ETH zürich

IT'IS FOUNDATION

EM-Neuro Modeling Across Scales for Bioelectronic Medicine

Lecture 1: Logistics & Motivation

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Outline for Today

- **Part I: Introduction & Course Logistics**
- **Part II: From Frog Legs to Firing Equations: A Brief History of Bioelectricity**
- **Part III: Motivation — Modern Bioelectronics & Neuroprosthetics**

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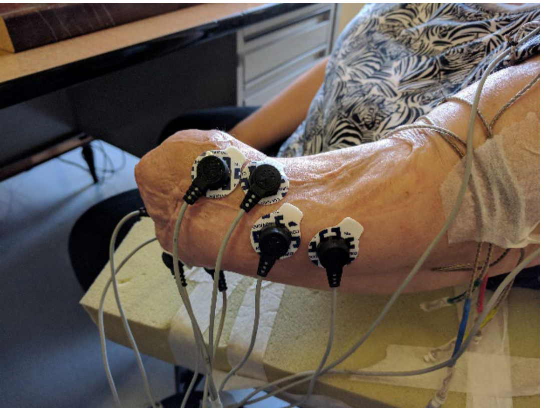
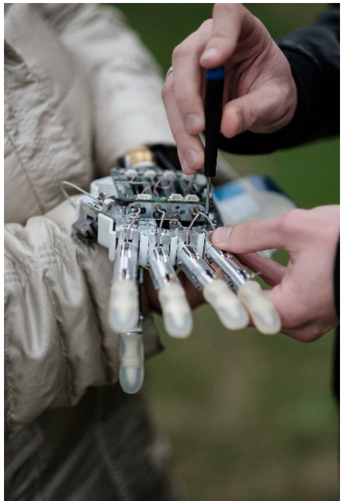
Learning Objectives

- Understand the logistics, organization and academic expectations of this lecture series
- Gain an appreciation of the historical developments that led to a modern understanding of the principles of the nervous system, and the development of bioelectronics
- Appreciate the current state-of-the-art in bioelectronic interfaces and neuroprosthetics (with examples)
- Prepare yourself for 13 weeks of high-octane intellectual stimulation and hands-on learning, together ☺
- And the privilege of research with important societal impact

Credit: Silvestro Micera, Stanisa Raspopovic, et al.





Why Computational Modeling?

Analyse

- Insight beyond what's experimentally accessible; well-controlled, dense information; visualization

Optimize

- Device design, performance, safety

Understand & Troubleshoot

- Mechanism elucidation, problem identification

Reduce Time-to-Market

- *In silico* prototyping & testing

Perform Trials

- *In silico* trials; reduce bench/animal/human trials

Personalize

- Image-based anatomy, patient-specific properties/processes, treatment planning

Intelligent, Model-Predictive Control

- Models as part of the device — closed-loop, real-time, state-driven control

Regulatory

- FDA, ASME V&V 40 increasingly require computational evidence for safety & efficacy

But, Can We Trust Models?

The Central Question

- Computational modeling increasingly *required* by regulators (FDA guidance, ASME V&V 40-2018)
- Used to: identify worst-case configurations, compare devices, make absolute predictions, increase population coverage, drive device algorithms…

We *CAN* Trust Models, But We Need…

- Verification: is the model/algorithm correctly implemented? (Code vs. solution verification)
- Validation: does the model adequately reproduce relevant real-world behavior within the context of use?
- Degree & quality of V&V must be commensurate with risk and credibility impact
- Burden on the modeler: don't distract with pretty pictures

Why This Is Hard in Life Sciences

- Complex anatomo-physiological environment
- Multi-physics coupling (EM + thermal + neuronal dynamics)
- Large inter-/intra-person variation in geometry & properties → population coverage needed
- Physiological/biological models: equations less well-defined than physics; poor parameter knowledge
- *In vivo* measurements for validation are often inaccessible
- → Dedicated **Lecture 12**

Image: [40]

The Central Question

- Computational modeling increasingly *required* by regulators (FDA guidance, ASME V&V 40-2018)
- Used to: identify worst-case configurations, compare devices, make absolute predictions,

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Image: [40]

Course Tooling & Software Stack

NEURON (Yale/Duke)

- Compartmental neuron models, mechanism insertion (NMODL), Python API, HPC support
- Ecosystem: ModelDB, eBRAINS integration

Sim4Life (ZMT Zurich MedTech)

- Multiphysics/multiscale: EM solvers (FEM, FDTD), thermal, acoustics, neuronal dynamics (T-NEURO)
- Image-based modeling (AI, iSEG), posable and morphable Virtual Population (ViP) anatomical models, tissue property database
- CAD tools, parameterized modeling, validation documentation, multi-objective optimizion

o^{2}S^{2}PARC (NIH SPARC Platform)

