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Silk Fibroin in Bioelectronics Structural Engineering, Oriented Crystallization, And Long-Term Implantable Interface Strategies.

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KEYWORDS

Silk Fibroin (SF), Bioelectronics, Biomaterials, Implantable Devices, Wearable Sensors, Neural Interfaces, Biocompatibility, Biodegradability, Flexible Electronics.

ABSTRACT:

Introduction: Silk fibroin (SF) is an attractive biomaterial for bioelectronic devices because of its biocompatibility, mechanical and optical properties, and water processing capability. But traditional SF-based bioelectronic devices have poor long-term stability due to uncontrolled degradation, moisture-induced instability, biofouling and fatigue.

Objectives The objective of this review is to present recent progress in structural engineering methods such as oriented crystallization and pre-stretching, to enhance stability and functionality of SF-based bioelectronic devices.

Methods: The literature of modified SF materials was reviewed with methods of improving molecular orientation and β-sheet formation. Their effects on mechanical properties, dielectric responses, degradation rate and electrical conductivity were evaluated, as well as their in vivo stability and biocompatibility.

Results Modifications resulted in enhanced mechanical and dielectric stability, and controllable degradation. Crystallinity improved tunability of conductivity, thus ensuring electrical stability. Likewise, increased moisture and biofouling resistance and better in vivo compatibility highlight the potential of engineered SF for prolonged use in neurointerfaces, wearable sensors, and in vivo.

Conclusions: Structurally engineered silk fibroin shows great promise as a durable and dependable material for long-term bioelectronic applications. By improving molecular alignment and controlling crystallinity, many of the limitations seen in traditional silk-based systems can be effectively addressed. These advancements enhance stability and performance, making silk fibroin a strong candidate for use in long-term implantable devices, including neural interfaces, wearable sensors, and continuous physiological monitoring systems..

1.0 Introduction Silk Fibroin in Modern Bioelectronics

Silk fibroin (SF)- a protein that is commonly referred to as the structural component of Bombodrix more silks- has proved to be one of the most promising materials in contemporary bioelectronics.(1) It is popular due to an unusual set of characteristics: it is biocompatible, mechanically adjustable, biodegradable, optically clear, and can even be processed in water.(2) With the continuous shift of bioelectronic devices via the silicon-based rigid component into the soft, bio-integrated structure, which is being performed by skin and tissue, these characteristics allow silk to have a pronounced advantage over standard synthetic surfaces.(3) Silk fibroin is manufactured at the molecular scale by the

deposition of closely-packed crystalline b-sheets into a weaker, amorphous framework.(4) The unusual structure enables the researcher to precisely control the stiffness, elasticity, water stability, and degradation rate of the structure through just a controlled processing cycle.(5) The ease of casting, printing, patterning or molding SF with no harsh solvents makes it readily assume various forms such as thin flexible films, fibers, hydrogels, microneedles and even whole-biodegradable electronic platforms.(6) Such formats may be combined with rigid and soft conductive materials and therefore silk presents a flexible transition between biological tissues and electronic devices.(7) In bioelectronics, SF plays a number of functions simultaneously: an elastic platform to wearable and epidermal sensor, an implantable or transient circuit dielectric layer, an encapsulant that is biocompatible which shields delicate components and a dynamic substance, particularly one combined with conductive polymers, nanoparticles, or nanomaterials of carbon.(8) Such versatility has seen the formation of devices based on silk being used in skin mounted sensor, dissolvable implants, neural interfaces, optical and biochemical sensors, and even edible or environmentally friendly electronics.(9) Seeing how well it can fit its own into tissues, support delicate biomolecules, and dissolve under command, it also can be highly valuable to next generation health monitoring and transient diagnostic systems.(10) Nonetheless, there is one obstacle, which is long-term stability. Biodegradability is perfectly suited to a temporary or resorbable implant, although it restricts the application of unmodified SF in chronic implants or continuous physiological implants, where mechanical and dielectric characteristics need to be maintained over months or years.(11) This has made recent studies consider what can be done utilizing various methods like augmenting crystallinity, crosslinking chemicals and most interestingly oriented crystallization that can elevate water resistance and structural strength as well as electrical performance to a considerable degree.(12) This review emphasizes the increasing use of silk fibroin in bioelectronics, existing issues, and mechanisms to overcome the current challenges with potential future solutions, including the way orientation crystallization can get the long-term survival of the bioelectronic technologies, which can be implanted and sustained in the future.(13)

Figure 1 In this figure, the article is talking about silk fibroin (SF) as a very versatile biomaterial that can be modified in terms of its properties by applying various techniques, such as sol-gel processing, gel casting, precision film forming, and controlled extraction. Its principal properties are biocompatibility, biodegradability, water solubility, transparency and the capacity to carry drugs and as a result, this property has enabled it to be used in numerous ways.Some of the large application areas feature in the external sections include implantable medical devices (drug delivery, transient electronics, scaffolds), wearable devices (electronic skin, smart insoles, tattoos), energy harvesters (flexible TEGs and wearable PEGs), multi-channel sensors (humidity, temperature, strain), and flexible electronic systems (memristors, LED wearables, air filtration). Generally, SF represents a universal system of highly bioelectronic and biomedical technologies.

