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CELLULAR ELASTICITY (STIFFNESS), PLASTICITY, AND VISCOELASTIC NATURE OF ANIMAL TISSUES INCLUDING BODY FLUIDS- PHYSIOLOGICAL, AND BIOPHYSICAL ASPECTS-I

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ABSTRACT

All matters possess three main physical features namely, hardness, flexibility and fluidity. These physicomechanical properties are distinctly different in varying degrees in solids, liquids and areal/gaseous form of materials. The hardness exists in decreasing order while flexibility and fluidity are in reverse order. Biological matter has specific shape and size which responds to the external forces applied on them. These features follow the basic mechanics of physical sciences. Biological materials are also behaving in physicomechanical pattern. The physical forces are sensed by biological matters which also exhibit these physicomechanical features. The bones are solid in nature, while other soft tissues represent the flexible matter, such as muscular, connective tissues and tissues made of cells. The body fluids like blood, lymph, cerebrospinal, synovial fluids represent the liquid features present in a biosystems. Cell membrane and other membranous constituents exist in fluid state. All these are made-up of more of less fixed and set molecules which are arranged in specific pattern. The features of elasticity, plasticity and viscoelasticity are among the physicomechanical bases of biological materials also. These biological tissues show very intense relationship with mechanical forces and these forces act as the basis of the mechanophysiological aspects of biological matter. Even the biomolecules which regulate the force-induced functionalities show distinct correlation. The mechanism is broadly accepted but their intricate aspects are still obscure. With advancement in technology, methodology, conformational and physiological dynamics of biological materials is becoming more relevant and helpful in understanding the complexities of physiological aspects of life. These mechanical forces are intricately and inexorably associated with the living being and represent the normal healthy and diseased state. The components of biological matter exhibit a capacity to sense these physical changes occurring under physical forces in precise manner. Their response is time dependent behaviour with qualitative and quantitative degrees of mechanosensing and mechanotransduction manner. These interactions involve the unit cell, cell organelles, cytoskeleton, extracellular matrix, glycocalyx, cell membrane and interstitium. There is a need to understand the complexities of interactions, mechanical regulatory functions of conformational dynamics of each functional unit of cell and the biomolecules interacting in the various biological phenomena. Hence, an effort is made to ponder and delve in this realm of interactions between physical aspects of the biological materials.

KEYWORDS: biomechanics, elasticity, Hooke's law, loading path Poisson's ratio, plasticity, viscoelasticity, stress, strain, self-limiting mechanism, unloading path.

OVERVIEW

One of the most common human tendencies is to ponder and delve in the topic of origin of life. The phenomena like system theory, science, art and other off-shoots appear to exist are the outcome of human tendencies to find the intricacies life. Thereafter, because of the inquisitive nature of man, it starts observing behaviour of the objects and try to observe as the interplay in a wholistic view. This process of observation acts as a focal point for the emergence of various phenomena or a complex system at a specific 'integrative level'. One can see the phenomenon of life based on the observations derived from biological sciences turnout to be emerged from chemical and physical sciences. Their constitutional components are homogeneous and commensurable.[1,2]

All matters possess three main features namely, hardness, flexibility and fluidity, the physicomechanical properties in varying degrees. In solids, liquids and areal states the hardness exists in decreasing order while flexibility and fluidity are in reverse order. Biological materials also behave as per physicomechanical pattern.

All structures have specific shape, size and molecular build-up which ensure the specialized behaviour and functionality in the ambient environment. Biological matter i.e., cells and the tissues also possess similar features and exhibit specific behviour and functionality within body and in relation to members of the niche. The possession of specific shape, size and molecular make-up indicate the extent of mechanical features which play significant role during cellular adhesion, migration, and other cellular functions within the biological cells, tissues and organs. The cell membrane, cytoskeleton, intracellular connections between cell organelles. The intercellular adhesion forms the functional bases of mechanical entity of biological matter.[3,4]

A unit cell membrane is made up biomolecules (lipids, proteins) forming fluid limiting membrane component that encloses all the cell organelles. It contributes to the membrane functions like controlled movements of molecules across it, elasticity, viscosity, inter and intracellular signalling, inter and adhesion and cohesion, migration etc. It expresses tension, compression, and sheer stress. These mechanical features are expressed; let force is sigma (σ), force (F), area (A), Boltzmann constant (energy related) (K), temperature (T), radius of the cell (R):
[Then stress on the membrane can be represented stress= force/area; which is = 2K .T/radius]

The cytoskeleton is made up of protein fibers like microtubules, microfilaments, and sinter intermediate filaments; which form a well-knit network and extend throughout the cell cytoplasm. Structurally, it provides mechanical support to the cell and its components, helps to maintain shape and size which ensure specific function. These protein fibers provide play significant role in causing stiffness, expressing cellular viscosity and cellular functions. This component of a cell considered as a complex of network which is subjected to different mechanical forces like tension, compression and sheer stress. One may express its mechanical features; let, its modulus of elasticity i.e., E represents Young's modulus of elasticity (E), stress as sigma (σ), strain as epsilon (ε), force as F, area as A, original length as L and change in length as (lambda length)ΛL; [then Young's modulus of elasticity E= stress σ/ strain ε = (force F/area)/(change in length ΛL/original length L)].
Cellular adhesive nature in the form of intercellular adhesion and between extracellular matrix through glycocalyx represents another aspect of mechanical feature of cell. It signifies the cellular strength, sustainability and stability which are helpful in the cellular processes like cell migration, development, healing and repair of the tissue. This feature can be represented as follow:
Adhesive force F ($F_{adhesion}$), Boltzmann constant (K), Temperature (T), length (l) and energy of adhesion as ($E_{adhesion}$) where $F_{adhesion}$ is the adhesion force, k is the Boltzmann constant, T is the temperature, l is the length scale, and $E_{adhesion}$ is the adhesion energy.

[The force of adhesion (F *adhesion*) = (Boltzmann constant temperatures T)/ length scale l]

An offshoot of biological sciences, the biomechanics relates with the forces, structure and shape of the organisms including unicellular to multicellular biosystems. Such congregation of interdisciplinary studies concerning cellular processes, properties of tissues and functionalities reflect on the biological, medicinal and engineering approach of the biological sciences.

Like materials in physics concept, biological matters also exhibit these physicomechanical features, for example, skeleton components like bones among vertebrates and chiton in invertebrates are solid in nature; while other soft tissues represent the flexible and fluid nature like muscular and soft tissues made of cells and blood, lymph cerebrospinal, synovial fluids represent the liquid features. Cell membrane and other membranous constituents are accepted to be a fluid state. All these are made-up of more of less fixed and set molecules which are arranged in specific pattern. The features of elasticity, plasticity and viscoelasticity are the among the physicomechanical bases of biological materials also.[5,6]
In last few years there has been intense study on the mechanobiological aspects of cells and tissues. In addition to general concept of stiffness in tissues, the corelation between cells-substrata, rheological movements of body fluids, soft and hard biological matter. The nature of biological matter to resist deformation and if it occurs then return to original shape and size is quite ambiguous along with the physical forces interacting. How these forces act during various cellular activities like cell migration, phagocytosis, exocytosis, developmental movements in embryonic cells? This aspect seems to be more relevant in layered epithelial, mesenchymal and collagen tissues.[7]

ELASTICITY, PLASTICITY AND VISCOELASTICITY IS A SELECTIVE FEATURES OF MATERIALS

Elasticity is the physicomechanical ability of a material that exhibits the direct corelation between applied force and the degree of deformity of physical and biological material. The deformability may be in stretching form under force and regaining original shape and size when the force (stress) is removed. This feature is applicable to metals, polymers, rubber, and biological tissue, if not in totality at least partly. Thus, one may find this feature in the field of physics, biological sciences, biomedicine. The stretching and regaining original shape and size can be observed in blood vessels, cardiac muscles, body muscles. This faculty also fluctuates in accordance to body exercise, age, nutrition.

Under physics and materials sciences, the matter deforms (varying degree) under stress and recovers in its absence following 'Hooke's law. This feature represents the direct relationship between stress and strain and no loss of mechanical energy and reversible deformation. Loading and unloading curves follow same path. Each material exhibits specific elastic limit beyond which there is either permanent deformation or breaking of materials. This principle holds good for most of the materials and in the construction works from bridges to biomedical implants and dentistry. Further, the matter in material science show elastic and plastic elasticity. The deformation is reversible in elastic elasticity while it is not the case in case of plastic deformation.

