

HYPOTHESIS

THE LIVING MATRIX: A MODEL FOR THE PRIMARY RESPIRATORY MECHANISM

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Presented here is a physiological model for the primary respiratory mechanism, palpable fluctuations in the tissues to which practitioners of cranial manipulation, visceral manipulation, and lymphatic drainage attribute healing effects. According to this model, the primary respiratory mechanism initiates metabolism and assures nutrients and waste products an efficient transit through the extracellular space. The extracellular matrix is an open, unstable system prone to changes of ionic concentration and macromolecular organization. The cells imbedded in the extracellular matrix are functionally coupled with it through integrins, receptors within the

cell membrane. Integrins convey mechanotransduction: activation of intracellular enzyme systems and DNA through changes in extracellular electromechanical information. Utilizing the primary respiratory mechanism, clinicians effect improvements in varied conditions, some of which are reviewed.

Key words: Osteopathic manipulative treatment, cranial manipulation, extracellular matrix, visceral manipulation, lymphatic drainage, craniosacral therapy

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INTRODUCTION

Many practitioners utilize a palpable fluctuation in the connective tissues called the primary respiratory mechanism (PRM). Those who perform cranial osteopathy, craniosacral therapy, lymphatic drainage, and visceral manipulation utilize the PRM in diagnosis and treatment. The PRM was first conceptualized by William Garner Sutherland, DO. While observing a disarticulated skull, he asked himself the question, "What function do the sutures have?" The answer came as a flash of inspiration: "Made for articular mobility indicating a respiratory mechanism."¹

No one had previously supposed that the sutures display motion characteristics, and Sutherland initially dismissed the idea. However, he could not entirely put it out of his mind, and he eventually undertook the task of disarticulating another skull to prove that motion in the skull is not possible. He proved the contrary. Clearly displayed before him were monuments in bone of a respiratory motion carved by a vital mechanism.² Stimulated by this observation, Sutherland pursued a lifelong study from which emerged the discovery of a physiological phenomenon that is evident in the entire organism. This mechanism proved to be useful in both diagnosis and treatment of "somatic dysfunction," the osteopathic concept that distorted connective tissue—not just joints, but also muscles, ligaments, and especially fascia—is associated with dysfunction of organs, nerve impulses, and the delivery of blood, as well as venous and lymphatic drainage.

Dr Sutherland named the phenomenon that he discovered the *primary respiratory mechanism*, because he wanted to imply that it (1) represents in the organism the first evidence of vitality (primary), (2) is responsible for the exchange of nutrients and waste products such as oxygen and carbon dioxide (respiratory),

and (3) displays a pattern of activity (mechanism). Sutherland declared that the body primarily depends on this respiratory mechanism for the maintenance of its health, and without it, the organism could not live.^{3(p16)}

This paper presents a theoretical model to physiologically explain what is evident by palpation as the PRM. In essence, this model explains *tissue* respiration. To explain *pulmonary* respiration, one would describe the function of the respiratory center in the brain stem, thoracic motion, and alveolar gaseous exchange. The model of the PRM presented here explains tissue respiration by describing pulsatile activities of cells and the extracellular matrix that surrounds them. Here we find exchange between the nutrient capillaries and cells on one hand and between the cells and lymphatics on the other. These exchanges of nutrients and waste products both must transit the "no-man's-land" called the extracellular matrix, or simply the "matrix." Therefore, the matrix plays an essential role that determines the health and function of all the cells of the body. The matrix not only manages these exchanges of nutrients and waste, but also "contains" the cells of all tissues, is the meeting place of nerve endings, blood and lymphatic capillaries, immune functioning cells and their products, as well as hormones and many other cell-signaling chemicals. *The matrix is where the action is.* Let us look at the characteristics of the matrix that are necessary for and that express themselves in vital activities.

EXTRACELLULAR MATRIX

Within the structure of the extracellular matrix we find cells, fibers, and ground substance, all of which play essential roles relative to the performance of the PRM. The fundamental cell of the matrix is the fibroblast, which produces essential components of the matrix—its fibers and ground substance. Other cells include many that wander in and out of the matrix, such as the various white blood cells found in the blood stream. Macrophages and mast cells take up more permanent residence in the matrix. These resident cells and the wandering lymphocytes and polymorphonuclear leukocytes perform the usual detoxifying

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and immune functions in the matrix with which we are familiar in the blood.

