This is an invited “roadmap” technology standards talk, which by definition is forward-looking.

Many technologies, concepts, and indications are investigational and/or off-label, and are not approved for commercial sale in the US.

Thanks to Investigators from UCSF, University of Washington, University of Florida, and UMC Utrecht for kindly allowing me to share data from their investigator-initiated trials.

Tim is an employee and shareholder of Medtronic, Inc. but are trying to stay agnostic to and speak for general industry trends and opportunities.

Tim has IP in the area of neurotechnology, some captured in this presentation, particularly for sensing and algorithms.
NEUROMODULATION FOR DISEASE THERAPY –

Medtronic DBS Therapy for Parkinson’s Disease, Tremor, and Dystonia: Product technical manual must be reviewed prior to use for detailed disclosure.

Indications:
Medtronic DBS Therapy for Parkinson’s Disease: Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Parkinson’s Disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson’s disease of at least 4 years’ duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration.

Medtronic DBS Therapy for Tremor: Unilateral thalamic stimulation of the ventral intermediate nucleus (VIM) using Medtronic DBS Therapy for Tremor is indicated for the suppression of tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability.

Medtronic DBS Therapy for Dystonia: Unilateral or bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS Therapy for Dystonia is indicated as an aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above.

Contraindications: Medtronic DBS Therapy is contraindicated for patients who are unable to properly operate the neurostimulator and, for Parkinson’s disease and Essential Tremor, patients for whom test stimulation is unsuccessful. The following procedures are contraindicated for patients with DBS systems: diathermy (e.g., shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy), which can cause neurostimulation system or tissue damage and can result in severe injury or death; Transcranial Magnetic Stimulation (TMS); and certain MRI procedures using a full body transmit radio-frequency (RF) coil, a receive-only head coil, or a head transmit coil that extends over the chest area if they have an implanted Soletra Model 7426 Neurostimulator, Kineta Model 7428 Neurostimulator, Activa SC Model 37602 Neurostimulator, or Model 64001 or 64002 pocket adaptor.
Warnings and Precautions: There is a potential risk of brain tissue damage using stimulation parameter settings of high amplitudes and wide pulse widths and, for Parkinson’s disease and essential tremor, a potential risk to drive tremor using low frequency settings. Extreme care should be used with lead implantation in patients with an increased risk of intracranial hemorrhage. Sources of electromagnetic interference (EMI) may cause device damage or patient injury. Theft detectors and security screening devices may cause stimulation to switch ON or OFF and may cause some patients to experience a momentary increase in perceived stimulation. The DBS System may be affected by or adversely affect medical equipment such as cardiac pacemakers or therapies, cardioverter/defibrillators, external defibrillators, ultrasonic equipment, electrocautery, or radiation therapy. MRI conditions that may cause excessive heating at the lead electrodes which can result in serious injury, including coma, paralysis, or death, or that may cause device damage, include: neurostimulator implant location other than pectoral and abdominal regions; unapproved MRI parameters; partial system explants (“abandoned systems”); misidentification of neurostimulator model numbers; and broken conductor wires (in the lead, extension or pocket adaptor). The safety of electroconvulsive therapy (ECT) in patients receiving DBS Therapy has not been established. The lead-extension connector should not be placed in the soft tissues of the neck due to an increased incidence of lead fracture. Abrupt cessation of stimulation should be avoided as it may cause a return of disease symptoms, in some cases with intensity greater than was experienced prior to system implant (“rebound” effect). Onset of status dystonicus, which may be life-threatening, may occur in dystonia patients during ongoing or loss of DBS therapy. Patients using a rechargeable neurostimulator for Parkinson’s disease or Essential Tremor should check for skin irritation or redness near the neurostimulator during or after recharging, and contact their physician if symptoms persist. Depression, suicidal ideations and suicide have been reported in patients receiving Medtronic DBS Therapy for Movement Disorders, although no direct cause-and-effect relationship has been established.

Adverse Events: Adverse events related to the therapy, device, or procedure can include intracranial hemorrhage, cerebral infarction, CSF leak, pneumocephalus, seizures, surgical site complications (including pain, infection, dehiscence, erosion, seroma, and hematoma), meningitis, encephalitis, brain abscess, cerebral edema, aseptic cyst formation, device complications (including lead fracture and device migration) that may require revision or explant, extension fibrosis (tightening or bowstringing), new or exacerbation of neurological symptoms (including vision disorders, speech and swallowing disorders, motor coordination and balance disorders, sensory disturbances, cognitive impairment, and sleep disorders), psychiatric and behavioral disorders (including psychosis and abnormal thinking), cough, shocking or jolting sensation, and ineffective therapy.

Safety and effectiveness has not been established for patients with previous surgical ablation procedures, dementia, coagulopathies, or moderate to severe depression, patients who are pregnant, or patients under 18 years. Parkinson’s disease and essential tremor: safety and effectiveness has not been established for patients with neurological disease other than idiopathic Parkinson’s disease or Essential Tremor. Essential tremor: safety and effectiveness has not been established for bilateral stimulation or for patients over 80 years of age. Dystonia: age of implant is suggested to be that at which brain growth is approximately 90% complete or above.