According one of the principle of physics, that regulates the application of 'deforming force' and response of the object (biological or physical); the response of the object is in the form of partly or completely displacement (elasticity) (without) breaking or not able to regain original shape (plasticity); this law is called 'Hooke's law. So, Hooke's of physics expressed as direct proportion between force applied and degree of deformation occurred. The degree of elasticity and plasticity depends on the nature of the physical forms of object. As seen in engineering field the elasticity is denoted by Young's modulus, bulk modulus and sheer modulus but with respect to the biological matter (biological matter also exhibits the properties of physical objects with different modes of applications. Even biological matter experience physical stress, and attains related degree of strain; hardness of biological matter, like bone, cartilage and to some extent ligaments and tendon more, specifically, those which are associated with movements and locomotion. The unit of elasticity under these moduli is 'Pascal' (Pa).[8]

Matter exists as solid, fluid (liquid and gaseous) and ethereal form and matter in each state behaves differently. Their impacts are different when their external parameters change. The external physical forces are similar and affect the matter in solid form, fluid form and ethereal state; the matter behave differently under i.e., heat, electrical, magnetic or radiations. Since, a common man does not feel or experience ethereal state in obvious manner there exists inability to conceive the concept of matter in this state. Generally, one understands the dimensions of matter in three states (solid, liquid and gaseous) but the dimensions of matter in ethereal state are mostly obscure. In such scenario the concept of constitutive equation may or may waver and possibly becomes beyond our perception. The biological material can be conceived as solid, fluid (liquid, gaseous, gel like) and ethereal states. In all possibilities the biological material behaves differently correspondingly. In all these perceptions the matter and time concept is applicable when matter is in solid, fluid state but not in ethereal state.

Cell and biological tissues are not purely elastic materials like rubber ball or spring, because the biological cell and tissue exhibit 'time dependent mechanical response'. These biological matters dissipate some fraction of energy/load/stress they experience and get deformed, thus, are categorized as viscoelastic matter. This phenomenon is based on the specific molecular mechanism. The material and its mechanical concept are linked with the structure (constitutional) of the materials during its response when under load/stress/energy. Materials can be categorized on the bases of the degree of deformity they undergo. This deformity can be temporary or permanent. The degree of deformity is variable and it relates with the 'mechanical loading' and is relation to 'stress-strain test'. The mechanical stress is defined as the 'force per unit area' and its units are 'Pascal per square meter' (N/m^2). The stress can be in shear or normal. The degree of deformation is expressed as strain. The correlation between stress and strain is expressed based on 'constitutive equation'. This equation represents correlative interaction between the external physical forces and its response in the form of stress and strain quantitatively and qualitatively. In this aspect, the constituents of the material under study, play decisive role with respect to the behaviour. This correlation is expressed via 'constitutive equation' and it is based on the mathematical model which has the capability to describe the behaviour with respect to the external parameters related with the matter under question. This physical external behaviour is in relation to the form of stress, forces, temperature fluctuations of the ambient environment and any effective fields like electric or magnetic or electromagnetic in nature. In all probabilities, this constitutive equation exhibits relation between 'kinematic quantities' such as strain or deformation and 'kinetic quantities' like strain or deformation. These features are specific for each state, type, size and shape of the matter and these factors help in the behaviour of matter under 'material sciences' and also to the personnels linked with this branch of science. But, these mathematical representations may not explain the material behaviour concerning conservation of either momentum or energy as per the physical principles. The correlation between the impacts of external forces and the response of the matter is expressed in constitutive equations.

Linear elasticity or Hooke's law: In this case the stress is linearly correlates with strain up to some limits. There is no loss of energy and the matter reverses the deformation it has undergone due to the temporary duration of strain applied. In this case the loading and unloading courses follow same path.

Poisson's ratio (symbol: v pronounced as nu) represents the measure of Poisson's effect. (Named after French mathematician Simeon Poisson). This effect describes the deformation of matter (in solid mechanics) occurring in direction at right angle to the direction of applied external force, i.e., expansion or contraction. The matter is either compressed or expanded due to external force applied. It is the negative of the ratio between transverse strain to the axial strain. This deformation is in direction either transversal elongation or the axial compression.[9] Most of then materials exhibit Poisson's ration, and it has negative values between 0.0 to 0.5 nu. The soft matters like rubber, have higher modulus values as compared to sheer modulus. The matter of molecular organisms, their constitutional molecules resist to bending or deformation, stretching, e.g., steel, glass, concrete and other similar matters. These matters exhibit reorientation of load-bearing components and entropic elasticity. During reorientation of the molecules in such matters show constituting molecules arranged as loose rope and when subjected to load this arrangement appear to be tout rope like appearance.[10,11]

The biological tissues along with their ambient environment appear to be complex structurally and exhibit biological heterogeneity. As a part of the body biosystem constantly experience varied type of forces and undergo 'structural-functional relationship'. In all possibilities the cellular contractile force influences their substrate and also the adjoining cells and tissues. The modulus of elasticity which may be referred to as stiffness of the cells and the substrate modulate and affect different cells in many ways. Their conjugated influence is seen in the processes like their motility, gene expression, cellular proliferation and differentiation. The insight in to the mechanism of these influences provide the glamps of the application the such forces. This behaviour clearly indicates the biological matter react quite similar to any other matter. If so, the this opens the possibilities of application of concept of Poisson's effect in case of biological matter. The biomaterials show very good limits of supporting scaffold and transmit cells and forces of tissues; these features are expressed on the basis of elastic modulus and Poisson's ratio.[12] The elastic behaviour of scaffolding gets quantified as per the direction of loading but Poisson's ratio defines the extents of contraction or expansion in transverse direction and at right angle (tangential) to the loading direction of scaffolding.

The representation of physiological conditions of specific thickness of sheet of cells can be depicted by finding mechanical interactions occurring between microfilaments, microtubules, cell-adhesion pattern in a specific in-plane loading (forces that act parallel to the surface or cross-section of a structure). This mode helps to understand the pulsing conditions of negative in-plane Poisson's ratio as seen during uniaxial interactions between tests of embryonic epithelia. Parameters like fluctuations in thickness of layer of cells influence phenotypes. Further, this mode of algebra helps to understand gene expression, signalling pathways, and any other feature that may change the forces that act on the sample understudy.[13]

All materials in nature can be considered to be having positive Poisson's ratio (rubber, cork, glass, gold, copper, clay, alloys of aluminium, titanium, stainless steel, concrete etc., (≈0.3 to 0.5) in spite of the fact that there exist materials with negative and zero values. The prime difference between the positive valued matters contracts transversely under load/force. The materials with negative Poisson's ratio expand in axial as well as in transverse directions. Examples of matter with negative Poisson's ratio (also called auxetics) are crystalline mater, carbon allotropes, foam, polymers, laminates etc. The negative Poisson's ratio is intrinsic feature of the materials and cannot be adjusted.[12,14,15] If one wants to manipulate this feature, one has to regulate the pore-interconnectivity and interior architecture of matter, both these aspects are difficult to handle. The man-made matters are easily these features are suitably adjusted and put to desired purposes.[12]

There are reports on the presence of negative and Poisson's ratio materials in the biological materials. The Poisson's ratio is very helpful in studying the interactions between cells and the biological materials and the tuning of Poisson's should be attained and maintained.[16,17] This aspect is very significant in the 'tissue engineering'. In some cases, with respect to biological tissues a material with negative and/or Poisson's ratio seems to be precise functionally emulate the interaction of the original biological tissue, polyethylene diacrylate is one such materials.[12]

Nonlinear elasticity: In this case stress in nonlinear in nature and relates to either higher or lower degree of strain. One can observe those materials which exhibit plasticity, viscoelasticity and/or nonlinear tendency, their behaviour under application of external force gets illustrated through time dependent or nonlinear responses.

Elasticity of a matter and biological tissues play role in the analysis of its structure, mechanics of non-Newtonian and Newtonian fluids, Thermal expansion, pressure due to pores, electrical and magnetic fields. The symmetry isotropic and/or anisotropic symmetries of matter, homogeneity and directional related entities. The linear elasticity is mostly seen in solid objects and explains the deformity of matter in relation to stress and strain (stress) it is the internal force that tries to restore force per unit area arises in material in response to the externally applied force/load. It may be defined as internal distribution of force that resists the deformation ($\sigma = Force/area$). The concept of linear elasticity expresses that the small deformations (may be called infinitesimal or very close to zero but not zero) strain and linear relationship between the units of stress and strain is direct sequential relationship, hence, this is regarded linear in nature. This relationship is valid as long as the 'yielding point' is not attained. 'Yielding point' is a condition or a stage when elastic behaviour stops and plastic behaviour sets in. In normal practice, this concept is more accepted in material science but to some extend it is likely to be applicable to biological tissues also, more specifically bones, ligaments and tendons. Structurally, these tissues exhibit properties very similar to solid materials like hardness, tendency to act as stiff tissues in comparison to other tissues like muscular and cellular tissues. Generally, the elasticity concerned as a parameter in the field of analysis of material and finite analysis of elements used in engineering. The stress-strain curve shows the 'yield point' at which elasticity becomes limited and the start of beginning plastic behaviour of a given matter. Beyond the yield point the def7ormation occurred remains for ever and is non reversable, this state is called 'plastic deformation'.

