic diffusion for polarization of cells membrane in an inherently filled electrolyte composition of the tissue's environment (e.g., Debye– Hückel theory). The spin-layer polarization of biochemical cue opens a networking operating system that run with G-protein coupled signaling pathways for transcriptional networks up to mesenchymal stromal cells activation. The leaf layer, which is involved in immunometabolism, plays a role in the axiomatic concept of thermodynamics for controlling the delivery of energy exchange and system transformation [32]. For instance, imbalances in supply and demand in the molecular oxygen chain led to the failure of structural challenges as it is well known that traffic flows control reactive oxygen and nitrogen species and other redox active molecules, which perform the essential functions of immunity. In this context tissues origin from integumentary system has bioelectric property for density of 1109 kg/m³, heat capacity of 3391 J/kg/°C, thermal conductivity of 0.39 W/m/°C, heat transfer rate of 1.65 ml/min/kg and heat generation rate average of 1.65 W/Kg [33].

Relevance and Conclusion

As defined above, Low Frequency Ultrasound exerts a non-linear bioactivity on tissue weight fractions of wound through its longitudinal and transverse relaxation times, as well as acoustic properties. Effectiveness for frequency from 25 to120 kHz to a wound tissue's permittivity of 1.13^{e+3} and conductivity from $2,21^{e-4}$ to $5,47^{e-4}$ S/m (skin and soft tissues), is estimate in time domain response (i.e., Cole-Cole equations; [34]). The attribution is a function of multi-state-morphology in time-to-event. This model allows a wound management analysis over time allows to measurement the transition intensities at different time scales using a 'clock-forward' approach [35]. Time-to-heal in wound quantifies a sensitivity index for different treatment topologies to calculate response rates and provides a vector for classifying a mixed population's response to treatment in a taxonomy management. Conceptually, the analysis characterizes the class of linear fluctuation (i.e., α-Levy and Gaussian distribution) of continuous random tissue rearrangement in one-tail tests of status morphology over time. As mentioned above, stochastic random walks are Wigner matrices which intersect metabolic pathways depending on the two- way immune cell communication during the host response phase [36]. These matrices are the reference- based imputation of analysis because any agent that involves conditional interactions is an operator for differential equations with varying effects, including the failure rate benchmark.

Wound Healing in Time-to-Failure Analysis

The bio-physical gates of wound are a temporal perturbated tissue's thermodynamics constraints of skin-brain axis origin with biocommunication workflow having quantum properties [37-39]. In terms of Young's modulus, the spatial-temporal poli-axial strength arrangements are mediated by mesenchymal stroma stem [40]. The piezoelectric mechano-transduction forces and the temporospatial intensities of LFU are a photon-spin operator by interacting permittivity and conductivity in a quantum inference mechanics. In quantum biology, the generated kinetic energy of Alfvén waves plays a linear Sono-Hydro-Gen process for extracellular matrix deposition containing hydrogen element [41]. The conditional phenomenology is the increases of oxygen levels (blood flow and vessel formation) stem cell proliferation (regeneration) up to accelerates wound closure in full thickness. From the spin-layer polarization side, the hidden Markow chain of hydrogen-bonded dynamic networks results closed to cell-tissues energy exchange in a generated dielectric relaxation time [42,43]. The hierarchical lecture is that the non-healing wounds results in lifetime failure of tissue's state-space anisotropy respond to LFU treatment through the host's mechanosensitive forces and immunometabolism for the ongoing space- time rearrangement. In mathematics, the game for failures covers the Cauhy-Euler equation with a variable coefficient for a space-time equilibrium between a spin-relaxation-time operator, which is capable of engaging human tissue for permittivity [44]. The finite time of 12 weeks for wound-hard-to-heal and casual matrix is distributed in space-time, which is represented by Duhamel's bathtub curve, in this assumption. Any treatment to an applied zero input as a zero status falls in the fractional linear regression for a censored continuous result (i.e., Tobit model). In mathematics, and more specifically in partial differential equations, the central part of the bathtub curve is the half-life of static failure rate of healing and the random sequence of care [45]. The last part of stress-out breakdowns is by accelerating the occurrence. The probability free of events switches over occurrence to middle and final curve levels. LFU as designed in a quantum speedup properties have shown to change the distribution of healing failure rates from the onset of debridement. Given that, the criticality quality attributes for LFU faced with the dielectric properties of tissues and host response can reach the rank profile of a bioactive factor with the effect of regenerative processes [46].

