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Neuromodulation:
Comprehensive
Textbook of Principles,
Technologies, and

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Therapies, Second Edition, serves as a comprehensive and in-depth reference textbook covering all aspects of the rapidly growing field of neuromodulation. Since the publication of the first edition seven years ago, there has been an explosion of knowledge in

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neuromodulation,
optogenetics,
bioelectronics
medicine and brain
computer interfacing.
Users will find unique
discussions of the
fundamental principles
of neuromodulation
and therapies, and how
they are applied to the
brain, spinal cord,
peripheral nerves,

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autonomic nerves and various organs. The book focuses on comprehensive coverage of spinal cord stimulation, non-interventional and interventional brain stimulation, peripheral nerve stimulation, and the emerging fields of neuromodulation, including optogenetics

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and bioelectronics
medicine. Provides a
comprehensive
reference that covers all
aspects of the growing
field of

neuromodulation

Written by

international, leading
authorities in their
respective fields of
neuromodulation, pain
management,

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functional
neurosurgery and
biomedical engineering
Includes new chapters
on optogenetics,
bioelectronics
medicine and brain
computer interfacing
Optogenetic
technologies have been
the subject of great
excitement within the
scientific community

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for their ability to demystify complex neurophysiological pathways in the central and peripheral nervous systems. Optogenetics refers to the transduction of mammalian cells with a light-sensitive transmembrane protein, called an opsin, such that

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illumination of the target tissue initiates depolarization; in the case of a neuron, illumination results in the firing of an action potential that can control downstream physiology. The excitement surrounding optogenetics has also extended to the clinic

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with a human trial using the opsin ChR2 in the treatment of retinitis pigmentosa currently underway and several more trials potentially planned for the near future. In this thesis, we focus on the use of viral techniques to transduce peripheral nerve tissue to be responsive to light. We

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characterize the properties of optogenetic peripheral nerve transduction, optimizing for variables such as expression strength, wavelength specificity, and time-course of expression. Within the scope of this thesis, three new methods for optogenetic peripheral

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nerve stimulation are described: (1) a method for optogenetic motor nerve control using transdermal illumination, (2) a method employing unique wavelengths to selectively target optogenetic subsets of motor nerves, and (3) a method for extending

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optogenetic expression strength and timecourse. The work is important because it lays the foundation for future advancements in optogenetic peripheral nerve stimulation in both a scientific and clinical context.

Application of optogenetic and pharmacogenetic tools

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to study the neural circuits underlying emotional valence, feeding, arousal and motivated behaviors has provided crucial insights into brain function. Expression of light sensitive proteins into specific neurons and subsequent stimulation by light (optogenetics) to

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control neuronal activity or expression of designer receptors exclusively activated by designer drugs (DREADDs) in specific neuronal populations with subsequent activation or suppression of neuronal activity by an otherwise inert ligand (pharmacogenetics)

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provides control over defined elements of neural circuits. These novel tools have provided a more in depth understanding into several questions about brain function.

These include: •

Regulation of sleep-wake transition by the interaction of hypocretin neurons of

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lateral hypothalamus
and noradrenergic
neurons of the locus
coeruleus •

Regulation of feeding
by AGRP and POMC
neurons in arcuate
nucleus of the
hypothalamus • Place
preference and positive
reinforcement by
activation of DA
neuron of VTA •

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Place aversion by
activation of VTA
GABA and lateral
habenula neurons •
Opposing influences
on reinforcement by
activation of D1 and
D2 expressing medium
spiny neurons of dorsal
striatum and nucleus
accumbens The list still
grows... From cell type
specific manipulations

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to signaling properties in the cell (Dietz et al 2012) with unprecedented temporal resolution, these tools revolutionize the exploration of pathways/connectivity. Recent years also witnessed the extension of applying these tools from studying

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emotional valence and motivated behavior to reactivation of memory. c-fos based genetic approaches allowed us to integrate light sensitive opsins or DREADD receptor into specific neurons that are activated by certain learning events (for example fear) (Garner et al 2012; Liu

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et al 2012). In this Research Topic, we welcome researchers to contribute original research articles, review articles, methods and commentary on topics utilizing optogenetic and pharmacogenetic tools to study the neural circuits underlying emotional valence, motivation,

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reinforcement and memory. We believe the Research Topic will shine light on various questions we have about brain function by using novel optogenetic and pharmacogenetic tools and will hopefully inspire ongoing research to overcome the hurdles of using

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these tools to advance clinical applications.