ARE BIOLOGICAL MATERIALS SIMILAR TO PHYSICAL MATTER?

The ongoing discussion directs that the biological matter i.e., cells with its organelles, components of its ambient environment along with its entirety is a product of matter. Whatever it feeds on, its body represents a systematic and synchronized kinetic aggregation that represents 'life'. There are observations that reflect on the materialistic nature of biological matter as this complex matter exhibits good numbers of properties that follow the principles of physical matter and science. These efforts facilitate the understanding the applications and mechanisms of mechanical/physical forces on the biological matter may it be cellular or body-fluids. The active role of mechanical forces and the principles during the embryo formation, development, cellular movements during embryonic development and body fluid. Even response-stimuli, transduction, immune and pathological status, healing and rejuvenation along with sustenance processes are governed by the physical forces. The problem arises when it is very difficult to record or document the impacts of these mechanical forces on biological materials very subtle, feeble and fast. One needs equally delicate and sensitive gadget. These gadgets must enable the observers to record the broad range of responses. Thus, though biological matter is simple but has become a multidisciplinary topic to ponder and delve.[18]

CELLULAR PLASTICITY: This ability describes the proficiency of a cell to regain its original status after undergoing deformation or capacity to alter the phenotype or function in accordance to its environment or internal cues. This mode of cellular alteration is applicable during dedifferentiation, transdifferentiation and lineage-switching, allowing cells to adapt during development, tissue repair, or regeneration.

'Dedifferentiation' a cellular process in which a post mitotic cell, specialized, mature cells become a less specialized, attains more primitive state or becomes stem-cell like within its own lineage, it enters cell-cycle, proliferate into a new functional cell playing crucial role during regeneration and tissue repair more specifically in plants and lower animals. 'Trans-differentiation'-a process in which differentiated cell or cells (specialized) somatic cell directly change their identity/identities and becomes another type of specialized cell without first changes into any intermediate, pluripotent stem cell stage. 'Lineage switching'- a rare process and occurs in hematological malignancies. It is observed during post-chemotherapy or immunotherapy such as CAR-T therapy. A primary acute leukemia, in this case, the leukemic cells when relapse, they change from their original lineage i.e., originally these are lymphoid leukemic cells (B ALL), into different lineage i.e., 'acute myeloid leukemic cells (AML)'. During this change-over there can be partial or total change into immunophenotype and have poor clinical outcome. These processes permit cells to adapt during development, tissue repair or regeneration.[19] Cellular elasticity, rigidity and viscoelastity play their structural and functional role in maintaining the cellular structural integrity. On the onset of any infection, immune response and pathological status affect these cellular features and result in disturbed cellular efficacy.

Under normal conditions, original basic integral structure and functionality is maintained but when a cell faces some external, internal 'cues' or fluctuations the cell exhibit some changes in its shape and size and after the change gets over the cell regains its original/normal structural and functional status. This feature reflects on the extent of the memory of cell about its basic original shape, size and location along with its functional limits or its ability to regain the original structure and functionality. The cellular plasticity is useful during the processes like differentiation, tissue remodelling, migration, developmental process, regeneration and maintaining homeostasis. All these ensure the appropriate cellular structural, functionality and provide scope of physical, biomolecular adjustment.

It is of common observation that cellular plasticity is lost or becomes totally dysfunctional during the stages of cancer, malignant transformation therapeutic resistance. Although these cellular features are basic but reflect great deal about developing required therapies and in the direction of varied medico-pathological status in an individual.[19,20,21] Some of the cellular processes like epigenetic modification, accessibility of chromatin materials, expression of genes and signalling-pathways related to growth factors, cytokines, signalling communication with the components of extracellular matrix, play significant regulatory role in the cellular plasticity. The group migration of cells in an important process during morphogenesis, maintenance of homeostasis, and in physiopathological conditions. This phenomenon is the coordinated and synchronized complex process involving mechanical interactions between cells-substrate, cell-cell adhesion and specific viscoelastic behaviour. On the onset of pathological conditions, more specific, cancer; the cellular plasticity is responsible for tumor heterogeneity, metastasis and resistance to therapeutic applications.[19]

There is interrelationship between the mechanical i.e., compositional, structural integrity, and cellular plasticity, elasticity and rigidity. Thus, when one changes this balance there is a secretive trigger in expression of gene, cytoskeleton, and the components of extracellular matrix and glycocalyx an then cell membrane, this triggering of change travels to the cell and its parts; a decision is made to respond specifically to that mechanical change/stress and in due course of time some mechanical changes ensure the cellular adaptation. In this process plasticity and elasticity both, there is are alterations in components of cytoskeleton, extracellular matrix, glycocalyx which induce cellular biomolecular adjustments (either minor or major). There may be adhesion, cohesion or repulsion during these alterations. Overall, these adjustments reflect on the degree of deformation, and regaining the original shape and size of the affected cell. These processes are better illustrated during developmental process, wound healing and remodelling during tissue adaption.[22]

A vast complex of biological pathways related to proliferation, metastasis, energy related metabolism, infiltration and trespassing-tissues, cancerous-metastasis, under the influence of concerned genetic interplay. A factor -1A, (HIF-1A) linked with metabolic and pathological molecular processes when the test tissue and adipose tissue results in oxidative stress, inflammation, and induce diabetes and/or cancer. Structurally, HIF 1A basically, primarily regulates major transcriptional process pertaining to development and progress among the test cells. Structurally, this factor is ‘helix-loop-helix PAS with protein domain’. This factor also plays a gene-expression controlling role during angiogenesis, glucose metabolism, inflammation and oxidative stress. In individuals suffering from obesity and hypoxic adipose-tissue , the rate of expression of H1F-1a, factor elevates and results in chronic inflammation, and dysfunctioning of adipose tissue.[23] During these physiopathological conditions cellular components of exhibit mechanical continuum as seen in materials sciences, the cellular feature i.e., elasticity exhibit its resistance towards physical forces that influence the natural size and shape of the cell prior to the application of distortion and its release. The cellular ability to response and regain the materialistic cellular dimensions after the force is not in use. This force may be due to the changes in the intra and extra cellular fluid and or ambient fluid. Gel like biological materials exhibit deformation under force (adequate load), in addition to changing the shape these biological materials also show resistance to do so, (plasticity). Thus, over all the elastic behaviour of materials, specifically in case of metals, each metal possesses a specific size, shape, of ‘atomic lattice’. This lattice changes under the deforming force and regain its original form after this force is removed. In cases rubber and other polymers, the polymer chains undergo stretching under the deforming force; these polymer chains attain their original position in the absence of this deforming force.[24,25]

On can observe the applications of elasticity, plasticity and rigidity on biological materials, like epithelial muscular, connective and conductive tissues. All these biological tissues (cellular organisation) follow these principles.[26] There are specific cases of biological materials like stem cells, cancer cells (pathological cells, sickle celled red blood cells). Stem cells exhibit the migration and multiple-lineage-differentiation processes. Cancer cells infiltrate and invade the normal healthy tissues while the tissue exhibit repairing proliferating processes. All these are possible only on the bases of application of elastic, plastic and viscoelastic nature. Thus, basically, cellular elasticity and cellular plasticity are the functional bases of cellular shape, structural and functional resilience and regaining the original form and shape. These biological cells have functional and phenotypic adaptability. Thus, the cellular dynamics towards the physicochemical cues and responses (sensitivity), development, regeneration, transduction, progression of pathological conditions, healing process, are all due to these physical properties. Further, the current applications like regenerative medicine, remedial therapy and tissue engineering have physical foundation to sustain life.

