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Diffusion Tensor Imaging in the Human Spinal Cord: Development, Limitations, and Clinical Applications

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ABSTRACT
Diffusion tensor imaging (DTI) is currently the only non-invasive *in vivo* assessment of white matter tract integrity. Capitalizing on the diffusion properties of water within an axon, DTI enables the visualization of tissue structure at a microscopic scale. Furthermore, measurements of anisotropy and diffusivity enable the detection of subtle details of the effects of injury that cannot be detected using conventional magnetic resonance techniques. Recently, DTI has been applied to the spinal cord, and results have demonstrated it to be a valuable tool for assessing the extent of white matter damage in numerous spinal cord–related conditions including multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, myelitis, and spinal cord tumors. The purpose of this review is to discuss the technical limitations of the imaging method within the spinal cord, review possible solutions, and highlight the current uses and the potential clinical application of this technique.

Keywords: diffusion tensor imaging, human, spinal cord, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, myelitis, spinal cord tumors

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Nanoscale Drug Delivery Systems for Enhanced Drug Penetration into Solid Tumors: Current Progress and Opportunities

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ABSTRACT
Poor penetration of anticancer drags into solid tumors significantly limits their efficacy. This phenomenon has long been observed for small-molecule chemotherapeutics, and it can be even more pronounced for nanoscale therapies. Nanoparticles have enormous potential for the treatment of cancer due to their wide applicability as drug delivery and imaging vehicles and their size-dependent accumulation into solid tumors by the enhanced permeability and retention (EPR) effect. Further, synthetic nanoparticles can be engineered to overcome barriers to drag delivery. Despite their promise for the treatment of cancer, relatively little work has been done to study and improve their ability to diffuse into solid tumors following passive accumulation in the tumor vasculature. In this review, we present the complex issues governing efficient penetration of nanoscale therapies into solid tumors. The current methods available to researchers to study nanoparticle penetration into malignant tumors are described, and the most recent works studying the penetration of nanoscale materials into solid tumors are summarized. We conclude with an overview of the important nanoparticle design parameters governing their tumor penetration, as well as by highlighting critical directions in this field.

Keywords: Tumor penetration, solid tumors, nanoparticles, cancer, liposomes, polymeric micelles, drug delivery

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Pathological Speech Signal Analysis Using Time-Frequency Approaches

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ABSTRACT
Acoustical measures of vocal function are important in the assessments of disordered voice, and for monitoring patients' progress over the course of voice therapy. In the last 2 decades, a variety of techniques for automatic pathological voice detection have been proposed, ranging from traditional temporal or spectral approaches to advanced time-frequency techniques. However, comparison of these methods is a difficult task because of the diversity of approaches. In this article, we explain a framework that holds the existing methods. In the light of this framework, the methodologic principles of disordered voice analysis schemes are compared and discussed. In addition, this article presents a comprehensive review to demonstrate the advantages of time-frequency approaches in analyzing and extracting pathological structures from speech signals. This information may have an important role in the development of new approaches to this problem.

Keywords: pathological speech detection, voice quality assessment, feature extraction, classification, time-frequency features

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Preface: Detection, Modeling, and Compensation of Organ Motion and Deformation–Part I

Tobias Preusser, Matthias Gunther, Horst Karl Hahn
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pages **97-98**

Motion Compensation Strategies in Magnetic Resonance Imaging

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ABSTRACT
Image quality in magnetic resonance imaging (MRI) is considerably affected by motion. Therefore, motion is one of the most common sources of artifacts in contemporary cardiovascular MRI. Such artifacts in turn may easily lead to misinterpretations in the images and a subsequent loss in diagnostic quality. Hence, there is considerable research interest in strategies that help to overcome these limitations at minimal cost in time, spatial resolution, temporal resolution, and signal-to-noise ratio. This review summarizes and discusses the three principal sources of motion: the beating heart, the breathing lungs, and bulk patient movement. This is followed by a comprehensive overview of commonly used compensation strategies for these different types of motion. Finally, a summary and an outlook are provided.

Efficient Finite Element Methods for Deformable Bodies in Medical Applications

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ABSTRACT
Simulation techniques for deformable bodies are of major relevance for a broad range of medical applications. In recent decades, a lot of work has been performed to improve simulation methods, allowing interactivity or even real time. However, this work often focused on applications such as computer games or virtual environments, where physical accuracy is not a primary goal. The goal of this report is to give an overview of efficient physics-based techniques for deformable objects, focusing on finite element methods, and to discuss the applicability of these techniques in medical scenarios. As a result, we focus on techniques that are amenable to simulating highly resolved meshes, which for instance can be generated from computed tomography (CT) or magnetic resonance (MR) images, and we review the so-called corotated finite element method that has shown a high potential in recent years. Specifically, we will capture in detail the related work in this field and demonstrate the current state of the art in efficient deformable bodies simulations.