2.0 Silk Fibroin as a Functional Biomaterial for Bioelectronic Interfaces

Silk fibroin (SF) has become a versatile choice of bioelectronic interface since it has a unique property of biocompatibility, mechanical control, optical transparency, and mild, aqueous processing.(14) The hierarchical nature of its structure means that its crystals formed out of b-sheet are encased by a softer amorphous network providing researchers with finer control over the properties of their aids to include stiffness, elasticity, water stability, and degradation.(15) It allows SF to be flexible to ultra-soft, tissue-like electronics, as well as more traditional rigorous devices. Silk as a substrate has an outstanding flexibility and conformability, together with the ability to be compatible with conventional microfabrication techniques. These can be used to design ultrathin wearable biosensors, neural interfaces and entirely biodegradable circuits.(16) By being either, a dielectric or an encapsulant, low dielectric constant, high breakdown strength and thickness, and capability to form seamless, consistent films, together with its low dielectric constant, high breakdown stress, and implantable devices, will make silk a reliable performer in the organic transistor, capacitive sensor, and implantable systems.(17) It is also possible to make SF assume active functions in combination with conductive polymers, carbon nanomaterials, metal nanoparticles, or ionic additives. These composites have the ability to support conductive or ionically active components broadening the scope of biomedical applications of silk into biosensing and soft electrode application, and therapeutic interfaces.(18) Since silk inherently stabilizes fragile biomolecules such as enzymes, antibodies, drugs, etc. it also facilitates integrated biochemical bioproducts sensing and bioactive electronics.(19) The next significant benefit of silk is that it has an excellent biocompatibility. It incorporates well into tissues, suppresses swelling, and assists to achieve stable chronic contact. Its versatility in creating a wide variety of structures in films, fibers, hydrogels, microneedles, porous scaffolds allow the designer to create interfaces at all scales as well as application requirements.(20) One drawback is also that SF is biodegradable, which is an advantage with transient electronics but puts long-term implants constrained. The existing measures of enhancing crystallinity, chemical crosslinking, and most importantly oriented crystallization are trying to enhance the water resistance as well as structural permanence.(21) These progresses are making silk fibroin a better candidate as a next-generation bioelectronic technology that is tissue amenable.(22)

2.1 Table Functional Roles and Advantages of Silk Fibroin in Bioelectronic Interfaces

Functional Role	Key Properties	Bioelectronic Applications
Substrate	• Flexible and conformable • Tunable mechanical modulus • Compatible with microfabrication (printing, lithography) • Aqueous, solvent-free processing(23)	• Wearable/epidermal sensors • Ultrathin flexible circuits • Neural recording platforms • Biodegradable/transient electronics(24)
Dielectric Layer	• Low dielectric constant • High breakdown strength • Uniform thin-film formation • Moisture-resistant when crystallized(25)	• Organic field-effect transistors (OFETs) • Capacitive sensors • Implantable circuits(26) • Energy storage or passive components(27)
Encapsulant/Packaging	• Biocompatible and non-inflammatory • Tunable dissolution rates • Protects electronics from(28) moisture/enzymes • Can stabilize biological molecules(29)	• Implantable electronics • Transient devices with controlled degradation • Drug-loaded electronics and biosensors(30)
Active Functional Material	• Forms conductive composites with CNTs, graphene, PEDOT: PSS, metal nanoparticles(31,32) • Ion-conductive silk hydrogels • Stabilizes enzymes, antibodies, peptides(33)	• Chemical/biochemical sensors • Ionotropic components • Soft electrodes • Optical and electrochemical biosensing(34)
Biointegration & Tissue Interface	• Excellent biocompatibility • Low inflammation and immune response(35) • Matches soft tissue mechanics • Supports long-term tissue contact(36)	• Neural and cardiac interfaces(37) • Skin-mounted electronics • Bioactive therapeutic devices(38)
Structural Formats	• Films, fibers, hydrogels, microneedles, scaffolds • Patternable and moldable architectures(39)	• Multi-scale interface engineering • Microstructured sensors • Flexible, implantable device platforms(40)
Biointegration & Tissue Interface	**Challenge:** Intrinsic biodegradability limits long-term stability(41) **Solutions:** Crystallinity enhancement, crosslinking, oriented crystallization(42)	• Chronic implants • Durable biosensing platforms(43)