TISSUE VISCOELASTICITY

This is the ability of a matter which helps in retaining its elastic energy as the solid matters do and loose mechanical energy as fluids do. In simple terms, (i)- the viscoelastic materials exhibit features like time-based deformation as long as load or force persists. (ii)-These materials have ability to hold the stress and in due course of time till stress declines, i. g., this tendency is regarded as ‘relaxation of stress’, (iii)- these viscoelastic materials have capacity to dissipate energy which is mostly in the form of heat. This feature indicates that the loading-process of external force follows different route (path) and when this external force is reducing or load is declining, the paths is different, i.e., force/loading path and unloading path are different (exhibit hysteresis phenomenon), (iv)-When viscoelastic materials exhibit temperature related behavior. At relatively higher temperature these materials behave like viscous matter and less elastic and at lower temperature it is more elastic and less viscous. The viscoelastic nature of biosystem indicates the energy storing and dissipating phases. During these phases, the cells, tissues and the organs contents get displaced or shift from their normal conditions when force is applied and rearrange after the force is removed. In most cases the biological matter exhibits phase of relaxation and regaining original position and this behaviour is time dependant (time domain) and frequency dependant (frequency domain). The time domain represents the changes between stress and strain in relation to time. The frequency domain concerns with the interrelation between storage and loss moduli in relation to angular velocity. The viscoelasticity with reference to linear models is applicable to viscoelastic liquids like Maxwell model (any simple rheological system of viscoelastic matter, it is combination of Hookean spring-elastic solid, and Newtonian viscus fluid. Expresses stress relaxation effectively and predict continuous, linear expansion under a constant stress) and Jeffreys model (linear viscoelastic model exhibits elastic and viscous behaviour). It is applicable to viscoelastic solids like Kelvin-Voigt model (basic framework in viscoelasticity having elastic and viscous features), the Zener model (simplest standard model expressing stress relaxation and creep recovery mode) and Four-parameter model (connected all the four mentioned models as one unit). There is different model for jamming state. Thus, one may say that viscoelastic is case specific.[7.27.28] Among the cellular functions, migration of cells is of crucial significance, more so, during morphogenesis, during the embryonic developmental period and homeostasis in healthy state. Even when during pathogenesis, the movements of cells is of significance. Collective and individual cellular migration takes place in synchronized manner involving cells, cell-substrate interactions and cell-cell adhesion. The mechanical and dynamic behaviour of these components induce viscoelastic tendencies in these components during migration of the cells. Further, role of cytoskeleton, (actin in particular), cellular adhesion, extracellular matrix plays major role and its mechanism need thorough understanding under healthy and diseased conditions.[29]

VISCOELASTICITY (RHEOLOGY-STDY OF DEFORMATION AND FLOW OF SOFT TISSUES AND LIQUIDS)

NEWTONIAN FLUIDS/LIQUIDS HIGHER VISCOSITY; MAXIMUM ENERGY DISSIPATED (WATER, DRINKS	**NON-NEWTONINAN, VISCOLEASTIC, MODERATE ENERGY DISSIPATED, MEDIUM VISCOSITY AND MEDIUM ELASTICITY LIQUID SOLIDS Examples-polymers, paints, silly putty, biological matter**	**HOOKEAN MATERIALS, ELASTIC MATERIALS, MINIMUM ENERGY DISSIPATED, LEAST OR NO VISCOSITY, MAXIMUM ELASTICITY SOLIDS**

To simplify the definitions: the solids have spring like behaviour i.e., solid deform under stress (may not be observed with unaided eyes) when subjected to stress and immediately attains original shape once the stress is removed. Materials that show distinct flow or movement are viscous and are referred to having viscosity, i. e., these resist external force (strain) in a given time. Strain relates with time as long as the external force is applied. The materials that complete the cycle of application of stress and its release, the energy applied is not completely recovered. It dissipates between the duration between stress and strain. The viscoelastic material when stretched remains as the deformed size and shape and the energy used to bring this change drops in due time. Materials when subjected to persistent external force maintain their deformation for longer period of time.[28]

BIOLOGICAL TISSUES IN RELATION TO ELASTICITY, PLASTICITY AND VISCOELASTICITY

A biological cell has an ability to change its shape, size, as per the need for its survival within specific limits. Generally, this describes the ability to reversible deformation under mechanical stress. These needs/conditions may be intracellular and/or extracellular in nature and are due to fluctuations within intra and extra cellular cues from ambient environments. The basic compositional aspects of a cell show specific shape and size, an organized assembly and distribution of specific groups of biomolecules. There exists a dynamically stable homeostatic state within the intra cellular components, cytoplasm and the ambient fluid media. This is an optimum homeostatic state and it has to be maintained throughout the cellular lifespan. There are changes in the shape and size of cells during life activities, like locomotion, feeding, phagocytosis and endocytosis. The biosystem responds to any type of external as well as internal cues/stimuli but these are restricted to their minimum limits initially. These responses or movements may be in the form of moving away or attacking, or being still. The fluctuations occur within specific limits. If the stress or strain is intense then these are harmful and painful conditions. Cellular components such as cytoskeleton, involving actin filaments, microtubules, along with intermediate filaments, the mechanical features of cell membrane and other membrane of the cell organelles also participate in these cues-response interactions. The extracellular matrix, intracellular and extracellular pathways also participate in these interactions.[30] These pathways are tuned to establish optimum suitable structural and functional efficacy of the related units. Further, these abilities ensure the cellular responses to the various cues and undertake processes like, proliferation, differentiation, if needed, migration, colonization, avoiding unpleasant, toxic and insulting components. These responses show a tendency of timely repairs in case any disruption or damage and successful cellular survival. The ability of temporary cellular deformation facilitates to tide over unavoidable forces and may hinder survival. Under severe infection or pathological state, the abnormal deformities may result in malignant transformation of normal and stem cells, which can result in pathogenesis or progressive tumorigenesis.[31,32]

The biological tissues along with their ambient environment appear to be complex structurally and exhibit biological heterogeneity. As a part of the body of biosystem constantly experience varied type of forces and undergo 'structural-functional relationship'. In all possibilities, the cellular contractile force influences their substrate and also the adjoining cells along with the tissues. The modulus of elasticity which may be referred to as stiffness of the cells and the substrate modulate and affect different cells in many ways. Their conjugated influence is seen in the processes like their motility, gene expression, cellular proliferation and differentiation. The insight into the mechanism of these influences provide the glamps of the application of such forces. This behaviour clearly indicates the biological matter react quite similar to any other matter. If so, then, this opens the possibilities of application of concept of Poisson's effect in case of biological matter. The biomaterials show very good limits of supporting scaffold and transmit cells and forces of tissues. These features are expressed on the basis of elastic modulus and Poisson's ratio.[12] The elastic behaviour of scaffolding gets quantified as per the direction of loading but Poisson's ratio defines the extents of contraction or expansion in transverse direction and at right angle (tangential) to the loading direction of scaffolding. All materials in nature can be considered to be having positive Poisson's ratio (rubber, cork, glass, gold, copper, clay, alloys of aluminium, titanium, stainless steel, concrete etc., (≈0.3 to 0.5) in spite of the fact that there exist materials with negative and zero values also. The prime difference between the positive valued matters, they contract transversely under load/force. The materials with negative Poisson's ratio expand in axial as well as in transverse directions. Examples of matter with negative Poisson's ratio (also called auxetics) are crystalline mater, carbon allotropes, foam, polymers, laminates etc. The negative Poisson's ratio is intrinsic feature of the materials and cannot be adjusted,[12,14,15] If one wants to manipulate this feature, one has to regulate the 'pore-interconnectivity' and interior architecture of matter, both of these aspects are difficult to handle. The man-made matters have these features and can be suitably adjusted and put to desired purposes because of their specific physical features.[12]

EFFECTS OF THE CHANGE IN THE DEGREE OF ELASTICIY, PLASTICITY, VISCOELASTICITY

The cellular elasticity is also referred to as 'stiffness' or rigidity'. The change in the degree of elasticity (stiffness or deformability) disrupts the homeostasis of the epithelial cells. Change in elasticity i.e., stiffness in epithelial cells disrupt the ability of the tissue to manage the mechanical stress, ability to act as barrier for the exo and endo molecules and cell migration. The prime cause of stiffness is the alteration in the actomyosin contractability.[30] Since, the epithelial cells form the inner lining of most of the organs, blood vessels, cavities, in the body of vertebrates it plays vital governing role and act as barrier integrity, wound healing morphogenesis. When there is a change in the elasticity of these cells many downstream impacts take place.[33] When elasticity (stiffness) increases the epithelial cells become abnormally rigid and lose their functionality with reference to the ambient environment. These functionalities include wound repairing gets delayed and impaired.[34] These cells become prone to mechanical injuries whenever the stiffness increases and ensure detachment whenever tissue gets stretched.[35,36] As the development proceeds and as an individual ages, the epithelial cells lose their elasticity and become more rigid mechanically. Cytoskeletal F-actin microfilaments play major role in increasing stiffness in these cells. This status leads to the loss of elasticity of the tissue organs.[37] This feature regulates the physical characteristics; the elasticity of these cells is very dynamic and is controlled by actin cytoskeleton and intercellular junctions. The changes in the status of elasticity have high physiological impacts, like, tissue remodelling and morphogenesis. Under this impact, tissue folding takes place which includes dynamic changes in contractility and cell elasticity which in turn controlled by actomyosin ring for bending, stretching and folding during embryonic development.[38]

Under biological elasticity compositional component also plays very significant role during their functionality. Primarily, elastin protein is forms around 90% by volume ensheathed by fibrous fibrillin. The elastin molecules store energy of deformation and furnish 'snap-back-force'. The peripheral microfibrils guide the fibers to assemble and maintain tissue surrounding them. The molecular structure of fibrin is very disordered and flexible. This molecule and its heavy cross-linking orientation (forming a net-work that helps to distributes the stress) permits easy stretchability under lesser or smaller loads. These fibres are responsible for the rigidity, shape, size and physical strength of a given cell. These fibers also and their functions depend on the accessory proteins. These accessory proteins are linked with each of the filament and the component of the cell. These proteins regulate, coordinate the congregation of these filaments with specific cellular location. Motor proteins play significant role in the functioning of components of cytoskeleton and the specific location of the cell.[14,30]

The constituting molecules in a tissue/cell are arranged either in an order or in a disordered manner. These molecules have some energy which hold them in that specific manner/mode. Thus, a molecular state is holding some energy and it is called 'entropy'. When energy (stress) is applied same energy tends to rearrange the constituting molecules, thereby, the 'entropy shifts'.