Nanoscience has become one of the key growth areas in recent years. It can be integrated into imaging and therapy to increase the potential for novel applications in the field of photomedicine. In the past commercial applications of

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nanoscience have been limited to materials science research only, however, in recent years nanoparticles are rapidly being incorporated into industrial and consumer products. This is mainly due to the expansion of biomedical related research and the

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burgeoning field of nanomedicine.

Applications of Nanoscience in Photomedicine covers a wide range of nanomaterials including nanoparticles used for drug delivery and other emerging fields such as optofluidics, imaging and SERS diagnostics.

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Introductory chapters are followed by a section largely concerned with imaging, and finally a section on nanoscience-enabled therapeutics.

Covers a comprehensive up-to-date information on nanoscience Focuses on the combination of photomedicine with

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nanotechnology to enhance the diversity of applications. Pioneers in the field have written their respective chapters. Opens a plethora of possibilities for developing future nanomedicine. Easy to understand and yet intensive coverage, chapter by chapter. A Realist's Guide to

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Stem Cell Therapy

Optogenetics

Optogenetics: An
Emerging Approach in
Cardiac

Electrophysiology

Optogenetic Tool

Development and

Interrogation of

Frequency-dependent

Signaling in the

Hippocamposeptal

Pathway

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Optogenetics 34

Success Secrets - 34

Most Asked Questions
on Optogenetics -
What You Need to
Know

The Scientific
American Brave New
Brain

*This book aims to
present, educate
and inform
individuals about*

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Alzheimer's disease in a comprehensive manner. Its scope ranges from the discovery of the disease, epidemiology and basic biological principles underlying it, to advanced stem cell therapies used in the treatment of Alzheimer's. It

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adopts a 'global' perspective on Alzheimer's disease, and include epidemiological data and science from countries around the world. Alzheimer's disease is a rapidly growing problem seen in every country around the world. This is the

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*first and only
comprehensive
book to cover
Alzheimer's disease,
and includes the
most updated
literature and
scientific progress in
the field of dementia
and Alzheimer's
disease
research. Most
books on the market*

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*that focus on
Alzheimer's disease
are targeted at
caregivers as
practical advice on
how to deal with
loved ones with the
disease. This book
instead is a
comprehensive and
popular science
book that can be
read by anyone with*

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*an interest in
learning more about
the disease. Dr
Jefferson Chen MD,
PhD, co-author,
participated in the
world's first surgical
clinical trial using
shunts to treat
Alzheimer's disease.
His first-hand
involvement in a
clinical trial for*

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*patients with
Alzheimer's disease
and experience
treating Normal
Pressure
Hydrocephalus
(NPH) which is
commonly
misdiagnosed as
Alzheimer's disease
lends a unique
perspective. This
book with appeal to*

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*a wide audience,
regardless of their
scientific or
educational
background.*

*A scientist assesses
the potential of stem
cell therapies for
treating such brain
disorders as stroke,
Alzheimer's disease,
and Parkinson's
disease. Stem cell*

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therapies are the subject of enormous hype, endowed by the media with almost magical qualities and imagined by the public to bring about miracle cures. Stem cells have the potential to generate new cells of different types, and have

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*been shown to do so
in certain cases.*

*Could stem cell
transplants repair
the damaged brain?*

*In this book,
neurobiologist Jack
Price assesses the
potential of stem cell
therapies to treat
such brain disorders
as stroke,
Alzheimer's disease,*

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Parkinson's disease, and spinal cord injuries. Certainly brain disorders are in need of effective treatments. These disorders don't just kill, they disable, and conventional drug therapies have not had much success in treating them. Price explains

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that repairing the human brain is difficult, largely because of its structural, functional, and developmental complexity. He examines the self-repairing capacity of blood and gut cells—and the lack of such capacity in the brain; describes

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the limitations of early brain stem cell therapies for neurodegenerative disorders; and discusses current clinical trials that may lead to the first licensed stem cell therapies for stroke, Parkinson's and macular degeneration. And

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he describes the real promise of pluripotential stem cells, which can make all the cell types that constitute the body. New technologies, Price reports, challenge the very notion of cell transplantation, instead seeking to convince the brain

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itself to manufacture the new cells it needs. Could this be the true future of brain repair?