The most common fibrous product of the fibroblasts is collagen. It is ubiquitous serving as a structural protein. It is unique in that it is not very distensible and excludes water from its dense form, a unique feature giving collagen a special structural characteristic. Dense collagen exists outside the metabolic processes that normally occur within a watery medium. It offers stability as a scaffolding around which the rest of the more malleable extracellular matrix and parenchymal cells are organized. Furthermore, collagen provides essential piezoelectric properties to the matrix. Along with elastin and other structural proteins like fibronectin, collagen displays polarity within its molecular structure. One part of the molecule holds a positive charge compared to another part that is relatively negative. Molecules of collagen line up so that the positive charges lie in the direction of the organism's growth, development, and forces for healing.

Another product of the fibroblast, the ground substance has been found to be anything but amorphous, which was the common belief prior to the invention of more powerful microscopes and experimental designs of the last few decades. The largest molecule in the human organism exists in the ground substance of the matrix: hyaluronan (or hyaluronic acid). This polymer is so long that it crosses over itself as it fills the space between cells. Bonded to the hyaluronan backbone are proteoglycans. These are composed of brushlike structures with their own backbones of core proteins to which the bristles are attached. The bristles are made of glycosaminoglycans, or GAGs: heparin, keratin, chondroitin, and dermatan. Glycosaminoglycans are highly sulfated, rendering a domain of strong negative charge to the matrix, which attracts water.

In cartilage, the best-known extracellular ground substance, we can more easily conceptualize some of the fundamental characteristics of the matrix. It acts as a sponge, absorbing great volumes of water. Because of the water, it serves as nature's shock absorber. It is very slick and gel-like. It also excludes other substances from its midst, unless influences beneficial to life, as we shall soon discuss, allow oxygen and nutrients admission.

The extracellular matrix and the connective tissues, in general, create the form of the organism made from patterns of structural iterations from the gross physical level to subcellular mechanics. Structures are created to house functions on all levels of organization, from gross motor activity to the enzymatic activity of the cells.⁴ Although function initially precedes structure, once the structure is established by growth and development, the function becomes dependent on the structure. The extracellular matrix performs the fundamental function of creating structure by laying down structural proteins, like collagen. The matrix is also closely allied with function at the cellular and subcellular level, as we shall see. The matrix influences the parenchymal cells that it contains. These influences include the activities of morphogenesis and metabolism.^{5,6}

The matrix is piezoelectric, marrying electrical and mechanical functioning. Applying an electric stimulus to the matrix causes mechanical motion (vibration) and applying physical force (stretch, compression, or torsion) generates electricity.^{5(p111)} The matrix is a semiconductor, that is, electrons are equally shared by all the

structural proteins and other charged elements in this complex meshwork. Energy fluctuations spread rapidly through the matrix through changes in liquid crystalline water. The energy transmissions are used by the cells as information.^{5(p53)}

Because the matrix is open to outside influences and unstable, it is prone to oscillation. Matrix macromolecules are capable of oscillation due to their spiral structure.^{5(p107)} Scientists observe oscillations of pH, ion concentration, and degrees of polymerization of the matrix macromolecules.^{5(p50),7,8}

Gelation and Solation

The extracellular matrix is viscoelastic. Changes in viscosity appear as variations in the swelling of the hyaluronan⁹ and other glycosaminoglycans of the matrix. We can also think of changes of viscosity in terms of variations in polymerization of the matrix macromolecules and in terms of fluctuations of the redox potential.^{10(p2)} As these enormous polymers swell or depolymerize, the "pore size" of the matrix permits larger molecules to pass through the extracellular fluid. As the polymers become more polymerized, molecules are restrained from moving through the vital space between the nutrient capillaries and the parenchymal cells. The extreme example of gelation of the matrix, when polymerization is maximal, is observed after vital functions leave the organism. This state is called *rigor mortis*.