3.0 Limitations of Conventional Silk-Based Bioelectronic Devices

Minimal Kontrol over the Kinetic Degradation in vivo. Though the rate of degradation of silk can be modified with the processes, crystallinity tuning, and crosslinking, it is not yet easy to predict how this composite will degrade within the body.(44) Physiological conditions are diverse with respect to the enzyme activity, pH, fluid flow, inflammation and mechanical forces.(45) Such variations imply that a device that is created to fade away at the end of a certain time span might either disintegrate prematurely or stay longer than it is supposed to.(46) It makes it difficult to design time-sensitive transient devices and difficult to get a regulatory approval where reproducibility is mandatory.(47) Complicated Interaction with Biospecies Fluids and Proteins. Silk fibroin is permeable to these proteins, electrolytes, and biomolecules in the tissues that are surrounding it.(48) This makes it more biocompatible, but presents a number of issues. Protein adsorption has the capability to sensitive the surface charge and disrupt electrophysiological signals and the biofouling effectively attenuates the sensor accuracy over time as well.(49) It can be degraded by the rate of enzymes and biomolecules and swelling because of the fluid uptake can lead to delamination in multilayer structures.(50) Of particular concern are neural probes and biochemical sensors which demand relatively low noisy interfaces.(51) Problems of Achieving Long-Term Electrical Reliability. The sensitivity of silk to moisture provides numerous possibilities of electrical failure. Metal traces can be corroded as water gains access to it, and sodium ion can have an upsetting effect on conductive polymers;(52) recurrent swelling-shrinkage can result in the separation of conductive layers. Cyclic strain may crack the conductor composite. All these combined causes the effects of drift, increased noise levels, and ultimate loss of signal, which restricts the usefulness of untouched silk in longitudinal implants or in persistent monitoring apparatus.(53) Processing Thermal and Chemical Constraints. Being a protein substance, silk is not able to stand high temperatures and rough solvents. Denaturation or yellowing can be obtained during heating and conventional processing chemicals in microelectronics can damage the matrix. Technologies that involve metal deposition, etching, and photolithography usually demand modified technologies or protective layers so as not to compromise the structure.(54) These factors complicate the ability to wire silk to high-performance semiconductor or nanoscale-built fabrication methods of high-performance electronics. Restricted Mechanical Strength as a Dynamic Physiological Environmental Constraint.(55) Silk is elastic, yet it does not adjust to the extreme motions of such tissues as the heart, gut, or skeletal muscles.(56) Stretching or bending many times can wear out films made of silk faster than the same elastomers (PDMS or Ecoflex). Cyclic deformation can also cause removal of b-sheet structures resulting in mechanical weakening with time. These are some of the constraints to the conventional SF in devices that would need to operate in the high-strain environments that are nonstop. Limitations in High-Density Microelectrode Integration.(57) The recently developed bioelectronic systems are becoming more and more dependent on high density microelectrode arrays having their geometries that are specific. The sensitivity of electrodes, patterns, and dielectric properties to the swelling, softness, and dimensional change of silk in wet conditions may produce swollen electrodes, distorted patterns and changed dielectric.(58) This instability may end in signal cross- talking or short-circuits. This complicates realisation of the micron scale resolution needed in neural recording or mapping with high compared to more dimensionally stable synthetic polymers. Scalability and Standardization Shortcoming. Massive manufacture of electronics made of silk is not without challenges owing to the natural variation.(59) The source of cocoon, and methods of extracting the silk together with the storage medium have Hongkwe on the molecular weight, purity, and content in the b-sheet of silk.(60) The differences may lead to observable changes in electrical, mechanical and degradation behavior. There are no standard specifications that are biomedical-grade silk fibroin therefore, reproducibility and commercial scaling can be more challenging. Federal and Translational Barriers.(61) Although silk can be used up to now because it is essentially biocompatible, hybrids that involve metals, carbon nanomaterials, MXenes, or other conductive fillers bring new safety issues. Each component has to be tested in terms of stability over the long term, toxicity, inflammatory effect, and harmless degradation product. Multi-material systems are also in need of massive mechanical, chemical and electrical reliability testing.(62) The bioresorbable electronics do not have a proper route of regulation, and thus, their translation to the clinic is a slow and tedious process.(63)

3.1 Table Key Limitations of Conventional Silk-Based Bioelectronic Devices

Limitation	Description / Impact on Bioelectronic Performance
Unpredictable Degradation Kinetics In Vivo	Degradation varies with enzyme levels, pH, inflammation, and mechanical forces; can lead to premature device failure or prolonged persistence; complicates design of transient implants and regulatory evaluation.(64)
Interactions with Biological Fluids and Proteins	Protein adsorption alters surface charge and signal fidelity; biofouling reduces sensor accuracy; enzymatic activity accelerates degradation; swelling causes delamination in multilayer devices.(65)
Poor Long-Term Electrical Reliability	Moisture ingress causes corrosion of metals and degradation of conductive polymers; swelling–shrinkage cycles disrupt interfaces;

	conductive composites crack under strain; results in drift, noise, and signal loss.(66)
Thermal and Chemical Processing Restrictions	Sensitive to heat and harsh solvents; prone to denaturation and structural damage during fabrication;(67) requires modified lithography and metallization techniques; limits compatibility with CMOS and high-resolution microfabrication.(68)
Limited Mechanical Endurance Under Dynamic Loads	Fatigues more quickly than elastomers under repeated deformation; β-sheet disruption weakens structure over time; unsuitable for tissues with large or continuous movement (heart, gut, skeletal muscle).(69)
Challenges in High-Density Microelectrode Integration	Swelling and softness cause electrode displacement and pattern distortion; dielectric instability may lead to short-circuits; difficult to achieve sub-20-µm precision for high-resolution neural and electrophysiology devices.(70)
Scalability and Batch Variability	Natural source variability affects molecular weight, purity, β-sheet content; impacts electrical and mechanical properties; lack of standardized silk fibroin specifications limits reproducibility and commercial scaling.(71)
Regulatory and Translational Barriers	Hybrid devices with metals or nanomaterials require extensive biocompatibility and toxicology testing; multi-material architectures need rigorous reliability studies;(72)absence of established pathways slows clinical translation.(73)

4.0 Importance of Long-Term Stability in Chronic Biopotential Recording

Chronic biopotential recording systems are one of the most critical in terms of their long-term stability. These implants can be as long as months or even years in the body serving tissues that are experiencing constant motion, recovery and adaptation.(74) It may be long-term EEG or ECoG monitoring, intracortical neural recording, cardiac electrophysiology, or chronic EMG tracking, the device has to be reliable to provide valid signals without drift, degrading, or failure with time.(75) The fundamental principle of long-term functionality lies at the capability to maintain constant electrical contact between the electrode and an adjacent tissue.(76) The signals of biopotential, particularly very small ones such as neural spikes, require a low-impedance interface that is always maintained.(77) A small dislocation of the electrode, a minor alteration in material characteristics or even natural alteration of local tissues may cause noise, signal distortion or ultimately failure. Accumulating over a long period of implantation, these little disturbances lead to one of the most challenging tasks of designing a chronic device such as the establishment of a stable electrode-tissue interface. Biological reaction of the body complicates it further.(78) All implanted materials result in a certain level of reaction. Inflammation, protein adposition, glial scarring in the brain, or fibrotic encapsulation of a device in muscles or a heart can take a long time (weeks or months) to develop. Such changes may physically isolate electrodes with target cells, or make the interface more resistant, undermining or distorting signal recordings.(79) In order to reduce these problems, long-term implants should not just be biocompatible, but soft, flexible and able to retain similar characteristics on their surfaces throughout their life. Implanted materials are also under a lot of stress in the internal environment of the body.(80) The degradation of the material may be caused by physiological fluids, repetitive movement, changes in temperature, and biochemical activity.(81) Typical ways of failure are swelling due to hydration, conductive layer corrosion, delamination, and mechanical fatigue due to repeated movement. In moisture sensitive or biodegradable materials such as silk fibroin these problems can occur much faster, since natural degradation can cause alteration of dielectric properties or loss of mechanical integrity before the device has achieved its target lifespan. Dielectric stability is another critical factor with respect to long- term reliability.(82) Such differences in the values of dielectric constant, swelling in the presence of moisture or early breakdown of dielectric may both distort the signals and create leakage currents undermining accuracy and safety. Since large arrays of electrodes have a high density, geometric variation on a small scale can cause space resolution errors or result in increased cross-talk, with severe impact on long-term mapping resolution. Long-term stability is necessary not only to ensure the accuracy of the data, but also to ensure the comfort and safety of patients.(83) Surgical devices that malfunction early may need revision surgery, disrupt a continuous treatment or follow up or result in misinterpretation of clinical results.(84) Long-term stability has now emerged as a major challenge in commercializing bioelectronic technologies to actual clinical application as regulatory requirements are starting to look more closely at chronic performance data.(85) In general, stability in the long-term is important as it minimizes biological and mechanical complications, optimizes patient risk, and reduces signal fidelity, which is necessary to achieve successful implantable bioelectronic systems.(86) Enhancing chronic survivability, by means of better materials, interfaces, and architecture--are other areas of interest in the design of next-generation bioelectronic technologies.(87)