Breast Image Registration and Deformation Modeling

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ABSTRACT
Image-based examination of the breast facilitates the detection of breast diseases, particularly of present benign and malignant lesions. For computer-aided processing of serial and multimodal clinical data, both for visual correlation and quantitative analysis, automated image-registration methods are an indispensable tool. The wide range of modalities and the high variability of breast appearance have led to a large diversity of proposed approaches for tissue deformation modeling and image registration. In this article, we review current developments in breast image registration techniques, and comment on their clinical relevance, individual capabilities, and open challenges.

Brain-Machine Interfaces: Electrophysiological Challenges and Limitations

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ABSTRACT
Brain-machine interfaces (BMI) seek to directly communicate with the human nervous system in order to diagnose and treat intrinsic neurological disorders. While the first generation of these devices has realized significant clinical successes, they often rely on gross electrical stimulation using empirically derived parameters through open-loop mechanisms of action that are not yet fully understood. Their limitations reflect the inherent challenge in developing the next generation of these devices. This review identifies lessons learned from the first generation of BMI devices (chiefly deep brain stimulation), identifying key problems for which the solutions will aid the development of the next generation of technologies. Our analysis examines four hypotheses for the mechanism by which brain stimulation alters surrounding neurophysiologic activity. We then focus on motor prosthetics, describing various approaches to overcoming the problems of decoding neural signals. We next turn to visual prosthetics, an area for which the challenges of signal coding to match neural architecture has been partially overcome. Finally, we close with a review of cortical stimulation, examining basic principles that will be incorporated into the design of future devices. Throughout the review, we relate the issues of each specific topic to the common thread of BMI research: translating new knowledge of network neuroscience into improved devices for neuromodulation.

The Challenge of Integrating Devices into the Central Nervous System

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ABSTRACT
Implanted biomedical devices are playing an increasingly important role in the treatment of central nervous system disorders. While devices such as deep brain stimulation electrodes and drug delivery systems have shown clinical success in chronic applications, other devices such as nerve guidance substrates and recording electrodes that operate over a very short length scale have not had the same kind of clinical impact. By reviewing what is currently known about the brain tissue response to implanted electrodes, the authors propose that the foreign-body response, which changes the tissue structure immediately surrounding implanted devices, may be the reason near-function devices are stalled in preclinical development. The article concludes by reviewing recent efforts to reduce the foreign body response, which shows promise to accelerate the clinical development of this new generation of biomedical devices.

Wireless Microstimulators for Neural Prosthetics

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ABSTRACT

One of the roadblocks in the field of neural prosthetics is the lack of microelectronic devices for neural stimulation that can last a lifetime in the central nervous system. Wireless multi-electrode arrays are being developed to improve the longevity of implants by eliminating the wire interconnects as well as the chronic tissue reactions due to the tethering forces generated by these wires. An area of research that has not been sufficiently investigated is a simple single-channel passive microstimulator that can collect the stimulus energy that is transmitted wirelessly through the tissue and immediately convert it into the stimulus pulse. For example, many neural prosthetic approaches to intraspinal microstimulation require only a few channels of stimulation. Wired spinal cord implants are not practical for human subjects because of the extensive flexions and rotations that the spinal cord experiences. Thus, intraspinal microstimulation may be a pioneering application that can benefit from submillimeter-size floating stimulators. Possible means of energizing such a floating microstimulator, such as optical, acoustic, and electromagnetic waves, are discussed.

State of the Art and Future Challenges in Neural Engineering: Strategies for Nervous System Repair Foreword / Editors' Commentary (Volume 2)

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ABSTRACT
This issue of Critical Reviews in Biomedical Engineering is volume two of a three volume series focused on neural engineering. The theme of this volume is "Strategies for Nervous System Repair." These articles present a range of biomedical engineering strategies to improve outcomes with specific focus given to neural tissue engineering and biomaterial strategies for the repair of spinal cord and peripheral nerve injury. These articles emanate from a unique workshop presented at the 2009 Biomedical Engineering Society Annual Meeting in Pittsburgh, PA, titled "Tissue Engineering of the Nervous System: Approaches and Strategies for the Repair of Peripheral and Spinal Cord Injuries." At times, neurobiologists can be wary of tissue engineering due to a misunderstanding of an engineering approach, or due to an engineer's design that disregards aspects of the surrounding biology, neuroanatomy, or the goals of the surgeon. For instance, novel biomaterial scaffolds are frequently proposed; however, the biology beyond the material is not often considered. In other cases, the efficacy of a new tissue-engineering approach is not evaluated against the gold standard clinical treatment or in the best injury model. This workshop brought leading neurobiologists, clinicians, and engineers together to redefine and revitalize the tissue engineering approach to nervous system repair. Presentations from leading experts addressed the state of the art, identified key challenges, and discussed the most promising opportunities for progress. The articles in this volume were formulated from the resulting discussions.