Under this condition, energy of the molecules get rearranged and/or get displaced temporarily or permanently causing temporary or permanent deformation. This reflects on the physicochemical nature of cells to be a mechanical and chemical machines that utilize energy under the influence of applied force; this physiological scenario also influences the extracellular matrix and interstitial fluid alike.[14,30]

In case of fibrin, the molecules are present in quite disorderly manner and exhibit the chances of rearrangement under the applied force/stress, moreover, these molecules have cross-links and form network. The cellular components like cell membrane, cytoskeleton, glycocalyx, and the extracellular matrix along with its interstitial fluid concerned with forces originating due to the cellular dynamic material involving viscoelastic features specifically to the tissue.[14,30]

When energy/force is applied the disordered molecules get rearranged in more orderly manner resulting in reduction of entropy (higher the degree of disorder higher is the entropy). In case of fibrin, which constitutes elastin tissue, this entropy-based mechanism provides around 70% of recoiling force in the tissue. Since, the energy tries to maintain a balanced state the stretched molecules have tendency to come back to their natural disordered manner i e., from higher-entropy state to the normal state, as a result, the molecule/tissue attains its original shape loosing minimal of energy. Similar basic principle is applicable to rubber-band, polymers, as the constituting molecules prefer to attain their disordered state rather than orderly state. The entropy governed structural disorder facilitates the structural cellular adaptability. The cellular variability and adaptability reflect the structure of a cell at a given time.[39]

The biological cells and tissues exhibit fairly good range of mechanical properties. These properties enable them to coordinate with their respective ambient structural and biomolecular constituents and accomplish their respective functionalities. Generally, these accomplishments involve protein tyrosine phosphorylation and cortical forces produced by myosin. These factors are the part of mechanism involved in the cellular interactions with their respective surrounding biological environment and add to the complexities of the organisms.[40]

The connective tissue is made-up of proteins fibers. These protein fibers and few cells are responsible for active connectivity among the various tissues and organs in a biosystem. The connective tissues in most of the system-organs consists of elastin which is well distributed in the tissues of the organs including blood vessels, reproductive tubular structures, ureters and any organs that need to be flexible. These organs have to tolerate some fluid pressure as these act as fluid conducting tracts. The blood vessels are under constat pressure originated due to systolic and diastolic cyclic movements. Even the lymphatic vessels play major role in distributing and to maintain homeostasis by circulating lymph within body. These parameters play significant role in maintaining flexibility or elasticity or rigidity of cells and tissues. Primary functional feature of these vessels is to conduct blood and lymph. This feature permits to accommodate the fluctuations in the pressure (pressure spikes) in the fluid flowing through them. The pulse of heart is measured because of this feature in the blood vessels present in the peripheral zone of the body. Thus, flexibility is very essential and it relates with histological make-up of these vessels. If their walls lose the flexibility, their ability to accommodate the fluctuations of pressure gets affected. This condition is referred to as ‘hardening of wall of blood vessels’. This may occur due to senescence, personal habits and physiopathological disorders.[41] This state also concerned with cardio-vascular disorders. Quite often the hardening of blood vessels is seen in diabetic condition. The blood glucose (access) interacts with the proteins like collagen and elastin then undergo glycation process, the end products of this process affect the elasticity of blood vessels. The blood sugar adds to the cross-links and result in disturbed molecular orientation in the fibrin molecules. This interaction grossly affects the cushioning effect of the walls of the blood vessels and contribute to the cardiovascular status. Even lungs have a functional flexibility during the respiratory movements. Diaphragm, intercostal muscles, and the elastic tissue present in the pulmonary histological make-up play significant functional role during pulmonary respiration (inhalation and exhalation process). Any destruction to the pulmonary histological structure like destruction of air sacs, dysfunctioning of elastic (fibrin structure) results in loss of recoiling efficacy of the lungs. The amount and rate of areal flow get affected resulting in loss of pressure-volume corelation between the air in lungs and the air in ‘air sacs’ of lungs. This condition affects the evacuation efficacy of lungs. Similar condition is seen during emphysema.[42,43]

When cells are cultured, they interpret the nature of the surface to which they contact. This behaviour reflects on their ability to manipulate the traction-mediations of the concerned cells and the nature of adhesion cells undergo. This interface action depends on the ligands for adhesion offered at the surface and cell membrane (depending on the surface properties of cell and the substrate. This tendency of the cellular interaction is essential mechanical phenomenon as far as material science is concerned.[15]

SKIN ELASTICITY AND IMPACT OF SENESCENSE

It is of common observation that whenever we pinch the skin, thereafter, it retains its original position. This feature is related to the ‘presence of elastin and collagen fibrous network’ in the dermal region of the skin. In due course of time, this network of elastin and collagen gets either degraded or disoriented because of chronological aging and the UV radiations: this effect is 'elastosis' or 'solar elastosis'. The UV radiations in the sun-light enhance the formation of elastic and the newly formed elastin fiber get arranged in a non-appropriate manner. This incorrect rearrangement results in disturbed protein scaffolding in an incorrect ratio and this results in the formation of 'thick disoriented clumps' which are functionless and in disorganized state. This uneven net-work reduces the recoiling efficiency of the dermal elastin-collagen net-work. Another impact of UV radiations includes the elevated enzymatic activity of ambient structural materials of the matrix forming 'biological debris'. The aging process results in delayed clearing process which causes the accumulation of damaged matter. This whole process converts the thin and shining skin in to leathery, thick and sagging structure which has lost the recoiling efficiency.[43-a]

There is a suction device called 'cutometer' to measure the elasticity of skin. Basically, it pulls the skin under controlled such vacuum and releases the skin. The mechano-sensers on the skin regulate the stretching and recoiling of the skin. Thus, there is a time and extent of the skin gets sucked and the time it recoils. This ratio provides the initial stretch and the elastic recovery. This practice helps to evaluate the age of the skin, degree of antiaging treatment, resilience of the skin.[44]

Tendons and ligaments have immense role in the movements of organs and the organism among biosystems. The working of these tissues is based on the 'elastic-versus-plastic' out-line of physics. Tendons tissues are robust, powerful and tough in nature and have primarily collagen fibers. These are able to store and release energy and this ability enable them to facilitate the running and walking processes. These act as mechanical bridges to transfer force of movements and the stability of joints. Their constitutional components the collagen fiber function as rigid stabilizers providing 'spring like facility' (absorbing impacts during jumping, falling, running, standing, sitting, getting up etc. Under routine, day to day life, collagen present in tendon fibers stretch and regain original size while doing so these store the energy. The major non-collagen constituents of these fibers are small proteins like small leucine rich proteoglycans (decorin-control the diameter, biglycan and fibromodulin helps in fibrogenesis of collagen and control the fusion of fibrin, lumican), elastin and lubricin-anatomical bundles of skeletal muscle and nerve fibers wrapped in connective tissue, these are the functional units for movements), glycoproteins (tenascin-C, located in pericellular matrix and maintains the matrix), elastin and lubricin-present in fascicles and help in gliding and viscoelastic recovery), tenascin-C -present in injured area and maintain mechanical strain in matrix), aggrecan-present in high amount in compressive zones of tendon, hydrophilic and maintain stiffness and compressive resistance, and tenomodulin-a marker of tenocytes present in pericellular matrix and helps in growth and healing of tendon. These non-collagen components establish directionality of fibers, elasticity and adaptability of tendon.[14,45]

There is a critical threshold point known as 'deflection point'. When strain is above this threshold point the elastic nature of tendon breaks down. There are some functional changes in collagen fibers, like, sliding of collagen fibers past each other, their stretching reaches at molecular level, the amount of sheer force increases so much so that the structural configuration gets smashed chemically. This stage is called 'transition stage' and at this juncture elastic formation shifts to plastic formation. Any increase in loading the tissue renders rupture of bundle. When the suitable mechanical loading (strain) remains within the limits of elastic range the cellular signalling pathways send the necessary information and the rebuilding gets switched on. The process of rebuilding and gaining more strength increases and the stronger tissue is the result.