5.0 Oriented Crystallization Silk Fibroin. A Novel Physical Modification Approach

Oriented crystallization is acquiring significant momentum as one of the most promising physical approaches to improving the functionality of silk fibroin (SF) in the contemporary bioelectronic sensors and devices.(88) Traditional silk processing generally generates films and fibers that have randomly distributed b-sheet domains that cannot easily be controlled, and thus mechanical behavior, dielectric stability and long-term structural integrity are hard to control. Conversely, in oriented crystallization such b-sheet structures are rearranged into directionally improved networks.(89) This orientation is possible via a range of physical stimuli such as mechanical stretching, shear forces, directional freezing or the use of magnetic and electric fields that direct SF molecules into more regular and highly organized crystal assemblies.(90) The end product has better mechanical strength, better dimensional stability and higher predictability which is very vital in long-term or implantable bioelectronic systems.(91) This molecular alignment is not only mechanically reinforced to advantage the process. B-sheet networks made of high orientation have an important effect on enhancing the dielectric stability of silk to lower the moisture absorption rate, lower swelling, and also avoid random alterations of electrical properties under physiological conditions.(92) Such enhancements contribute to the sustained operation of the device, noise reduction, signal drift reduction, and a reduced risk of delamination which are beneficial in applications like neural interfaces, wearable biosensors, and bioelectronic patches which need to endure constant motion and have contact with fluids.(93) It is noteworthy that oriented crystallization does not require the use of chemical crosslinkers or likely harmful additives, which helps the crystallization method to retain the intrinsic biocompatibility and safety profile of silk.(94) Altogether, oriented crystallization is a clean, bio-safe, and very efficient modification technique that makes silk fibroin a good candidate of next-generation bioelectronic implants.(95) This strategy will give a powerful route to efficient, dependable and declined bioelectronic contact development since it permits minute control of mechanical soundness, degradation Kinetics and diffusion of dielectric properties.(96)

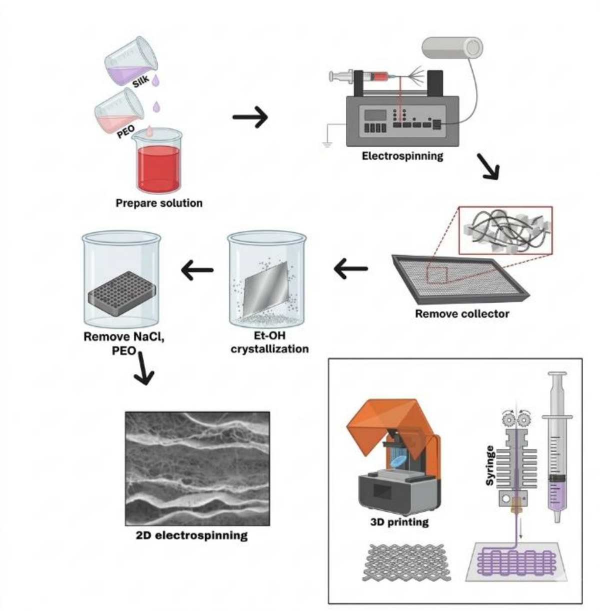

Figure 2

This image shows the sequential production of the nanofibrous materials made of silk fibroin (SF)-based materials through electrospinning. A homogeneous solution is first obtained by mixing silk fibroin with poly (ethylene oxide) (PEO). Electrospinning is then done on the solution to form fibrous mats deposited on a substrate. The fibers obtained are washed away using ethanol (EtOH) to cause crystallization and increase structural stability. PEO and salt (NaCl) are then removed to get pure porous silk fibroin structures. The material that is formed is in a nanofibrous form, as demonstrated in the SEM image. Also, the figure reveals the combination of electrospinning and 3D printing methods as a means of making structures more advanced.