In life, the matrix is vitalized and liquefied by factors that permit the movement of nutrients to and waste products from the parenchymal cells.^{5(p54),11(pp142,157)} The matrix polymers contain sulfated moieties that carry a strong negative charge when polymerized in the gel state. This attracts relatively large volumes of water that bind to the matrix macromolecules and help constitute the gel. The concentration of calcium ions is inversely related to the dimension of the hyaluronan polymers and to the amount of water that is bound to the polymers.¹² As calcium ion concentration decreases, water binds more tightly to the macromolecules of the matrix. As calcium ion concentration increases, bound water is free to flow. When the intensity of the negative charge of the matrix declines with its depolymerization, calcium ion and water flow to the next negatively charged element in the region—the cell membrane. Dissolved in the water are the nutrients that have diffused from the nutrient capillary into the extracellular matrix. The flowing water delivers the nutrients to the parenchymal cells. This mechanism of delivery is more efficient than mere diffusion (Figure 1).

The unbound, flowing water decreases the concentration of calcium ions by dilution, thereby decreasing calcium's depolymerizing function. Therefore, the macromolecules of the matrix repolymerize once again, increasing the viscosity of the matrix and binding relatively large volumes of water. Thus, we observe in the matrix a palpable cycle between gelation and solation.

Mechanotransduction

The influence of the matrix over neighboring cells is demonstrated in part by extracellular cyclic adenosine monophosphate (cAMP) and calcium ions that stimulate intracellular functions through the cell membrane-associated glycosaminoglycans and through cell surface receptors. Integrins are one group of cell

other sets of enzymes could be activated. By this means, mechanics instigates and regulates metabolic functions.

Cell Shape

Cell swelling and shrinkage has been associated with intracellular calcium ion concentration.¹⁵⁻¹⁷ Waves of intracellular calcium ions are responsible for many metabolic functions in the cell. Intracellular calcium waves and many other secondary messengers for metabolic functions are also stimulated at the cell membrane by cyclic adenosine monophosphate (cAMP) and calcium ions, so waves of calcium ions stimulate other waves of calcium ions. In this model, the calcium-triggered contraction of actin filaments in the cytoskeleton is associated with changes in cell volume.¹⁸⁻²⁰ Cycles of calcium waves in the cell have been recorded at rates from 0.1 to 12 cycles per minute.²¹ Cycles of electric potential having periods of four cycles per minute have been recorded in anesthetized dogs by microelectrodes in tissues of various organs: stomach serosa, liver, and kidney.^{10(p62)} Palpable cycles of fluid fluctuation are documented in the literature at rates between 0.1 and 14 times per minute.^{3,22}

Lymphatics

The terminal lymphatic channel is also controlled by the matrix. Calcium waves cause contraction of actin filaments that suspend the endothelial cells of the terminal lymphatic channel, thus opening the fenestrations between cells. Water that has been expelled from adjacent parenchymal cells from contraction of intracellular actin filaments flows through the fenestrations into the lymph vessel. As the calcium wave dissipates, the fenestrations close and trap the waste-laden water inside the lymph vessel. With the next calcium wave, more water flows into the terminal lymphatic channel, forcing the previous bolus of water up the channel. Thus, we have a pulsatile movement of lymphatic fluid in the lymph vessels.

Autonomics

This model further entertains the concept that the whole mechanism so far described is controlled by the autonomic nervous system, which is represented everywhere in the matrix by nerve endings. Traube-Hering waves, first described in the mid-19th century, operate by oscillations of the sympathetic nervous system. Like a thermostat that responds to temperatures that fluctuate above a preset level to turn off the heat and to temperatures below the setting to turn on the heat, fluctuations of blood pressure in the arteries seem to search about a mean pressure. Slow fluctuations of the pulse pressure in arteries seem to be controlled by oscillations in sympathetic tone, according to Guyton and Harris.²³ It has been shown that the Traube-Hering wave is consistent with a palpable phenomenon that cranial practitioners report as the PRM.²⁴

Summary

In summary, oscillations of the matrix through the interplay of calcium ion concentration and unbound water move nutrients from nutrient capillaries to parenchymal cells and waste products from cells to lymphatics. Cell contraction under the influence of calcium ion initiates metabolism within the cell through

the mediation of integrins. Lymph is pumped up the terminal lymphatic channel by this oscillatory mechanism. The ubiquitous endings of sympathetic nerves control this activity through oscillations of rates of firing that originate in the higher centers. All of this fluctuant activity is palpable. Health is delivered by the fluctuation. Furthermore, palpating this activity offers an opportunity to influence it, thereby therapeutically affecting the delivery of health.