Biomedical Engineering Strategies for Peripheral Nerve Repair: Surgical Applications, State of the Art, and Future Challenges

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ABSTRACT
Damage to the peripheral nervous system is surprisingly common and occurs primarily from trauma or a complication of surgery. Although recovery of nerve function occurs in many mild injuries, outcomes are often unsatisfactory following severe trauma. Nerve repair and regeneration presents unique clinical challenges and opportunities, and substantial contributions can be made through the informed application of biomedical engineering strategies. This article reviews the clinical presentations and classification of nerve injuries, in addition to the state of the art for surgical decision-making and repair strategies. This discussion presents specific challenges that must be addressed to realistically improve the treatment of nerve injuries and promote widespread recovery. In particular, nerve defects a few centimeters in length use a sensory nerve autograft as the standard technique; however, this approach is limited by the availability of donor nerve and comorbidity associated with additional surgery. Moreover, we currently have an inadequate ability to noninvasively assess the degree of nerve injury and to track axonal regeneration. As a result, wait-and-see surgical decisions can lead to undesirable and less successful "delayed" repair procedures. In this fight for time, degeneration of the distal nerve support structure and target progresses, ultimately blunting complete functional recovery. Thus, the most pressing challenges in peripheral nerve repair include the development of tissue-engineered nerve grafts that match or exceed the performance of autografts, the ability to noninvasively assess nerve damage and track axonal regeneration, and approaches to maintain the efficacy of the distal pathway and targets during the regenerative process. Biomedical engineering strategies can address these issues to substantially contribute at both the basic and applied levels, improving surgical management and functional recovery following severe peripheral nerve injury.

Biomaterial Design Considerations for Repairing the Injured Spinal Cord

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ABSTRACT
With increasing regularity, biomaterials are being designed with the goal of promoting repair of the injured spinal cord. Most often, the efficacy of novel biomaterials is tested using in vitro models; however, their true potential will be realized only after they are applied and evaluated in standardized in vivo spinal cord injury (SCI) models. The purpose of this review is to (1) provide a primer on SCI research including an overview of common pathogenic mechanisms that may respond to biomaterials and the in vivo models and outcomes assessment tools used to evaluate therapeutic efficacy; (2) review the types of biomaterials that

have been tested in these models; (3) discuss which biomaterials might be applied to these models in the future; and (4) recommend future engineering strategies to create better in vivo models and assessment tools.

Microfluidic and Compartmentalized Platforms for Neurobiological Research

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ABSTRACT
Methods to compartmentalize neurons allow distinct neuronal segments (i.e., cell bodies, axons, dendrites, or synapses) to be accessed, visualized, and/or manipulated. Compartmentalization has resulted in multiple studies that would not otherwise be possible in vivo or in traditional random cultures, such as investigations of axonal transport, biochemical analysis of axons, and axonal injury/regeneration. Chambers for compartmentalizing neurons were first developed for long projection peripheral neurons in the 1970s using machined Teflon dividers and relied on manually applied grease layers to spatially and fluidically separate distal axons from their cell bodies. More recently microfabrication and soft lithography techniques have been used to create compartmentalized microfluidic platforms, relying on microgrooves contained within a solid barrier through which axons and dendrites are able to extend, but not their cell bodies. These platforms are unique in their ability to culture central nervous system (CNS) neurons and allow high-resolution live imaging. These microfluidic platforms have allowed new investigations of axonal and synaptic biology in the CNS. Moreover, these microfluidic platforms offer improvements for other neural cell and tissue preparations. In this review we discuss traditional methods for compartmentalization, compartmentalized microfluidic platforms, and their use for neurobiology. Lastly, we discuss the use of these platforms for defining and manipulating synapses both pharmacologically and by electrical stimulation and recording.