Optogenetic neuromodulation is giving scientists an unprecedented ability to modulate neural circuits, providing specificity with regards to

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location, cell type, as well as neuromodulatory effect. On the other hand, electrical stimulation and lesions, methods commonly used to study neural circuits, are lacking in specificity, often affecting both local cells and passing

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axons, as well as multiple cell types. Our laboratory has been at the forefront of the field of optogenetics, having developed, for use in mammalian systems, Channelrhodopsin-2 (ChR2), an algal light-activated cation channel that

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*depolarizes neurons
in response to blue
light, and*

*Natronomonas
pharaonis*

halorhodopsin

*(eNpHR), a chloride
pump that*

hyperpolarizes

*neurons in response
to amber light.*

*These proteins can
control neuronal*

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activity with millisecond timescale precision, and through promoters, they can be targeted to specific cell-types in heterogeneous tissue. Along with its specificity, light stimulation with optogenetic tools often allows the

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recording of neural activity without the artifact that obfuscates recordings with electrical stimulation. The advantages provided by optogenetics allowed us to make a breakthrough in determining the

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therapeutic mechanism of deep brain stimulation, a robust treatment for Parkinson's disease in which stimulating electrodes are implanted deep in the brain. Using optogenetics, we replicated the effect of deep brain stimulation by

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modulating cortical inputs into the region where the stimulating electrode is normally placed. Combined with other corroborating publications, a hypothesis is emerging that electrical stimulation deep in the brain actually produces its

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effect by modulating cortical projections to the deep brain region. Based on this concept, several clinical studies are being done to better understand the cortical role in Parkinson's disease and determine whether cortical stimulation

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(potentially non-invasive), could be an alternative to the invasive implants currently used. In order to perform these experiments, we studied the transmission of visible light in brain tissue to estimate the volume of activation produced

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by optogenetic stimulation and developed a device to measure fluorescence in awake, behaving animals, allowing the quantification of virally transfected gene expression over time, as well as the localization of expression along

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axon bundles. The knowledge gained from these experiments will have a significant impact on future experiments in the broader field of optogenetics. Optical probes, particularly the fluorescent varieties, enable researchers

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to observe cellular events in real time and with great spatial resolution. Optical Probes in Biology explores the diverse capabilities of these powerful and versatile tools and presents various approaches used to design, develop, and

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implement them.

The book examines the use of optical probes to detect and track numerous molecular processes in living cells, including GTPase and kinase activities, membrane lipids, voltage, metal ions, metabolic signals, RNA, and

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histone modifications. It critically reviews the different probe designs and delves into the strategies for developing new fluorescent protein varieties with enhanced capabilities. It also covers sophisticated imaging techniques

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and equipment, such as intensity and lifetime-based fluorescence microscopy methods, used to visualize and track optical probes. In addition, the book goes beyond live-cell tracking to discuss the growing application of

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activity-based probes for performing pharmacological drug screening and probing molecular processes in living animals. It also discusses emerging techniques that are expanding optical probe-based approaches into

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new biological frontiers. With contributions from top international scientists, this book offers a thorough overview of the latest optical probes in cell biology and biochemistry. Both newcomers and established researchers will

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*discover how to
incorporate state-of-
the-art optical
probes and
fluorescence
imaging into their
research.*

*Strategies for
Optogenetic
Stimulation of Deep
Tissue Peripheral
Nerves*

Comprehensive

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*Textbook of
Principles,
Technologies, and
Therapies
What the Future
Holds and the
Scientists Making It
Happen
Essays by the
World's Leading
Neuroscientists
Emerging Trends in
Neuro Engineering*

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*and Neural
Computation*

*The Future of
Business*

This book, now in a thoroughly revised second edition, offers a comprehensive review of the rapidly growing field of optogenetics, in which light-sensing proteins are genetically engineered into cells in

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order to acquire information on cellular physiology in optical form or to enable control of specific network in the brain upon activation by light. Light-sensing proteins of various living organisms are now available to be exogenously expressed in neurons and other target cells both in vivo

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and in vitro. Cellular functions can thus be manipulated or probed by light. The new edition documents fully the extensive progress since publication of the first edition to provide an up-to-date overview of the physical, chemical, and biological properties of light-sensing proteins and their application in

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biological systems, particularly in neuroscience but also in medicine and the optical sciences. Underlying principles are explained and detailed information provided on a wide range of optogenetic tools for the observation and control of cellular signaling and physiology, gene targeting technologies,

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and optical methods for biological applications. In presenting the current status of optogenetics and emerging directions, this milestone publication will be a "must read" for all involved in research in any way related to optogenetics.