The recoiling ability of elastin network is maintained with help of 'lysyl oxidase' enzyme. This enzyme is copper dependent and ensures the cross-linking structure of collagen and elastin in extracellular matrix and provides the structural integrity to these tissues. This enzyme changes lysine residues into reactive aldehyde (also known as allysine), this component is very essential for the stability of this tissue. During cancerous and cardiovascular disorders, this enzyme activity gets irregular resulting in fibrosis. The mechanism involves 'oxidoreductase' process using copper ions as an enzyme activator in catalysing oxidative deamination of lysine and hydroxylysine residues. The activity of this enzyme plays significant role during fibrosis, cancer progression, skin/wound healing and reinstating firmness of skin.[46] Dietary copper is very important for this enzyme activity. If required quantity of dietary copper is not present then this interaction gets affected and even if this enzyme is formed and required amount of copper is absent then this interaction is not successfully carried out. This condition may result in deficient cross-linking of collagen and elastin molecules and the connective tissue matrix becomes poor in performance and structurally. Vitamin C plays a supporting factor for the synthesis of collagen and works as coworker in the with elastin in the concerned tissue, otherwise the maintenance and repair of the concerned tissue become ineffective. The tissues in skin, blood vessels, lungs and other elastic tissue perform at much lower level than the normal level.[44]

ELASTICITY IN MUSCULAR TISSUE

In anatomical aspects, it reflects on the stretching ability of the muscular and connective tissue and regaining its original shape and size or before load (stretch) being added and after load (stretch) being removed. Conceptually and compositionally, muscular and connective tissues are made of fibers (mostly proteinaceous in nature) and exhibit their respective 'resting length' and length under fully stretched (contracted length and stretched length). This functionality of muscular and connective tissue is of

great significant in relation to the all types of movements.
Physically, muscle elasticity correlates with the performance of work. Expansion of muscles is referred to as extension. There is some amount of contraction prior to extension; this behaviour expresses their 'high elasticity'. Muscles have a capacity to respond to change and these tissues react to the dynamic demands imposed on them. This is considered as 'demand elasticity'. This complete configuration provides specific structural integrity that facilitates smooth and synchronized movements.[22]

Animal cells along with muscles exhibit contractility which is a fundamental aspect of their functionality which include cellular migration, division and morphogenesis and the related movements. Along with other features, actomyosin-mediated mechanism plays significant role in preservation of contractility of animal tissue. It acts as a functional bases for creating mechanical stress during muscle contraction, cellular movements, cellular processes like migration, division and morphogenesis. This actomyosin mechanism is well elucidated in case of striated muscle-fibers not in case of smooth muscles. The sarcomeric organisation has been found to generate regulate the transmission of force through.[47]

As far as elasticity in animal muscular and connective tissue is concerned, this tendency is accomplished based on excitability, contractibility and extensibility. It may seem that the physical concept may not be applicable in biological materials. Cell is a biological matter well equipped with specific mass and volume along with some intrinsic and extrinsic biophysical limits. These features enable it to perform life activities as an individual entity. During its life span, it is bound to face some favorable and some adverse circumstances. Under normal structural and functional limits, it faces hydrological forces; these forces are bound to affect its mechanical, physiological, biochemical, biophysical structural and functionalities. It is fixed in location like localized in specific position and in specific position (so the term 'fixed' position within a tissue). In this situation, there are more or less fixed set of molecular and physical forces, in these circumstances cells are facing the forces of a flowing body fluid and the forces due to the substrate materials. These forces exert physical, molecular and hydrological set of forces of varying intensities within specific limits. These sets of forces are likely to vary during infections, inflammation, pathogenesis, repair and healing process, developmental stages and during other cellular functions like cell-division, response to pathogenesis. Even during these processes cells exhibit their 'affected properties' related to rigidity, (elasticity), plasticity and viscoelastity. Thus, these features constitute its fundamental structural and functional concepts. These features play significant roles while it delivers its responses to the internal as well as external cues and stimuli. Further, these features are also functionally important during its survival and sustaining the unsuitable life conditions to ascertain its successful survival in order to complete its life span. During the course of these interactions rigidity (stiffness), plastic and elastic nature/conditions are due to some conformational changes including biomolecular, electrostatic and behavioural changes which ensure its survival chances under the stressed conditions. At cytological level, there can be a change in its cytoskeleton, polarity, electrostatic potential, changes in its inter cellular connections links/junctions. These changes are reciprocal to the degree of stimuli and response, of course, on the general cellular health (30). The related studies help to understand the mechanism of tissue repair, tissue culture, tissue engineering and pharmacological preparations and remediations.[20,21]

VISCOELASTIC NATURE OF BIOLOGICAL CELLS AND TISSUES

In the field of physics, viscoelasticity relates with the expression of the physical matter under physical force that deforms the matter in question. The mechanism involved in such behavior of the matter like, polymers, composite physical matter, biological matter under varied conditions of stress and strain. The viscoelasticity is expressed in the form ability/degree of response of matter to the stress and strain during the time period of application of stress and the strain. This parameter is one of the most essential while designing the optimum structure and devices in the field of engineering and biomedical fields. The viscoelastic response to the external force, load or pressure of matter is time depended and as combined aspects of elastic and viscous behaviour. Initially, the load/stress on the material is in the form of elastical deformation (cannot be observed with unaided eyes) and this application of load extends for a period of time till it can deform viscosity. This expresses that the material has absorbed energy, dissipate stress. This state of complex behavior reflects on the overall behaviour of the matter under varied conditions of loading. The viscoelasticity of matter readily predicts the nature, functional aspects, ability to bear (hold/sustain) short- and long-term load bearing conditions, possibly, the age, duration of load bearing capacity, tolerance of vibrations and cycling loading. These features are essential in the field of materials science , engineering and biomedical engineering *(tissue healing, tissue regeneration in vitro)*.[48]

BIOLOGICAL AND PHYSICS CORRELATED CONCEPT OF ELASTICITY, PLASTICITY AND VISCOLEASTICITY IN BIOLOGICAL TISSUE

Cell and biological tissues are not purely elastic materials like rubber ball or spring, because the biological cell and tissue exhibit 'time dependent mechanical response'. These biological matters dissipate some fraction of energy/load/stress it experiences and to get deformed, this phenomenon is also referred to as 'viscoelasticity'. This phenomenon is based on the specific molecular mechanism. The material and its mechanical concept are linked with the structure (constitutional) of the materials during its response when under load/stress/energy.

It is of common observations that biological cells and the tissues along with their intracellular components and the components of extracellular matrix all these behave as one functional unit. This structural and functional unit exhibit energy dissipation and storage of stress (energy). This biological structural and functionally synchronized unit participates in the phenomena like growth, motion and homeostasis. The viscoelastic nature and behavior, both are the result of mechanical and biomolecular characters of the cytoskeletal network and cooperative interplay. These features primarily regulate the behavior of tendons, brain and ligaments. The macromolecular and intercellular inter and intracellular interactions play significant role in the expression of viscoelastic behavior of a biological tissue.

IMPACTS ON THE STRUCTURAL AND PHYSIOLOGICAL ASPECTS OF ELASTICITY, PLASTICITY AND VISCOELASTICITY OF CELL AND TISSUES

There is a structural and functional association between cells, extracellular matrix and the interstitial fluid. All the three components have to maintain a homeostatic intercellular ambient environment to achieve specific physiological goals. These three components facilitate the synthesis and functionality of the biological tissue as well as individual specific functions in coordination with the whole biosystem.[25,49] In spite of structural and functional mutual association, the characteristics of biological tissues relate to physics are equally essential; the physical behaviour to these components towards the external physical forces, pressures which are applied either accidently or intentionally like exercise, sports, physical work or exhaustion, etc. The physical force applied can cause stress and strain to the cells, extracellular matrix and the interstitial fluid. When such forces are within the limits of tolerance (of tissues) and may or may not be resulting in permanent damage or deformation to the biological entity as whole, affect the functionality.