CLINICAL ASPECTS

This model points out the importance of the PRM, fundamental to life itself. Without the oscillatory activity of the matrix and parenchymal cells, metabolism would be stunted or nonexistent. Moreover, the oscillatory activity is manageable by palpation. A compression of the fourth ventricle—CV4—has been used to demonstrate manual effects on the PRM.^{25,26} Studies show that recurrent otitis media is treatable with osteopathic manipulative treatment that emphasizes the PRM.²⁷⁻²⁹ In the pregnant female, osteopathy in the cranial field has proven to be beneficial in several ways. Fewer cases of preterm delivery and meconium staining were reported in one study.³⁰ In the newborn, over 90% of infants examined displayed palpatory findings of alterations of the PRM in the skull. About a third of this cohort demonstrated poor suckling ability, excessive crying, reflux, torticollis, and other symptoms of palpable strains in their heads, musculoskeletal, and neurological systems. Of this cohort, about one third displayed learning disabilities when they grew to school age.³¹ Treatment of children by using osteopathy in the cranial field improves their performance in school.^{32,33} Osteopathic manipulative treatment is also applicable to children with neurological deficits and seizures.^{34,35} These are a few examples of the clinical application of this model.

CONCLUSIONS

William Sutherland's discovery of the PRM places him on a par with William Harvey. Harvey was the first to proclaim that by the action of the heart there is a one-way circulation through the blood vessels,³⁶ contradicting the popular belief of his day that blood was circulated by a sort of pulsing action of the arteries and a suction of the liver, creating an ebb and flow mechanism.³⁷ Sutherland confirmed the existence of an ebb and flow mechanism, that it is essential, palpable, and useful in returning individuals to a state of health. Thus, both circulation and fluctuation are necessary for the maintenance of a healthy organism. Research to elucidate the model presented here will be useful in understanding how health is delivered to the tissues. It will promote a healing model rather than a disease model of medicine.

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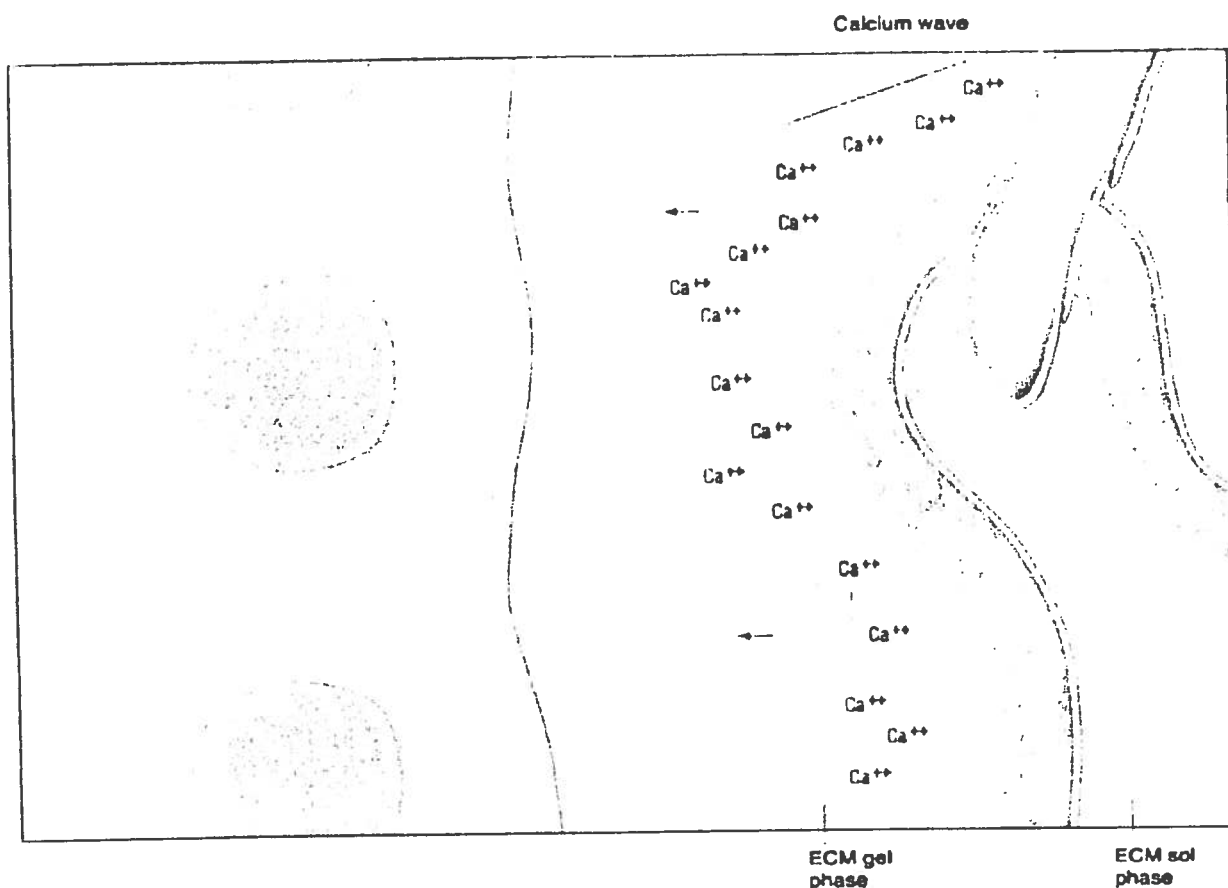