6.0 Pre- Stretching Treatment as a Significant Method of Tunable Silk Membranes.

Before the treatment Pre-stretching is a powerful physical approach to the tuning of the structural and functional properties of tunable membranes of silk fibroin in bioelectronic applications.(97) Silk is made up of crystalline b-sheet domains and amorphous regions made up of random coils and a- helical structures giving it a hierarchical structure. When these molecular regions are in the relaxed state they are randomly oriented and hence offer medium mechanical flexibility but also make them more sensitive to moisture and mechanical deformation.(98) As a polymer film is pre-stretched, the chains of the polymer are oriented in the direction of imparted strain. This orientation facilitates the conversion of amorphous structure to b-sheet crystalline structures to a greater extent, as well as enhances intermolecular hydrogen bonding.(99) Consequently, the internal structure of the membrane is made more compact and anisotropic with great impact on its mechanical, electrical, and degradation properties.(100) Mechanically, pre-stretched silk membranes have been shown to have good tensile strength, Youngs modulus and decreased creep deformation. The increased molecular packing increases the efficiency of load transfer in the material such that the membrane can endure the repetitive mechanical stress.(101) This is an important property of implantable bioelectronic devices that are in constant contact with physiological motions like cardiac pulsation or muscle contraction.(102) The structural organization is thus improved thus increasing durability and reliability of silk membranes in dynamic biological environments. The electrical behaviour of silk membranes is also pre-stretched. Higher crystallinity lowers the free volume of the polymer structure, and this restricts the uptake of water and thus a reduction in the variation of dielectric properties.(103) The b-sheet network with higher density enhances dielectric stability and lowers leakage currents which leads to similar electrical performance in the long term.(104) This stability is vital in the use of the material in neural interface, flexible biosensors and implantable electronic substrates where the material is required to transmit signals reliably.(105) One more significant benefit of pre-stretching is that it has an effect on degradation behavior. An increase in b-sheet content gives greater resistance to enzymatic and hydrolytic degradation, and extended life on the biological environment of silk membranes.(106) Through varying degrees of pre-stretching used in processing made material, researchers can directly regulate the degradation rate of the material to meet the particular requirements of a biomedical application, such as temporary implants or long-term monitoring devices.Pre-stretching also enhances the dimensional stability of the silk membranes under aqueous situations.(107) Silk membranes are prone to untreated swelling when exposed to moisture, and it may lead to changes of the thickness, structural distortion, or delamination in multi-layer bioelectronic systems. Pre-stretched membranes in contrast are seen to swell less because of the tightly packed molecular structure.(108) This is used to maintain structural integrity and electrode and conductive layer alignment in high-resolution bioelectronic devices.Also, pre-stretching can improve interfacial adhesion between silk membranes and conductive materials including metal thin films and conductive polymers.(109) The enhanced surface stability lowers the tendency to form cracks and mechanical drift in case of repeated bending or cyclic loading thus improving the total life of the device.(110) As a result, in pre-stretching, a simple method is used to scale and achieve chemical-free and easy to tune performance characteristics in silk membranes. It can be optimized to have the maximum mechanical strength, flexibility, electrical stability, and degradation kinetics without compromising the intrinsic biocompatibility of silk fibroin through the control of strain levels and processing conditions.(111)Due to these reasons, pre-stretched silk membranes have great promises in the future of wearable and implantable bioelectronic systems.(112)

7.0 Silk Bioelectronics Crystallinity-Conductivity Relationship.

The long-term stability and electrical performance of bioelectronic systems based on silk fibroin highly depends on how the relationship between conductivity and crystallinity is. Silk fibroin is a semi-crystalline biopolymer which is made of highly ordered b-sheet crystalline structure embedded into disordered amorphous structure.(113) The relative area, tilt and the arrangement of these domains have a considerable influence on charge transportation, dielectric behavior, sensitivity to moisture, and interfacial electrical properties. Knowledge and management of this crystal-conductivity association is thus critical in boosting the optimal silk resources applicable as a substrate, dielectric lattice, encapsulation, and composite matrices in wearable and implantable bioelectronic devices.(114)

7.1 Crystallinity Structural Origin in Silk Fibroin

Silk Fibroin is a protein with a crystalline structure formed by the arrangement of protein molecules in a regular manner. <|human|>7.1 Structural Origin of Crystallinity in Silk Fibroin Silk Fibroin is a protein, whose crystalline structure is created by the arrangement of the protein molecules in a regular way.(115)Silk fibroin has a repeating amino acid sequence, which is the substance of the crystalline structure of this compound and is mainly made of glycine, alanine, and serine.(116) These amino acids help to form tightly packed structures of b-sheet that is stabilized by intermolecular hydrogen bonding. b-sheet domains resulting are nanocrystalline regions that allow rigidity of structure and high molecular packing density. The amorphous regions, on the contrary, are composed of random coil conformations and less organized helices that are more mobile and have increased free volume.(117) The general level of crystallinity of the fibroin is determined by different processing factors like the rate of drying, solvent treatment, mechanical stretching, thermal annealing, and exposure to humidity. With the growth of b-sheet formation, the speed of the structure decreases as well as the mobility of the molecules, resulting in the increase in crystallinity.(118)

7.2 Ionic and Insulating Conduction Electrical Conductivity of Silk.

Silk fibroin acts as a good electrical insulator in its dry form since it does not contain any free charge carriers required to conduct the electrons. But on exposure to moisture, especially at physiological conditions, ionic conduction may proceed by the absorption of water molecules and mobile ions.(119) The degree of crystallinity is very important in the regulation of this electrical behavior. The crystalline silk structures are highly crystallized which results in compact molecular packing to limit water absorption and decrease ionic mobility to minimize leakage currents and enhance electrical stability.(120) Less crystallinity, on the other hand, causes the free volume in the structure to be high, allowing more water to be absorbed and protons or ions transported. Consequently, silk materials have the property of insulating conduction as well as ionic conduction depending on their crystallinity and environmental humidity.(121)