There has been intense research related to elasticity, stiffness in the biological tissues. These histochemical conditions related functionally to the cellular processes such as cellular spreading, growth, proliferation, migration, differentiation, embryonic development etc. During these cellular functionalities, the extracellular matrix plays significant role that help in cellular and physiological manoeuvring with a biosystem. The mechanisms of these phenomena involved are complex. This aspect can be investigated using specific elastomers, like, linearly elastic polyacrylamide hydrogels and polydimethylsiloxane (PDMS) as coating materials for the extracellular matrix proteins. This coating treatment ensures that degree of stiffness and their behaviour similar to natural biological tissues. Thus, this step is mostly used for accessing the degree of stiffness and investigation related to mechanical impacts on biological cells and tissues *in vivo*. Although, natural biological cells and tissues do not come under liner elastic material instead function involving more complex mechanism as these are considered to be viscoelastic. These biological materials exhibit mechanical plasticity and nonlinear elasticity. The observations indicate that the mechanical behavior of biological tissues and extracellular matrix facilitate the understanding of mechanisms involved in regenerative medicine, tissue culture, healing process and cellular functional phenomena.[20]

There are some of the specific parameters that influence the structural and physiological aspects of biological materials. Some of them are permanent i.e., constantly occurring in the biosystem. These are the locomotory movements, chasing the preys, running away from the predators, complex conformation of joints and their movements. These movements take place as per the need or as regular physical activities. Stationary muscular movements like heart systolic and diastolic movements, gastric and pulsating movements of peripheral blood vessels. All these interactions take place in synchronized orchestrated manner. One can notice the difference between stiffened state or normal state of tissues. Under these conditions the components of a tissue i.e., cell, interstitial fluid, extra cellular matrix exhibit external and internal stress or pressure and this pressure can be differentiated in the healthy state and pathological state. The related histological components tend to maintain a specific structural shape in which minimal energy is either wasted or stored and maintain a required energy balance. Any application of force, stress, pressure which is not in unison with the line of forces of cell, tissue results in either temporary or permanent deformity, damage or shatter, fracture, rupture, fragmentation, chipping of the cells, tissue or organs. During these conditions the recoiling force or stretch process can be affected. The hydrostatic balance of the interstitial fluid, components of extracellular matrix, and the cellular structure gets affected. The values of pressure of interstitial fluid can be negative or positive; in a normal tissue. This hydrostatic pressure is zero i.e., neither negative nor positive, this is so at least in small and soft tissues. In oedematous tissue the hydrostatic pressure of interstitial fluid is positive as a result its flow gets restricted and this region becomes swollen or puffy. Quite often this condition is commonly observed in aged individuals and also after heart or bone injury (fracture broken).[50,51,52]

ROLE OF CAPILLARY DYNAMICS INTERSTITIAL FLUID AND LYMPHATIC SYSTEM

There is functional and physiological link between tissues, interstitial fluid, extracellular matrix, lymph and lymphatic system, capillaries-network arteries, veins, major blood vessels, blood. Histologically, capillaries (fenestrated and non-fenestrated) appear to be the terminus where biomolecules interchange; hydrophilic biomolecules find it easy to exchange under the influence of Gibbs–Donnan equilibrium that exists between the plasma and interstitium in the biological entity. The interstitium has fluid and solid structural and functional components namely, collagen fibers and proteoglycan fibers and render the gel like fluid. This whole set-up leads to the concept of microcirculation which is an essential interfacial aspect of cells and the exchange and supply of biomolecules that maintain the functional integrity of this zone of biological tissue. The structural and physical proximity of the cells and the biomolecules in the ambient environment is such that a distance of 0.1 micrometre is covered by an oxygen molecule within 2 microseconds. This distance corresponds to the distance between an erythrocyte and the endothelial cells of capillaries. When this distance increases to 1 cm oxygen molecule takes around some hours to migrate. So, this explains the significance of microcirculation. This exchange of materials follows the principle of Fick's law. The functional bases of microcirculation are as per the Starling's principle.[53, 54] The force due to bulk-flow has a specific direction of flow and the lymphatic set-up brings about the mechanism for the overflow this aspect develops because protein molecules ooze from the existing capillaries in the region. The flow of lymph and osmotic pressure present in the interstitium also facilitate the required hydrostatic pressure in the interstitium. In all probabilities the biomolecules isolate or filter from the capillaries and the lymphatic system as a result maintain the balance between the plasma and interstitium avoiding the occurrence of oedematous. This set up functions as 'self-limiting mechanism' and facilitates the exchange of metabolites. There is generation of fluid which may take place as after effect of haemorrhage or defective cardiac function. Hence, this set-up is referred to as 'close system'. The major and microcirculation in kidney, glands and digestive tract the generation of fluid or absorption of fluid is needed. This demand is met not under the influence of Starling forces; hence, this set-up is considered as 'open system'.[43] The interstitium a secluded space acts apparently passive reservoir for holding filtered fluid during microcirculation to be released in the lymphatic system and join the general blood circulation. This entity has two components fibrous and fluid component; the fluid is the interstitial fluid and the fibrous components are bundles of collagen fibers, and proteoglycan filaments. The collagen fibers add to the structural aspects and provide tensile strength to this entity. The proteoglycan filaments form a 'brush like reticular fibrous structure' that holds water and regulate mass flux of fluid in this region. These fibers consist of 98% hyaluronic acid and proteins. In most of the healthy conditions approximately 1% of interstitial fluid has free water, this amount can increase in proportion to the degree of oedematous status but less than 50%.[55]

The flow of the interstitial fluid, lymphatic fluid and the fluid in capillaries is highly coordinated process. The inherent ability of contractility, sequential segmental contraction with respect to stretching takes place in the system. The other mode is based on the external compression applied intermittently due to the movements of skeletal muscle contraction, pulsatory activity of the ambient arterial vessels. During exercise, the rate of flow elevates up to 20 to 30 times but in the case sedentary life style it declines with higher values. Over all lymphatic flow in the product of proportionate hydrostatic and osmotic/oncotic pressure, permeability of capillaries, drainage of lymph and the hydrodynamic modulations base on Starling's laws.[56] Total lymphatic flow is dependent on relative hydrostatic and oncotic pressures, capillary permeability and lymphatic drainage. This can be summarized utilizing Starling's theorem of transcapillary haemodynamic status.

ROLE OF INTERSTITIAL FLUID AND EXTRACELLULAR MATRIX DURING PHYSICAL STRESS

The cells of tissues are kept immersed in interstitial fluid and it is mostly devoid of fibrous components (few are present). Basically, this fluid is a derivative of plasma of blood and its some of the components are electrolytes like sodium, potassium, calcium, chloride, nutrients, some gases, and waste and unwanted metabolites. It is dedicated to ensure appropriate exchange of metabolites between the blood and cells. All these exchanges are based on the permeability of the boundary membrane-partition between them, the hydrostatic pressure and the concentration of the metabolites across the partition membrane. As a result of these a suitable homeostasis is maintained. The extracellular matrix is a combination of complex of congregation of macromolecules and protein fibers like collagen, elastin, glycoproteins and proteoglycans. These constituting members contribute to the structural and functional aspects of the extracellular matrix. The aspects based on parameters with refence to physics, like elasticity, mechanical support, functional stability and the biomolecular signalling pathways are rendered effective. These components of tissue are primarily not only fluid but it acts as a scaffolding for holding cells. The components that play major role in sustaining the integrity of the specific tissue, and also mediate the intercellular exchange of information. In some tissues the components of extracellular matrix are interlinked with glycocalyx, cell membrane proteins and the components of cytoskeleton to ensure the stimuli-response behaviour between cell and their ambient environment.[9,57,58]

The both types of capillaries, fenestrated capillaries and non-fenestrated, are the sight of exchange of biomolecules and other metabolites between the plasma and tissue. This exchange of biomolecules across the wall of the capillaries follows a Gibbs–Donnan equilibrium. In addition to Gibbs-Donnan equation, the Starling forces also participate in this exchange. These Staring forces control the movements to and fro across the capillaries wall. These are hydrostatic and oncotic pressures. The Starling forces are i-hydrostatic pressure working outwards pushing on the wall and promotes fluid filtration out of capillaries; ii-interstitial hydrostatic pressure and opposes the filtration process (force) ; iii-Capillaries oncotic (osmotic) pulling pressure due to the larger protein like albumin which are restricted in the capillaries. These molecules try to drag fluid outside and promote reabsorption into capillaries; vi-interstitial oncotic (osmotic) pressure; an osmotic pulling pressure due to the proteins present in the interstitium, this force pushes the fluid out of the capillaries. Current investigations indicate that lymph flow is with higher pressure but the interstitial colloidal osmotic pressure is slightly lower than the hydrostatic pressure. Filtration occurs along the capillaries but the lymphatic set-up to maintain plasma-interstitial equilibrium and prevent oedema. In organs where absorption is dominant their movements of fluid not depend on the Starling forces.[60]