New research and innovations in the field of science are leading to

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life-changing and world-altering discoveries like never before. What does the horizon of science look like? Who are the scientists that are making it happen? And, how are we to introduce these revolutions to a society in which a segment of the population has become more and more skeptical of science? Climate

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change is the biggest challenge facing our nation, and scientists are working on renewable energy sources, meat alternatives, and carbon dioxide sequestration.

At the same time, climate change deniers and the politicization of funding threaten their work. CRISPR, (Clustered Regularly Interspaced Short

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Palindromic Repeats)
repurposes bacterial
defense systems to edit
genes, which can
change the way we live,
but also presents real
ethical problems.

Optogenetics will help
neuroscientists map
complicated neural
circuitry deep inside the
brain, shedding light on
treating Alzheimer's
and Parkinson's

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disease. Zimmer also investigates phony science ranging from questionable “health” products to the fervent anti-vaccination movement. Zimmer introduces readers to the real people making these breakthroughs. Concluding with chapters on the rise of women in STEM fields, the importance of US

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immigration policies to science, and new, unorthodox ways of DIY science and crowdsource funding, *The State of Science* shows where science is, where it is heading, and the scientists who are at the forefront of progress.

A groundbreaking tour of the human mind that illuminates the

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biological nature of our inner worlds and emotions, through gripping, moving—and, at times, harrowing—clinical stories “Poetic, mind-stretching, and through it all, deeply human.”—Daniel Levitin, New York Times bestselling author of *The Organized Mind*
Karl Deisseroth has

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spent his life pursuing truths about the human mind, both as a renowned clinical psychiatrist and as a researcher creating and developing the revolutionary field of optogenetics, which uses light to help decipher the brain's workings. In *Projections*, he combines his knowledge

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of the brain's inner circuitry with a deep empathy for his patients to examine what mental illness reveals about the human mind and the origin of human feelings—how the broken can illuminate the unbroken. Through cutting-edge research and gripping case studies from Deisseroth's own

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patients, Projections tells a larger story about the material origins of human emotion, bridging the gap between the ancient circuits of our brain and the poignant moments of suffering in our daily lives. The stories of Deisseroth's patients are rich with humanity and shine an unprecedented light on

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the self—and the ways in which it can break down. A young woman with an eating disorder reveals how the mind can rebel against the brain's most primitive drives of hunger and thirst; an older man, smothered into silence by depression and dementia, shows how humans evolved to feel not only joy but also its

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absence; and a lonely Uighur woman far from her homeland teaches both the importance—and challenges—of deep social bonds.

Illuminating, literary, and essential, *Projections* is a revelatory, immensely powerful work. It transforms our understanding not only

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of the brain but of ourselves as social beings—giving vivid illustrations through science and resonant human stories of our yearning for connection and meaning.

The rise of optogenetics as a standard technique to non-invasively probe and monitor biological function created an immense interest in the

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molecular function of photosensory proteins. These photoreceptors are usually protein/pigment complexes that translate light into biological information and have become essential tools in cell biology and neurobiology as their function is genetically encoded and can be conveniently delivered

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into a given cell. Like for fluorescent proteins that quickly became invaluable as genetically encodable reporters in microscopy and imaging, variants of photosensory proteins with customized sensitivity and functionality are nowadays in high demand. In this ebook we feature reviews and

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original research on
molecular approaches
from synthetic biology
and molecular
spectroscopy to
computational
molecular modelling
that all aspire to
elucidate the molecular
prerequisites for the
photosensory function
of the given proteins.
The principle property
of changing activity of

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biological function simply by application of light is not only very attractive for cell biology, it also offers unique opportunities for molecular studies as excitation can be controlled with high time precision. Especially in spectroscopy the usually fully reversible photoactivation of

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photosensory proteins allows researchers to to perform time resolved studies with up to femtosecond resolution. In addition, functional variants can be investigated and quickly screened in common biochemical experiments. The insights that are obtained by the here presented various yet

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complementary methods will ultimately allow us write the script for a molecular movie from excitation of the protein by a photon to activation of its biological function.

Such deep understanding does not only provide unique insights into the dynamics of protein function, it will also

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ultimately enable us to rationally design novel optogenetic tools to be used in cell biology and therapy.