7.3 The effect of crystallinity on the dielectric characteristics is discussed.

Dielectric behavior is an essential parameter of the bioelectronic system based on silk especially in capacitive sensors, neural interfaces and implantable circuit.(122) The degree of crystallinity has a direct effect on several dielectric properties, and they are the dielectric constant, dielectric loss, breakdown voltage, and frequency stability.(123) The higher the crystallinity, the higher the restriction of dipolar movement of the polymer chains resulting in reduced dielectric loss and oscillations of polarization. Increased crystallinity also enhances dielectric strength, and also resistance to electrical breakdown.(124) This means that the higher the crystalline content of the silk membranes, the more stable the impedance profiles in the presence of aqueous conditions, and this is critical to the chronic implantable devices that need to be signal-reliable over the long term.(125)

7.4 Crystallinity in Conductive Composites made of Silk.

Silk fibroin has also been used in conjunction with conductive polymers, carbon nanomaterials, metallic nanoparticles and other conductive substances as electrically active composites in several bioelectronic devices.(126) The crystal arrangement of the silk kelp plays a major role on the method of transporting the charge in these composites. Crystallinity makes it stronger as far as mechanics are concerned, and eliminates the development of microcracks that may interfere with the conduction routes.(127) Also, the ordered b-sheet structures give better interfacial bonding between the silk matrix and conductive fillers, and thus effective transfer of charge. Excessive crystallinity can however limit polymer chain movement and influence the dispersion of fillers.(128) Thus, a balance between the crystalline and amorphous areas should be considered optimal to ensure the mechanical or mechanical stability is ensured as well as efficient electrical conductivity.(129)

7.5 Interaction of moisture and electrical drift.

The uptake of moisture is significant in dictating the electrical properties of the silk materials.(130) The amorphous structures of silk can easily take up water, and this may enhance ionic conductivity, dielectric behavior, create impedance hysteria, and hasten the degradation of the material.(131) The attainment of greater crystallinity decreases the diffusion routes of water in the structure and, consequently, minimizes the swelling and stabilizes electrical parameters over time.(132) This moisture insensitivity is specifically significant in the case of implantable bioelectronics that can be used in physiological fluids over long durations.(133)

7.6 Charge Transport Mechanisms Psychical Processes.

The charge transport in silk based electronic systems may occur in a variety of ways, including ionic conduction by the presence of moisture, electronic conduction by conductive fillers and inter-facial polarization at material interfaces.(134) The high crystallinity usually inhibits the ionic conduction by reducing the intake of water and enhancing the preservative electronic conduction routes in the composites.(135) Thus, the best degree of crystallinity depends on the proposed device operation. Crystallinity Dielectric layers and insulating substrates should be high-crystallinity, ionic sensor use could be moderate-crystallinity, and balanced-crystallinity is necessary with flexible electrode systems that need mechanical and electrical stability.(136)

7.8 Trade-Offs and Strategies of Optimization.

Even though the increase in crystallinity enhances the mechanical strength and electrical stability, overcrystallization may decrease the flexibility and make the material brittle.(137) In order to obtain the best performance, researchers use many processing strategies to regulate crystallinity, such as the controlled mechanical stretching, gradual evaporation of solvent, mild thermal treatment and spatial crystallinity engineering.(138) The methods permit the accurate regulation of crystalline composition without reducing the viability of silk fibroin in biocompatibility.(139)

8.0 Chronic Biopotential Chronic Electronic Interfaces to a chronic chronicle.

Electronic interfaces made of oriented-crystalline (OC) silk represent a high-tech category of biointegrated materials that can be used to improve the mechanical and electrical stability of devices employed in chronic biopotential monitoring.(140) The processing of the silk fibroin membranes in these systems is performed to attain high level of molecular chain alignment and high 8-sheet crystallinity by controlled methods like mechanical stretching, directional drying and solvent or thermal annealing.(141) This structured crystalline structure is an enormous enhancement of mechanical strength, dimensional stability and moisture insensitivity of silk and therefore, is the most appropriate in long-term electrophysiological studies, which involve the use of electrical electrodes (electroencephalography (EEG), electrocardiography (ECG), electromyography (EMG)).(142) The level of intermolecular hydrogen bonding, high-order 200 -sheet domains, and reduced free volume increase tensile strength and minimize swelling of OC silk membranes in physiological conditions.(143) Such structural properties reduce mechanical mismatch and delamination in the multilayer bioelectronicly, and therefore they retain the structural integrity during repeated mechanical forces generated by the beating of the heart, muscle movement, or micromotion of the brain.(144) Besides mechanical advantages, OC silk has better electrical stability, hence, required to detect bioelectrical signals in the microvolt-millivolt.(145) Higher crystallinity leads to decreased ionic leakage, decreased dielectric loss, constant impedance over frequencies and higher dielectric breakdown strength.(146) The material prevents changes in ion-mediated conductivity and also limits water diffusion thereby maintaining uniform electrode-tissue impedance and enhances the signal to noise ratio during long-term recordings.(147) Mechanical compatibility with soft biological tissues is also another important benefit of OC silk interfaces. In contrast to hard electronic materials, OC silk provides an equal balance between strength and flexibility enabling the interface to be strongly adherent to tissue surfaces and to be resistant to fatigue caused by repeated deformation.(148) This flexibility minimizes micromotion at the electrode tissue interface and, therefore, decreases inflammatory reactions and fibrotic encapsulation which, otherwise, would deteriorate signal quality over time.(149,150) Moreover, OC silk membranes can be used as substrates or encapsulation surfaces of conductive materials that include thin metal electrode, conductive polymers and carbon-based nanomaterials.(151) The crystalline ordered network of the interfaces increases interfacial adhesion between the silk and conductive layers, minimizing cracks or delaminations during the long term functioning of the device and guarantees constant conduction of electrical signals in flexible detection devices.(152) Chronic bioelectronic devices are used in wet conditions with high concentrations of electrolytes, and thus, low water uptake and swelling of highly crystalline OC silk further enhance the stability in the long term, reducing the effects of electrochemical degradation and impedance shift.(153) Although being more crystalline, OC silk still has the same biocompatibility and biodegradability of silk fibroin, and the degradation rate can be accurately regulated by the content of β-sheet.(154) Increased crystallinity will reduce degradation over the long term, but moderate crystallinity will provide the possibility of controlled bioresorption into temporary implants, which do not

require surgical removal.(155) Because of this set of mechanical longevity, electrical stability, water resistance, and tunable biodegradability, OC silk-based electronic interfaces have great potential in chronic biopotential monitoring, such as long-term neural signal recordings, implantable cardiac rhythm monitoring, wearable EEG and EMG systems, and flexible epidermal electrodes, and allow the continuous and reliable recording of physiological signals in the long term.(156)