Sensitivity Index

In context review, the meta-analytic frequentist data on lowering healing time provides a weighted cross-effectiveness constant of 12 weeks as a *tau*-equivalent rank profile for LFU. Applying the β-regression approach, the probability density function of the post-debridement timeline is sensitive to the expected host response dynamics during the healing time. In analysis the sensitivity index in a Bayes- ian inference approach is represented by the macros of Weibull distribution curve in shape parameter of 1 over 3 months of healed wounds, which indicates that 63.20% of treatments succeed

[47]. The clinical benefits of LFU debridement combined with late re-generation stimuli are clinically significant on a recurrent basis, as shown in a meta-analysis.

Critical Process Parameter

In recent years, the in-depth study for sonophoresis has elucidated its biological effects through a Hartman effect. There are many ion passages in biological tissue formed by intermembrane space, intercellular spaces, and membrane pores, around which convex counterion layers are formed. This kind of counterion layer is believed to produce an α-dispersion in the same way as it does for the colloidal particles. The β-dispersion is mainly caused by membrane structure, which blocks ion movement under an external electric field. When membranes stack more tightly, the β-dispersion becomes weaker. The β-dispersion is largely affected by water content [48]. Less water content of the tissue means more air gaps or dry components, which will also block ion passage in the same way as membranes, thus, reducing the strength of the β-dispersion significantly. In this context, LFU may be considered a two-spin operator for exchanging anisotropic status to adverse depositional pathophysiology. The coupled composite is a stabilizer of the modification of physical properties through intermediates of mitochondrial dynamics and the mechanism for overcoming rapid structural disturbance in the return of homeostasis. Derived peptides, such receptor agonists, mobilize seven transmembrane-linked G-receptors by activating adenylate cyclase in signal transduction messengers and chemotactic aggregation by driving the cAMP-dependent pathway [49]. LFU α- and β-dispersions' hardness is influenced by the shape of the counterion layer, which can change depending on the shape of the colloidal shell-shaped layer that produces a particular form of α-dispersion. The critical process parameters of interest are intersection of acoustic coherence in excitation energy transfer and decay of coherences in the protein during process and distinct biological effects on cellular systems in equivalent in receptors, ligand, and signals on a systemic basis. Enzymes have been postulated to use quantum tunneling to transfer electrons from one place to another in electron transport chains. Tunneling refers to the ability of a subatomic particle to travel through potential energy barriers. Without quantum tunneling, organisms would not be able to convert energy quickly enough to sustain growth. Quantum tunneling acts as a shortcut for particle transfer; according to quantum mathematics, a particle's jump from in front of a barrier to the other side of a barrier occurs faster than if the barrier had never been there in the first place.

Linking to Critical Quality Attributes

Normal wound healing progresses through inflammatory, proliferative and remodeling phases in host response. It has been established that signal mediators and modulators of immune control channels, belong to this large-scale distribution over the *extra*- hypothalamic–pituitary–adrenal axis as first- order logic for bringing archaic phylogenetic molecules to response in rapid adaptation to occasional injury. One of the properties is within the cholinergic anti-inflammatory pathways that is critical for peripheral specialized cells in the reticuloendothelial system. Collagen, as a key component of the ex- tracellular matrix, plays critical roles in the regulation of the phases of wound healing either in its native, fibrillar conformation or as soluble components in the wound milieu. Impairments in any of these phases stall the wound in a chronic, non-healing state that typically requires some form of intervention to guide the process back to completion. Key factors in the hostile environment of a chronic wound are persistent inflammation, increased destruction of components caused by elevated metalloproteinases and other enzymes and improper activation of soluble mediators of the wound healing process. Wound size and degree of tissue loss are particularly challenging to restore tissue integrity and function, leading to impaired. This is particularly noticeable in wounds that convoke areas completed by the body's bio- mechanical functional profile, such as osteoarthritis, capsulitis, and synovitis, tendonitis, ligaments. In this circumstance, a high rate of repair results in matrix rigidity in healed wounds and varying loss of the cross-functional area of the biomechanics, which requires many sophisticated tissues transfer procedures. Comprehensive healing is problematic as a parameter for assessing high heterogeneity and complexity for matching groups or multivariate stratification in this area. Physiologically relevant animal study for mechanisms involved in normal and damaged wound healing frontal area are potential to benefit veterinary, as well human medicine. The primary objective is to introduce translational research that is aimed at solving unmet medical needs in life sciences and biotechnology across the spectrum of science and research studies. The horses for hard-to-heal chronic wounds are well-suited model such as in navicular area in wound repair. Chronicity as a large degree of tissue trauma in the wounded horse, includes multi-structure and functional component as critical phenomenology. One of the main topics is to determine tissues structural transformation by host response within receiving multi-component shear stress with or without infection. Recently, Veterinarians referenced that equine osteoarthritis and therapeutic LFU have moved away in few cases the navicular syndrome and extreme functional impairment with rearrangement of polyaxially strength without ankylosis or animal death [50]. Considering human-horse interactions and translational research this study represents a specific joint with critical quality, power, and expectation for humans.

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