The viscoelasticity of extracellular matrix plays major role in cellular and tissue dynamics. The extracellular matrix is an essential regulator in the developmental processes, cancer, fibrosis and under pathogenetic state. Its elasticity establishes the behaviour of cells and the tissue. All living tissues exhibit viscoelastic nature. There are few references regarding the viscoelastic behaviour of extracellular matrix. Generally, elasticity is considered to be the primary parameter that regulates the behaviour of a tissue. Extracellular matrix gets stiffened due to its elastic nature (force per unit area) and is required to cause strain (deformation). Mostly, the cells related to extracellular matrix provide the necessary forces that induce deformation in it. The influence of elasticity can be investigated using hydrogels, elastomers or any other set-up having tuneable elastic moduli (like polyacrylamide, polydimethylsiloxane). The extracellular matrix does not behave like totally elastic matter as they also have fluid in them. The liquids/fluids do continuously deform under the applied force that is in irreversible mode. The energy is not storing in viscus/fluid matters. It has been observed that the biological tissues and the extracellular matrix show initially instantaneously solid like elastic behaviour and later on the viscous-liquid/fluid like viscous response which is time dependent i.e., this behaviour is considered to be ‘viscoelastic’. Organs like liver, bone, breast, and brain exhibit viscoelastic behaviour but its effects are different in these organs. On can conclude that extracellular matrix is a primary regulates the physical integrity having higher mechanical abilities than the related cell.[61,62,63,64]

ENTROPY AND ENTHALPY CONCEPT AND CELLULAR FUNCTIONS

Biological matter also undergoes thermal transition features. The range is relatively quiet wide ranging from slow-low-temperature exposure to fast-high-temperature exposure. At the lower range the thermolabile enzymes are unable to perform their enzyme activities and the higher range is capable to coagulate proteinaceous bundles of collagen fibers. In any biological cells and tissues ‘entropy’ and ‘enthalpy’ play prime role in maintaining a functional energy balance homoeostasis. The entropy of any cell and biosystem indicates disorder or randomness of biosystem. In the biosystem, there is a possibility of energy shows tendency to increase in a given time period as it disperses. The increase in entropy takes place along with decrease in the order of the system. The cell has to maintain this entropy involving its regulatory pathway throughout the activity.

The enthalpy indicates the total energy content present in a system at a constant pressure.[65] This condition also depicts the total energy difference between the bond broken in reactants and bonds established in products formed in a given biological interaction. In an exothermic interaction, the energy is liberated to ambient environment and in endothermic biological interaction this energy is absorbed in the reaction system. The reciprocal influence or mutual action amongst entropy and enthalpy the basic concept to comprehend is the mechanism involved in maintaining their structure and functionality and the flow/shift of energy in the cell itself under consideration.[66]

Further, the variety of bonds like vander Waals, hydrogen, ionic, disulfide, and covalent get disorganised into irreversible thermal transition. The rate of such transitions depends on the number of the bonds get broken or disoriented. The relationship between the molar entropy (ΔS) and molar enthalpy (ΔH) i.e., Δ S[J/mol.K] and molar enthalpy (ΔH) i.e., ΔH[J/1.2343437] explain sauch transitions.[66]. Biologically such thermal transections are represented in the form of changes in optical scattering, mechanical contraction, loss of birefringence (splitting of single ray in to two distinct rays due to change in refractive index depending on the polarization and direction of light), and delayed necrosis observed after few days of thermal exposure. Mostly, during thermal transitions there is consistent increase in the order per additional stabilizing bond so that the ratio between molar entropy and molar enthalpy remains constant. For the sake of convention only affected hydrogen bonds (breaking or formed) are considered during considering thermal transition. The other types of bonds mentioned above yield same molar entropy (ΔS) and molar enthalpy (ΔH) ratio.[66a]

The dynamics of the subcellular structures plays significant role in the cellular adaptability specifically to environmental fluctuations. The organization and functions of cytoskeleton involving periodic assemblies of actomyosin is very important. In addition to the muscular type of tissue, there are plenty of non-muscular tissues and show much structural variations. In this process, the sarcomere-like periodic units having different lengths facilitate the optimization of stable force but also help to adaptive responses to the environmental cues by remodelling. There structural difference which contribute to the specific protein composition which are unique for the different types of cells. The mechanism and significance of these periodic units are not well understood in overall framework during the cellular behaviour. It is proposed that 'Shannon entropy concept' can evaluate and quantify the specific and effective binding strength of the contractile units.[67]

These sarcomere-like assemblies (units) influence the energy balance; possibly, these units consume more energy. These structural units are considered cause instability but the binding energy used is of higher value. These interactions help in sustaining and stabilizing the configuration of cytoskeleton and the generation. The adaptability of cytoskeleton in the different types of cells.[39]

Cells are dynamic histophysiological components of a biosystem and are dedicated to maintain the normal balance of energy and forces in accordance to their internal and external ambient environment. The cells respond to the mechanical forces, for this ability, cells undergo changes in their shape, movements and differentiate in accordance to the cues. In the process, the intracellular skeleton modifies or show fluctuations to accommodate the degree of stiffness, viscoelasticity, adhesiveness and elasticity. These modifications ensure the normal cellular integrity and functionality. This has been observed involving investigations based on molecular biology, physics and mechanical concepts. These observations indicate that in this process the cellular mechanical features, cellular ability of mechanotransduction and the related mechanism are involved. These observations have been quantitatively analysed on the role of the cytoskeleton during the changes in the degrees of elasticity, rigidity and adhesiveness.[68] Epithelial cells form the lining tissues of the organs and most of the body cavity. These cells form a polarized layer which is attached to the basement tissue made of polymeric layer of auto-accumulated extracellular matrix. This basement layer adheres to the epithelial cells tightly. For a well-organized and healthy organ, it is very essential that epithelial layer must have a specific shape and a tension. It has been reported that when the basement membrane gets degraded or disorganized the folding of epithelial layer takes place. It indicates the probable defective functioning of the organ.[69]

It is of common observations that during senescence the epithelial cells or epithelium gets rigid. Loss of rigidity is a reflection of good numbers of skin diseases. The rise in rigidity correlates with elevation of density of fibers of cytoskeleton. Still the mechanism of which type fibers become dense, is not clear. The observation obtained using atomic microscopy and immunofluorescence microscopy after pre and post treatment with cytochalasin-B indicate that the mostly F-actin microfilaments add to the rigidity of these cells. The cytochalasin-B inhibits the polymerization of F-actin. This observation is likely to help to check the age-related factors affecting epithelial cells.[69] Wound healing, morphogenesis during embryonic development and progression of cancer movement of epithelial cells is an essential process. This process is complex involving cellular motility and complex intracellular interactions which help to maintain intracellular integrity. There are specific fluctuations that establish the synchronized biophysical forces of the cells and generate traction forces which ensure the migratory movements in the cells involved. There are evidences that indicate the neighbouring and the distant cells have the ability to perceive, share and transmit the mechanical cues and the respond to the leading experience that is having the stronger traction forces. One more aspect of cell migration is faster collective migration at the wound edge as compared to the distant cells in the region of wound. The elastic modulus initiates the mechanical response at the point of onset of migration. While studying the elastic modulus E involving 'higher-spatial resolution' and 'low spatial resolution' (HT/LS) in kymographic imaging. On the onset of migration elastic modulus increase and even during normal movement of F-actin fibers, a component of cytoskeleton, show changes in elastic modulus in comparison to the stationary cells.[70]

CONCLUISION

Biological material consists of interstitium, connective tissues, extracellular matrix, interstitial fluid. different types of cells. The cells are ensheathed by glycocalyx which in turn encloses cell. Most of the cells are interlinked forming sheet like configuration and involve cell to cell adhesion, tight junctions, adherens junctions, desmosomes and gap junctions. These cells are epithelial, parenchymal, sensory cells, glandular cells. The cellular mechanism of each type of cells and its specific function vary. Among these functions include response to physical cues which is very essential for its self and survival of the biosystem as one unit. Like a physical matter biological matter also exhibits some of the physical features like elasticity, plasticity and viscoelasticity. These features follow most of the physical principles, if not in totality then at east to greater extent with varying degree of similarities. The mechanisms of biological cells and tissues are the bases of the biological phenomena like, cell growth, cell division, cellular movements within the biosystem, healing and adjustability to the environmental fluctuations within and outside the body. The ability to respond to the intra-and extra-cellular cues and to be aware of its physiopathological conditions and resist the damage as for as possible. Techniques like tissues culture, various microscopic technologies, applications of prosthetics, pharmaceutical practices, provide to assist the studies of cell mechanism. There exist some debatable issues like role of actomyosin network during stress conditions, influence of contractile nature of cytoskeleton on the viscoelasticity, role of motor proteins, role of actin-myosin network (cortex), the movement of biomolecules with the cell and energy balance of cell and interstitium. Processes like phagocytosis, endocytosis, exocytosis, pseudopodia, bleb formation and their working, maintain the hydrostatic pressure (tonicity of the cells). The rupture of membrane seems to be in coordination to the changes on physical process like elasticity, plasticity and viscoelastic nature of cell and tissues. These investigations can be probed by adopting force and time related techniques. Among these magnetic bead twisting, micropipette aspiration, particle tracking, optical tweezers, microplate rheology and atomic force microscopy are in use commonly. Each method has some benefits over the other, so selection of method should be in accordance to what aspect we desire to investigate.

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