9.0 Biocompatibility and In Vivo Performance of Silk Interfaces that are modified.

A paramount aspect in assessment of the silk fibroin (SF)-based bioelectronic interfaces is biocompatibility and in vivo performance particularly in biomedical implantable apparatus and long-term physiological monitoring system.(157) Altered silk interfaces made by using methods like pre-stretching, an oriented crystallization process, solvent annealing and composite incorporation have been created not only to improve mechanical and electrical functionality, but to maintain the high level of biological compatibility that silk itself has. Silk fibroin has been perceived to possess low immunogenicity, low cytotoxicity, high hemocompatibility and biodegradability is regulateable making it one of the most appropriate biomedical integrations.(158) Being a protein-based biomaterial, which is primarily based on amino acids, including glycine, alanine, and serine, silk fibroin may be slowly broken down by natural body enzymes and broken down into non-toxic by-products.(159) Silk, in contrast to many synthetic polymers, does not release toxic acidic products of degradation which could inflame or irritate areas of implantation. Significantly, the structural changes enhancing the crystallinity of the β-sheets are mainly those that affect physical structure of the material as opposed to those that affect chemical composition, thus in this case the material can maintain its native biocompatibility despite the processing changes to enhance the device functionality.(160,161) The effect of biological response to modified silk interfaces is highly dependent on the physical properties of the membrane such as surface roughness, balance between hydrophilicity and hydrophobicity, crystallinity and mechanical stiffness.(162) These parameters control the cell adhesion, proliferation, and differentiation on the material surface. Moderately crystallized silk membranes have been found to offer the best conditions to promote cell attachment in that they are mechanically stable enough and at the same time retain adequate surface wettability to adsorb proteins which is crucial to cellular interaction. Higher crystallinity does not tend to prevent cell adhesion needed proteins adsorption, but a slight decrease in water uptake is evident.(163) Various experimental works have shown that modified silk interfaces maintain high cell viability, generate low concentration of inflammatory cytokine production, and enhance positive tissue integration and less fibrotic capsule formation than many other traditional synthetic implant materials.(164,165) These biological reactions are especially beneficial in neural and cardiac bioelectronic devices that require the stable long-term tissue integration of the bioelectronics to be used in order to obtain reliable signal access. Another critical parameter of the performance of the silk-based bioelectronic systems is the in vivo degradation behavior.(166) The rate of degradation of silk fibroin highly relies on the crystalline structure and the proportion of 2-sheets.(167) Less crystallinity also means that the materials are more easily degraded as their amorphous regions are easier to attack by enzymes and water and more crystalline structures degrade slower and more predictably. In long-term bioelectronic use, degradation should be controlled since the material should have structural and functional integrity during the necessary period of use of the device.(168) Silk interfaces can thus be modified to stay stable over a period of weeks or months before breaking down to non-toxic compounds which can be recycled by the surrounding tissues.(169) This can be particularly useful in temporary biomedical implants and bioresorbable electronic systems, which are set to work over a limited time and then harmlessly vanish, without having to undergo surgical procedures.(170) Besides the biological compatibility and control of degradation, the electrical environment in physiological environments is also very important in the reliability of the implantable bioelectronics. The devices in vivo are constantly subjected to wet conditions, ionic body fluid, mechanical movement, and temperature change some of which can alter electrical characteristics.(171) Enhanced crystallinity and modified silk membranes show less swelling with moisture, constant impedance properties, low leakage currents and time-dependent stable signal-to-noise ratios.(172) These properties assist in stabilizing the electrical activity of long-term recording of biopotentials, e.g. neural activity or cardiogenic rhythms. The other critical consideration to mechanical devices that are implanted in dynamic tissues like the brain, heart or skeletal muscles where deformation of the devices takes place through physiological movement.(173) Silk interfaces that have been modified are characterized by

high-fatigue performance, great crack propagation resistance, constant adhesion performance with conductive layers, and low mechanical drift under extended conditions. Oriented-crystalline or pre-stretched silk structures in specific ensure structural reliability during cyclic loading conditions, enhancing the reliability of flexible implantable devices to a great extent.(174) Hemocompatibility and tissue compatibility are also noted to be relevant in applications that are in direct contact with blood or vascular tissues. Silk fibroin generally exhibits low platelet activation, low thrombus formation and good relations with endothelial cells, which implies a good blood compatibility.(175) Structural changes that enhance mechanical or electrical functionality do not add foreign chemical additives, and the interface made of silk can remain in contact with biological systems without changing its natural compatibility with the biological system and produces few chances of clotting or immune response.(176) Moreover, the data with modified silk interfaces can facilitate gradual tissue remodelling and alignment with adjacent biological structures, which make it possible to create stable bioelectronic interfaces during long implantation periods.(177) The possibility to blend the silk fibroin with bioactive molecules, growth factors, or antimicrobial agents is another benefit of this material as it can additionally improve the cellular responses and lower the risk of infection when the implantation occurs.(178) Furthermore, silk materials are optically transparent and permeable to some gases, which could be further used as the means of implementing sensing or diagnostic capabilities in multifunctional bioelectronic systems. Finally, the successful combination of the biological compatibility, mechanical stability, and electrical stability is the key to the long-term functional performance of implantable bioelectronic devices.(179) Engineered silk interfaces have constant electrode tissue contacts, low signal drift, controlled degradation, and low chance of device failure in long term implantation. Structural tunability combined with mechanical flexibility, electrical stability and natural biological safety makes modified silk fibroin a highly promising material platform in the next generation implantable and wearable bioelectronic technology, especially in chronic neural monitoring, cardiac sensing, advanced biosensors, and long term physiological recording systems.(180)