Structural Foundations
of Optogenetics
Neural Interface
Engineering
Handbook of Low-
Level Laser Therapy
Engineering Light
Delivery Into Biological
Tissue

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Projections

Deep Brain Stimulation

Think Tank: Updates in

Neurotechnology and

Neuromodulation

Research

The brain is a

remarkably

complex

structure,

composed of

hundreds of

neurons in simple

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organisms and up to hundreds of billions of neurons in large mammals. The recent advent of optically-modulated, molecular tools for neuroscience ('optogenetics') has allowed unprecedented

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*access to
simultaneously
modulate and
observe the
activity of
hundreds of
genetically-
defined neurons
with millisecond
resolution.
However, while
optogenetics has*

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*enabled rapid
advances in
neuroscience, this
powerful toolset
remains
constrained by a
limited
mechanistic
understanding of
light-gated
molecules,
including*

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channelrhodopsins (ChRs). Here, I describe my efforts to understand structural and dynamical mechanisms of ChRs, using three complimentary approaches. First, to extend the

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available high-resolution ChR structural insights, I employed X-ray crystallography to determine the structures of natural and designed anion-conducting ChRs (ACRs). Next, I used a

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*combination of
these atomic-
resolution
structures,
molecular
dynamics (MD)
computational
simulation, and in
vitro
electrophysiology
to assess
functional*

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*dynamics of ACRs,
leading to the
identification of a
variant with
improved channel-
closing kinetics.
Finally, I used
structure-guided
genome mining,
whole-cell patch
clamp
electrophysiology,*

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*and two-photon
imaging to
identify and
characterize a
new red-shifted
excitatory
channelrhodopsin
with large
photocurrents and
high light
sensitivity. Taken
together, this*

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work provides a framework for the engineering and discovery of better optogenetic tools and lays a foundation for future studies of channelrhodopsin biology.

Including a chapter by 2014

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*Nobel laureates
May-Britt Moser
and Edvard Moser
An unprecedented
look at the quest
to unravel the
mysteries of the
human brain, The
Future of the Brain
takes readers to
the absolute
frontiers of*

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science. Original essays by leading researchers such as Christof Koch, George Church, Olaf Sporns, and May-Britt and Edvard Moser describe the spectacular technological advances that will

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*enable us to map
the more than
eighty-five billion
neurons in the
brain, as well as
the challenges
that lie ahead in
understanding the
anticipated deluge
of data and the
prospects for
building working*

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*simulations of the
human brain. A
must-read for
anyone trying to
understand
ambitious new
research
programs such as
the Obama
administration's
BRAIN Initiative
and the European*

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*Union's Human
Brain Project, The
Future of the Brain
sheds light on the
breathtaking
implications of
brain science for
medicine,
psychiatry, and
even human
consciousness
itself. Contributors*

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*include: Misha
Ahrens, Ned
Block, Matteo
Carandini, George
Church, John
Donoghue, Chris
Eliasmith, Simon
Fisher, Mike
Hawrylycz, Sean
Hill, Christof Koch,
Leah Krubitzer,
Michel Maharbiz,*

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*Kevin Mitchell,
Edvard Moser,
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*"Discover the
groundbreaking
field of
optogenetics, a
biological*

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*technique that
uses light to
control cells in
living tissue.*

*Optogenetics
helps researchers
understand
biochemical
processes in live
organisms and
may someday be
used to treat*

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*blindness, neural disorders, and other diseases."--
This book provides an update for the rapidly developing technology known as "optogenetics", which is the use of genetically encoded light-sensitive*

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molecular elements (usually derived from lower organisms) to control or report various physiological and biochemical processes within the cell. Two ongoing clinical trials use

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*optogenetic tools
for vision
restoration, and
optogenetic
strategies have
been suggested
as novel therapies
for several
neurological,
psychiatric and
cardiac disorders.
This Special Issue*

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comprises two reviews and seven experimental papers on different types of light-sensitive modules widely used in optogenetic studies. These papers demonstrate the

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efficiency and versatility of optogenetics and are expected to be equally relevant for advanced users and beginners considering using optogenetic tools in their research. Neuroscience for

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*The Future of the
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*Neural circuits
underlying*

*emotion and
motivation:*

Insights from

*optogenetics and
pharmacogenetics*

*Engineering in
Medicine*

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*The Advances and
Applications of
Optogenetics
Optical Neural
Interfaces*