Neural Tissue Engineering and Biohybridized Microsystems for Neurobiological Investigation In Vitro (Part 1)

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ABSTRACT
Advances in neural tissue engineering have resulted in the development and implementation of three-dimensional (3-D) neural cellular constructs, which may serve as neurofidelic in vitro investigational platforms. In addition, interfacing these 3-D cellular constructs with micro-fluidic and/or micro-electrical systems has created biohybridized platforms, providing unprecedented 3-D microenvironmental control and

allowing noninvasive probing and manipulation of cultured neural cells. Cells in the brain interact within a complex, multicellular environment with tightly coupled 3-D cell-cell/cell–extracellular matrix (ECM) interactions; yet most in vitro models utilize planar systems lacking in vivo–like ECM. As such, neural cultures with cells distributed throughout a thick (>500 μm), bioactive extracellular matrix may provide a more physiologically relevant setting to study neurobiological phenomena than traditional planar cultures. This review presents an overview of 2-D versus 3-D culture models and the state of the art in 3-D neural cell-culture systems. We then detail our efforts to engineer a range of 3-D neural cellular constructs by systematically varying parameters such as cell composition, cell density, matrix constituents, and mass transport. The ramifications on neural cell survival, function, and network formation based on these parameters are specifically addressed. These 3-D neural cellular constructs may serve as powerful investigational platforms for the study of basic neurobiology, network neurophysiology, injury/disease mechanisms, pharmacological screening, or test-beds for cell replacement therapies. Furthermore, while survival and growth of neural cells within 3-D constructs poses many challenges, optimizing in vitro constructs prior to in vivo implementation offers a sound bioengineering design approach.

Cardiac Models in Drug Discovery and Development: A Review

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ABSTRACT
Cardiovascular diseases are among the leading causes of death in the developed world. Developing novel therapies for diseases like heart failure is crucial, but this is hampered by the high attrition rate in drug development. The withdrawal of drugs at the final hurdle of approval is mostly because of their unpredictable effects on normal cardiac rhythm. The advent of cardiac computational modeling in the last 5 decades has aided the understanding of heart function significantly. Recently, these models increasingly have been applied toward designing and understanding therapies for cardiac disease. This article will discuss how cellular models of electrophysiology, cell signaling, and metabolism have been used to investigate pharmacologic therapies for cardiac diseases including arrhythmia, ischemia, and heart failure.

Mathematical and Computational Models of Oxidative and Nitrosative Stress

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ABSTRACT
The importance of nitric oxide (NO), superoxide (O_2^-), and peroxynitrite ($ONOO^-$), interactions in physiologic functions and pathophysiological conditions such as cardiovascular disease, hypertension, and diabetes have been established extensively in in vivo and in vitro studies. Despite intense investigation of NO, O_2^-, and $ONOO^-$ biochemical interactions, fundamental questions regarding the role of these molecules remain unanswered. Mathematical models based on fundamental principles of mass balance and reaction kinetics have provided significant results in the case of NO. However, the models that include interaction of NO, O_2^-, and $ONOO^-$ have been few because of the complexity of these interactions. Not only do these mathematical and computational models provided quantitative knowledge of distributions and concentrations of NO, O_2^-, and $ONOO^-$ under normal physiologic and pathophysiologic conditions, they also can help to answer specific hypotheses. The focus of this review article is on the models that involve more than one of the 3 molecules (NO, O_2^-, and $ONOO^-$). Specifically, kinetic models of O_2^- dismutase and tyrosine nitration and biotransport models in the microcirculation are reviewed. In addition, integrated experimental and computational models of dynamics of NO/O_2^-/$ONOO^-$ in diverse systems are reviewed.

Role of Substrates in Diabetes Therapy:Stem Cell Differentiation and Islet Transplantation

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ABSTRACT
Type 1 diabetes affects more than a million people in the United States and many more across the world. While pharmaceutical interventions and insulin supplementation are the most commonplace treatment of diabetes, these are not essentially cures and can potentially lead to long-term complications. Transplantation of insulin-producing Islets of Langerhans from donor pancreas has been established as a promising alternative to diabetes therapy. While successful islet transplantation has the potential of providing a cure, the primary hurdles to be overcome for it to be clinically viable are the scarcity of donor islets and immune rejection of transplanted islets. Recent advances in stem cell culture and differentiation techniques have established stem cells as a likely source of transplantable islets. Different stem cell sources have been induced toward pancreatic differentiation using specific chemical perturbations along with use of specific substrates. An approach to overcoming the second hurdle of immune rejection of transplantable islets is to encapsulate the islets in specific biomaterials. In this review, we discuss the extensive use of various substrates for pancreatic differentiation of different stem cell sources, along with different biomaterial designs used for islet transplantation.