10. Applications and Future Perspectives

Bioelectronic interfaces based on modified silk fibroin do not only promise great opportunities in the contemporary biomedical devices but also introduce new possibilities in the future developments of healthcare technologies. The fact that they can combine structural strength with softness enables them to mediate the mechanical discontinuity between hard electronic devices and fragile biological tissues.(181) The property is especially useful in implants in the long-term neural implants, cardiac patches and soft epidermal sensors where mechanical mismatch is likely to cause inflammation or signal instability.(182) Through the precise modulation of β-sheet crystallinity, the electrical insulation, moisture resistance as well as degradation can be manipulated and so custom silk membranes can be tailored to particular clinical duration and functional conditions. Other applications in addition to conventional biopotential monitoring, there are investigations into silk-based platforms to use as integrated sensing platforms that can monitor electrical, chemical and mechanical signals simultaneously.(183) As an example, multimodal biosensors can be built on silk substrates to measure electrophysiological activity and pH, temperature or metabolic changes. They are also optically transparent and therefore can be combined with optoelectronic systems including optical stimulation or imaging-assisted neural interfaces. Moreover, innovations in microfabrication and additive manufacturing could also facilitate microfabricated and patterned silk electronics with microscale resolution, as well as high-density electrode array patterned interfaces with better spatial resolution in brain-machine interfaces. Future plans are projected to focus on scalable fabrication techniques, mixed material systems in addition to long-term clinical validation.(184) The use of biodegradable conductors and environmental processing technology may result in complete sustainability of electronic systems with a low environmental impact. Moreover, it is possible to imbue silk with wireless communication devices and energy-gathering elements to create self-powered implantable products that will be able to monitor their health constantly without needing a battery change.(185) With the ever-evolving interdisciplinary research, silk fibroin can be vastly replaced by a core in the design of safe, durable and adaptive bioelectronics in personalized medicine as well as long term therapeutic monitoring. In addition to biomedical applications of silk-based bioelectronics, bioresorbable medical electronics, smart drug delivery, and regenerative medicine are also emerging applications of silk-based bioelectronics.(186) Due to the ability of silk fibroin to stabilize sensitive biomolecules, researchers are seeking systems in which therapeutic agents, enzymes or growth factors are incorporated into

silk-based electronic systems. These versatile systems might be able to measure physiological cues and provide a regulated response to therapy at the same time, developing closed-loop bioelectronic therapies.(187) As an example, personalized and responsive healthcare technologies could be achieved by having implantable devices that react to abnormal neural or cardiac activity and release drugs in response to the signal detected.(188)The other potential avenue is the combination of silk fibroin and bendable and stretchable electronics to come up with next-generation wearable health systems. Silk-based epidermal electronics can adhere to the skin surface and the epidermal device can be used to continuously measure physiological parameters, including heart rate, muscle activity, hydration, and body temperature.(189) The systems can be active in long-distance health monitoring, rehabilitation, and early diagnosis. Moreover, optical transparency of silk offers the ability to combine it with optical sensors, photonic devices, bioimaging systems that have the potential to provide both electrical and optical monitoring of biological tissues simultaneously.(190)Silk-based bioelectronics is also growing in power with the development of nanotechnology. Graphene, carbon nanotubes, MXenes, and metallic nanowires used as nanomaterials in silk matrices can be very useful in increasing electrical conductivity, sensing sensitivity, and mechanical performance. These nanocomposites can then be hybridized creating biosensors that are highly sensitive and detect biochemical markers, neurotransmitters or metabolic compounds in very low concentrations.(191) Additionally, nanostructured interfaces based on silk can enhance electrode tissue interface which is of particular significance in neural recording and brain machine interface technology.Silk fibroin has become a candidate material in the environmentally-friendly and biodegradable electronic systems in the transient electronics field.(192) The artificial devices made of silk substrates and biodegradable conductors and semiconductors can then be dissolved once their purpose has been served, instead of requiring surgery to take out the implant in medical devices or discarding electronic waste in environmental sensors. These temporary electronics can be used in post-surgical monitoring, temporary neural stimulation and implantable diagnostic systems with a life expectancy of a set time before it can safely degrade in the body.(193)In spite of these developments, however, there are a number of obstacles that need to be overcome before bioelectronics based on silk can be used extensively in clinical practice. Mass production techniques should be established, so that the quality of materials, reproducibility, and low costs of production can be achieved. Processing protocols of silk fibroin should also be standardized to keep the batch-to-batch variation of mechanical, electrical and degradation properties to a minimum.(194) Along with that, there is a need to conduct an extensive long-term in vivo research to thoroughly comprehend the long-term biological reaction to devices made of silk and to develop a dependable regulatory system in order to obtain a medical authorization.(195)Future studies will also consider the enhancement of structural engineering engineering techniques including oriented crystallization, controlled crosslinking and hierarchical microstructuring as a means of further enhancing mechanical stability and electrical stability.(196) It can be also integrated with wireless communication systems, micro-energy harvesting technology, and soft robotics that could result in autonomy of implantable devices that could continuously monitor and provide therapeutic intervention without the use of external power sources.(197,198) Finally, the combination of biomaterials science, nanotechnology, and bioelectronics will see the use of silk fibroin as one of the platforms of medical devices of the next generation that are safe, adaptable, and able to interact with living tissues over the long-term.(199)

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