*This book focuses
on neuro-
engineering and
neural computing,
a multi-
disciplinary field
of research*

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*attracting
considerable
attention from
engineers,
neuroscientists,
microbiologists
and material
scientists. It
explores a range
of topics
concerning the
design and*

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*development of
innovative neural
and brain
interfacing
technologies, as
well as novel
information
acquisition and
processing
algorithms to
make sense of the
acquired data.*

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The book also highlights emerging trends and advances regarding the applications of neuro-engineering in real-world scenarios, such as neural prostheses, diagnosis of neural

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*degenerative
diseases, deep
brain stimulation,
biosensors, real
neural network-
inspired artificial
neural networks
(ANNs) and the
predictive
modeling of
information flows
in neuronal*

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networks. The book is broadly divided into three main sections including: current trends in technological developments, neural computation techniques to make sense of the

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neural behavioral data, and application of these technologies/techniques in the medical domain in the treatment of neural disorders. Technologies of the New Real explores the

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*human impact of
technology in the
twenty-first
century.*

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field. There has
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contains 34
answers, much*

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comprehensive
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*embracing guide
offers a thorough
view of key
knowledge and
detailed insight.
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introduces what
you want to know
about
Optogenetics. A
quick look inside
of some of the*

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subjects covered:

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aspects of treat-
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such as definitions, clinical aspects, neurobiological correlates, treatment options, and predictors of treatment response. The book is divided into three

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*the subjects,
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of the clinical
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is a fast-
growing field
concerning the
invention, and
use, of
molecules that
are
genetically
expressed in
cells, and
then either

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major neural
interfacing
technologies
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physical world**

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for repairing,
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are critical
for
information
processing,
and are
strongly
influenced by
inputs from
the medial

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septum. Hippoc
amposeptal
neurons
provide direct
inhibitory
feedback from
the
hippocampus
onto septal
cells, and are
therefore
likely to also

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play an
important role
in the
circuit; these
neurons fire
at either low
or high
frequency,
reflecting
hippocampal
network
activity

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during theta oscillations or ripple events, respectively. Since the hippocampal projection is sparse and long-range, the impact of high or low

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frequency
hippocampal
input on
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physiology has
not been
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with classical
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ogical or phar
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techniques. In

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order to
understand the
contribution
of defined
neuronal
subtypes, such
as hippocampal
neurons,
to brain
function, our
laboratory has
developed a

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technique
termed

optogenetics,
which
integrates
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targeting and
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manipulation
of genetically
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types in
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employs light
sensitive
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proteins,
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pumps and
channels that
can elicit or
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potentials.
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has already
proved
invaluable to
neuroscience,
but several
key

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limitations to
its

application
have become
apparent:

First,
increasingly
diverse
optogenetic
tools allow
more versatile
control over

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activity, but
since new
tools have
been developed
in multiple
laboratories
and tested
across
different
preparations
it is

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difficult to
draw direct
comparisons
between them.
As a result,
it has become
increasingly
challenging
for end users
to select the
optimal
reagents for

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their
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needs. Second,
as the power
of genetically
encoded
interventional
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tools for
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expands, the

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boundary of
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design is
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defined by
limits in
selectively
expressing
these tools in
specific cell
types. To
date, cell-

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type has
primarily
referred to
genetic
specificity,
achieved with
promoter-
driven
expression
either in
transgenic
animals or in

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viruses. This approach is limited in its ability to define a 'cell type': cells may be targeted based on only a single parameter, and genetic

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targeting does
not take into
account
anatomic
connectivity,
in many cases
the most
salient
feature of a
target
population.
The aim of

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this thesis is
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fold: 1) To
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pathway, using
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to gain cell-

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experimental
conditions to
extract
essential
principles and
identify key
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and 3) To
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of the hippocampal
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will increase
our
understanding
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part, and will
also

illustrate the
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firing
frequency in
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described will
be useful for

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neurons that
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therapists. The

scope includes

the mechanisms

and

abnormalities of

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metabolism,

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ansmission and
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astrocytes,
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the level of the
cerebral cortex,
thalamus, basal
ganglia,
cerebellum,
brainstem and
spinal cord
transmission
regulating
sensory
processing,
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function"--

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use in
regenerative
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applications,
which has in turn
spurred growing
numbers of
translational and
clinical studies.
However, more
work is needed if
the potential is to

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