Neural prostheses, neural rehabilitation engineering, and neuromodulation
Technologies for treating and managing consequences of stroke, spinal cord injury, epilepsy, genito-urinary function, pain, and multiple sclerosis; robot-assisted rehabilitation; deep brain stimulation for treating movement disorders
Neural Dynamics and Neurophysiology
Synchronization and control of neural activity in-vivo and in-vitro, spinal neural circuits, and stochastic resonance in neural networks, analysis and control of epilepsy
Neural Regeneration
Engineer materials and devices to facilitate the growth of neurons for specific applications such as the regeneration of peripheral nerve in case of injury or surgical resection, the regeneration of the spinal cord tissue for spinal cord injury and the regeneration of retinal tissue.
Neural and brain machine interfaces
Bio-inspired materials, cellular-level neural connection, EEG and microelectrodes for cortical control of assistive technologies, interfacing techniques with the peripheral nervous system
Neural Computation and Control
Computational neuroscience; simulation of nerve electrodes, musculo-skeletal systems, and biomechanics; advanced control algorithms

Advances in Surface EMG: Recent Progress in Detection and Processing Techniques

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ABSTRACT
This article is the first section of a review work structured in three parts and concerning a) advances in surface EMG detection and processing techniques, b) recent progress in surface EMG clinical research applications and, c) myoelectric control in neurorehabilitation. This article deals with the state of the art regarding a) the electrode–skin interface (equivalent circuits, skin treatment, conductive gels), b) signal detection modalities, spatial filters and front-end amplifiers, c) power line interference removal, separation of propagating and non-propagating potentials and removal of outliers from surface EMG signal maps, d) segmentation of surface EMG signal maps, e) decomposition of surface EMG into the constituent action potential trains, and f) relationship between surface EMG and force. The material is presented with an effort to fill gaps left by previous reviews and identify areas open for future research.

Myoelectric Control in Neurorehabilitation

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ABSTRACT
A myoelectric signal, or electromyogram (EMG), is the electrical manifestation of a muscle contraction. Through advanced signal processing techniques, information on the neural control of muscles can be extracted from the EMG, and the state of the neuromuscular system can be inferred. Because of its easy accessibility and relatively high signal-to-noise ratio, EMG has been applied as a control signal in several neurorehabilitation devices and applications, such as multi-function prostheses and orthoses, rehabilitation robots, and functional electrical stimulation/therapy. These EMG-based neurorehabilitation modules, which constitute muscle-machine interfaces, are applied for replacement, restoration, or modulation of lost or impaired function in research and clinical settings. The purpose of this review is to discuss the assumptions of EMG-based control and its applications in neurorehabilitation.

Responding to Change: Thermo- and Photoresponsive Polymers as Unique Biomaterials

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ABSTRACT

Responsive polymer systems that react to thermal and light stimuli have been a focus in the biomaterials literature because they have the potential to be less invasive than currently available materials and may perform well in the in vivo environment. Natural and synthetic polymer systems created to exhibit a temperature-sensitive phase transition lead to in situ forming hydrogels that can be degradable or non-degradable. These systems typically yield physical gels whose properties can be manipulated to accommodate specific applications while requiring no additional solvents or cross-linkers. Photo-responsive isomerization, dimerization, degradation, and triggered processes that are reversible and irreversible may be used to create unique gel, micelle, liposome, and surface-modified polymer systems. Unique wavelengths induce photo-chemical reactions of polymer-bound chromophores to alter the bulk properties of polymer systems. The properties of both thermo- and photo-responsive polymer systems may be taken advantage of to control drug delivery, protein binding, and tissue scaffold architectures. Systems that respond to both thermo- and photo-stimuli will also be discussed because their multi-responsive properties hold the potential to create unique biomaterials.

Mathematical Foundations of Biomechanics

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ABSTRACT

The aim of biomechanics is the analysis of the structure and function of humans, animals, and plants by means of the methods of mechanics. Its foundations are in particular embedded in mathematics, physics, and informatics. Due to the inherent multidisciplinary character deriving from its aim, biomechanics has numerous connections and overlapping areas with biology, biochemistry, physiology, and pathophysiology, along with clinical medicine, so its range is enormously wide. This treatise is mainly meant to serve as an introduction and overview for readers and students who intend to acquire a basic understanding of the mathematical principles and mechanics that constitute the foundation of biomechanics; accordingly, its contents are limited to basic theoretical principles of general validity and long-range significance. Selected examples are included that are representative for the problems treated in biomechanics. Although ultimate mathematical generality is not in the foreground, an attempt is made to derive the theory from basic principles. A concise and systematic formulation is thereby intended with the aim that the reader is provided with a working knowledge. It is assumed that he or she is familiar with the principles of calculus, vector analysis, and linear algebra.

Keywords: biomechanics, modeling, mechanobiology, biomathematics