Humanitarian Device (Dystonia): Authorized by Federal Law to aid in the management of chronic, intractable (drug refractory) primary dystonia, including generalized and/or segmental dystonia, hemidystonia, and cervical dystonia (torticollis), in patients seven years of age or above. The effectiveness of the devices for treating these conditions has not been demonstrated.
TAXONOMY OF POTENTIAL BCI APPLICATIONS

VISION: BRAIN-COMPUTER-INTERFACE AS A COMPONENT THAT A CLINICIAN CONFIGURES FOR OPTIMIZING OUTCOMES

Type 1: Use typical brain signals to control an actuator with existing motor signals
(Example, Utrecht UNP communicator)

Type 2: Use typical brain signals to control an implanted device
(Example, ET controller at UW, UFlorida)

Type 3: Measure deviations from “typical” brain signals, stimulate to nudge them back into a more normal state
(Example, PD beta/gamma thermostats)
Also consider wearables...etc
LESSONS LEARNED 1: MODULAR “SCIENTIFIC PAYLOADS” IN A SYSTEM

PROBE “TRANSFER FUNCTIONS” OF NEURAL NETWORKS → COMPONENT SPEC
APPLY LEARNING WITH ALGORITHMS DOWNLOADED VIA WIRELESS TELEMERTY

Existing Platform: Neurostimulator

Scientific Instrumentation Platform

- Ambulatory DATA Recorder
- Science Processor (Algorithms, Recording)
- Classifier & Control Policy
- A/D Converter
- Real-Time Telemetry Control
- 3-axis Accel
- ECoG & LFP
- Complex Imped. Z
- Chem. Sensing
- Future Needs?
- Digital Control and Memory Interface
- Bioelectrical Sensing Module
- Multiplexors
- Multiplexors
- Coupling Capacitors
- Stimulation and Sense Electrodes

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Stanslaski et al., IEEE Neural Engineering, 2011
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TOWARDS A CLOSED-LOOP DEEP BRAIN STIMULATION TREATMENT FOR ESSENTIAL TREMOR
E. Oprí1,2, J. B. Shute1,2, R. Molina1,2, K.D. Foote2, M.S. Okun2, A. Gunduz1,2
1J. Crayton Pruitt Family Dept of Biomedical Engr, Univ of Florida, Gainesville, FL;
2Center for Movement Disorders and Neurorestoration, Univ of Florida, Gainesville, FL

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EXAMPLE: “BRAIN INTERPRETER” FOR LOCKED-IN PATIENTS
COMMUNICATION BCI IN ALS

Data Courtesy of UMC Utrecht

Correlation with attempted finger movement task, red indicates high correlation based on 65-95 Hz power (ECoG)
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EXAMPLE: MOTOR INTENTION TO TITRATE STIMULATION
ADAPTIVE, PATIENT-SPECIFIC NEUROMODULATION

"Cortical brain computer interface for closed-loop deep brain stimulation,"
Herron, Chizeck, Ojemann et. al. (in review 2016)
“Cortical brain computer interface for closed-loop deep brain stimulation,” Herron, Chizeck, Ojemann, et. al. (in review 2016)
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EXAMPLE: PERTURBATIONS FROM STANDARD BRAIN RHYTHMS
MEDICATION RESPONSES AND DYNAMICS; MECHANISMS OF ACTION

Motor Cortex Signals

Electrode trajectories are schematic only

“Gamma Oscillations in the Hyperkinetic State Detected w/ Chronic Human Brain Recordings in Parkinson’s Disease,”
Swann, Starr, et. al.
Journal of Neuroscience 2016

13 NIH BCI Workshop 2016
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LESSON LEARNED 3: **PROACTIVE RISK MANAGEMENT**

EXAMPLE: MANAGEMENT OF RISK ASSOCIATED WITH NOVEL ALGORITHMS

- Common engineering practice is to define a “Safe Operating Area”
- Limits are defined in a design space, and engineers stay within it
- Example taken from power electronics

- API design concept: Clinician defines “Safe Operating Zone” for a subject
- Algorithms are limited to this phase space
- In case of issue, patient can “reset” to open-loop safe zone with default therapy setting
LESSONS LEARNED 4: VALUE DELIVERED? ECONOMICS MATTERS
STANDARDS FOR “QALY” ANALYSIS TO MOTIVATE DESIGN, REIMBURSEMENT
WHAT IS THE OBJECTIVE FUNCTION FOR YOUR APPLICATION?

Results + Process Quality
Customer Access Costs + Price

The Value Profit Chain
Heskett, Sasser, Schlesigner
HBS, The Free Press

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STANDARDS == BUILDING A TRANSLATION MINDSET

TRANSLATION REQUIRE A COMPLETE SYSTEM!

TECHNOLOGY, SCIENCE, HEALTHCARE ECONOMICS, CLINICAL ACCEPTANCE, PATIENT ACCEPTANCE, RISK MANAGEMENT, LIFECYCLE MANAGEMENT...

Brain Machine Interfaces: bi-directional interfaces & closed-loop prototyping tools

Patient Interaction: devices to trigger data recording

Cardiac/Physiology Monitors: miniature data recorders

Spinal Cord and Peripheral Interfaces: including firmware downloads and real-time telemetry links for adaptive stimulation control

Material Interfaces

Sensors

Interactive Feedback

Wireless telemetry and data portals

Databases, Modeling & Learning

Algorithms

Classifiers & Control Policy

Actuation Physics & Patterns

Caution: Limited by U.S. Law to Investigational Uses Only
ISO/TS 10974 (MRI AND DEVICES: A REFERENCE EXAMPLE?)

1st EDITION

- 4 sub-groups: RF, Gradient, EMC, and Labeling
- Both cardiac and neuro participants in standards creation
- Heuristic for a takeaway consideration:
  - Test Methods for common technologies are defined by standards (RF, Gradient, EMC, ...)
  - Acceptance criteria are within specific application areas and defined by system reqmts (e.g. cardiac pacemaker vs deep brain stimulator)