Figure 1. A diagrammatic representation of the theoretic model of a normal phase transition occurring in the extracellular matrix. Parenchymal cells on the left require a liquid phase of the matrix in order to receive nutrients from the capillary (red structure on the right) and to discharge waste to the terminal lymphatic vessel (green structure on the right). A gel phase of the ground substance is depicted in the extracellular matrix adjacent to the parenchymal cells and a liquid phase adjacent to the capillary. In-between, a wave of calcium ions is seen moving from right to left, which is changing the phase of the ground substance. Reproduced, with permission, from Lee.²²

surface receptors that transmit signal from the extracellular matrix to intracellular structures. Extracellular calcium ions must be present for the integrin molecule to perform a process called mechanotransduction. Mechanotransduction integrates mechanics and biochemistry at the molecular level.¹³ Mechanotransduction is piezoelectricity in action.

Integrins are located within the bilaminar cell membrane often where focal adhesion complexes are also found just inside the cell membrane. Focal adhesion complexes are groups of special proteins that act as "spot welds" at strategic places around the periphery of the cell adjacent to the interior of the cell membrane. In conjunction with the microtubules, intermediate filaments, and microfilaments, the focal adhesion complexes assure the shape of the cell. Microtubules, intermediate filaments, and microfilaments behave as tensegrity elements within the cell. That is, they determine the size and shape of the cell through tension and compression. Microfilaments, composed of actin, have contractile properties. Microtubules act as struts against which preset tension of the actin filaments pulls. The actin filaments adhere to these spot welds, but so do the integrins

that simultaneously protrude into and out of the cell and functionally connect the cell's interior to the exterior. Through the mediation of the focal adhesion complex, actin filaments contract in response to the influences coming through the integrins, "tuning" the cell to a preset vibration. This setting determines the cell's response to mechanical and electrical influences to follow. Extracellular fluctuations of pH, ion concentration, and so forth induce waves of intracellular calcium ions, influencing many intracellular functions, even into the nucleus and its genetic material.¹⁴

Further, any subsequent influence on the integrin molecule will distort the cytoskeleton by a contraction of the actin filaments through the mediation of the focal adhesion complex. Like dew drops on a spider web, enzymes that carry out the cell's primary functions are carefully arranged on actin filaments and microtubules inside the cell. As movement of filaments of the cytoskeleton—actin filaments, microtubules, and intermediate filaments—rearrange one chain of enzymes on one filament relative to another adjacent filament, important sequences of chemical reactions occur. When separated from each other,

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