- Cloud-based, reproducible scientific pipelines from modular building blocks
- Collaborative and FAIR (findable, accessible, interoperable, reusable)
- ~100 services: Sim4Life, AI tools, JupyterLab; dockerized runtime environments
- “App Mode”: turns complex pipelines into step-by-step applications usable by non-experts/clinicians

Also Used in This Course

- Python (NumPy, SciPy, matplotlib): exercises, analysis, custom scripting
- Brian / NEST: spiking neural network simulation (**Lecture 7**)
- TVB (The Virtual Brain): whole-brain modeling (**Lecture 8**); optional: MNE for EEG/MEG

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Course Outline

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DATE	LECTURE THEME
19.02	Motivation, logistics & tooling (EN, TNE)
26.02	Ion channels & membranes (EN)
05.03	Axon models, activating functions & electrical stimulation (EN)
12.03	EM field simulation fundamentals & coupled EM-neuro workflows (EN)
19.03	Peripheral nerves & interfaces for bioelectronic medicine (EN)
26.03	Spinal cord stimulation for neuroprosthetics and pain management & low-frequency exposure safety (TNE)
02.04	Morphology, synapses, microcircuits; point vs spiking networks (TNE)
09.04	No class: Easter break
16.04	Neural mass & whole brain models; hybridization (TNE)
23.04	Recording modalities, signal content & the reciprocity theorem (TNE)
30.04	Non invasive brain stimulation & temporal interference (TNE)
07.05	Image based/personalized treatment planning and optimization (EN)
14.05	No class: Ascension Day
21.05	Verification, validation, UQ, and reproducibility (EN)
28.05	Project presentations & synthesis (EN, TNE)

Room: ETZ E7
13:15-14:00 Lecture
14:00-14:15 Break
14:15-15:00 Lecture
14:00-14:15 Break
15:15-16:00 Exercise

Lecture Recordings & Slides

Provided Here
(will successively appear)

Exercise Outline

DATE	EXERCISE THEME
19.02	"Hello Neuron": integrate-and-fire in Python/NEURON
26.02	Point neuron phase portrait; basic time integration numerics
05.03	Recruitment prediction for myelinated axon using AF/GAF
12.03	EM (FEM) modeling of transcranial brain stimulation
19.03	Stimulation selectivity and signal content modeling for nerve interfaces
26.03	Guest (SCS – NeuroRestore)
02.04	Mini project work
09.04	No class: Easter break
16.04	Guest (Neuromodulation Spin-Off – Z43)
23.04	Mini project work
30.04	Guest (NIBS – Kinderspital)
07.05	Mini project work
14.05	No class: Ascension Day
21.05	Mini project work
28.05	Project presentations

Room: ETZ E7

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Course Logistics

Course Philosophy

- Its about understanding, not about knowing all the right coefficients in the formulas!
- Really!!!

Exam

- Oral exam (15 min) during semester break
- Question list distributed in advance; deepening follow-up questions during exam, depending on displayed understanding
- Students may exclude questions from two lectures of choice

Mini Project (+¼ Mark Bonus)

- Successful completion of mini project & written report → +1/4 mark
- May be done individually or in groups
- Instructors can facilitate group formation if desired — email us

Office Hours

- On-site (ETH campus) in-person office hours available by prior arrangement

Exercise Sessions (Weekly, Thu. 15:15–16:00)

- Supervised coding in Python / Sim4Life etc.
- Small mini-deliverables tied to lecture content
- Project clinic time: bring questions, get feedback on your mini project
- No formal grading — exercises build skills needed for the project and exam

Contacts

EN

Course instructors:

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- Dr. Taylor Newton: newton@itis.swiss

TNE

Exercise assistants:

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- Lucia Moya Sans: moyasans@itis.swiss
- Javier García Ordóñez: ordonez@zmt.swiss
- Nerea Carbonell: carbonell@itis.swiss

AMC

LMS

NC

JGO

IT’IS Foundation & Zurich43 Alliance

Who

- IT’IS Foundation for Research on Information Technologies in Society
- Independent, nonprofit research foundation, est. 1999 in Zurich
- Closely affiliated with ETH
- Part of Zurich43 — strategic alliance of ETH spin-offs: IT’IS, ZMT (Sim4Life), SPEAG, TI Solutions, SCALK, BNN

What

- Computational life and health sciences (CLaHS) for basic research, device safety & efficacy, translational research, personalized medicine, and *in silico* trials
- CLaHS investigation domains: neurostimulation, MRI safety, EM safety, hyperthermia, focused ultrasound, wireless power transfer, body area networks, vascular flow, human modeling, MRI simulation

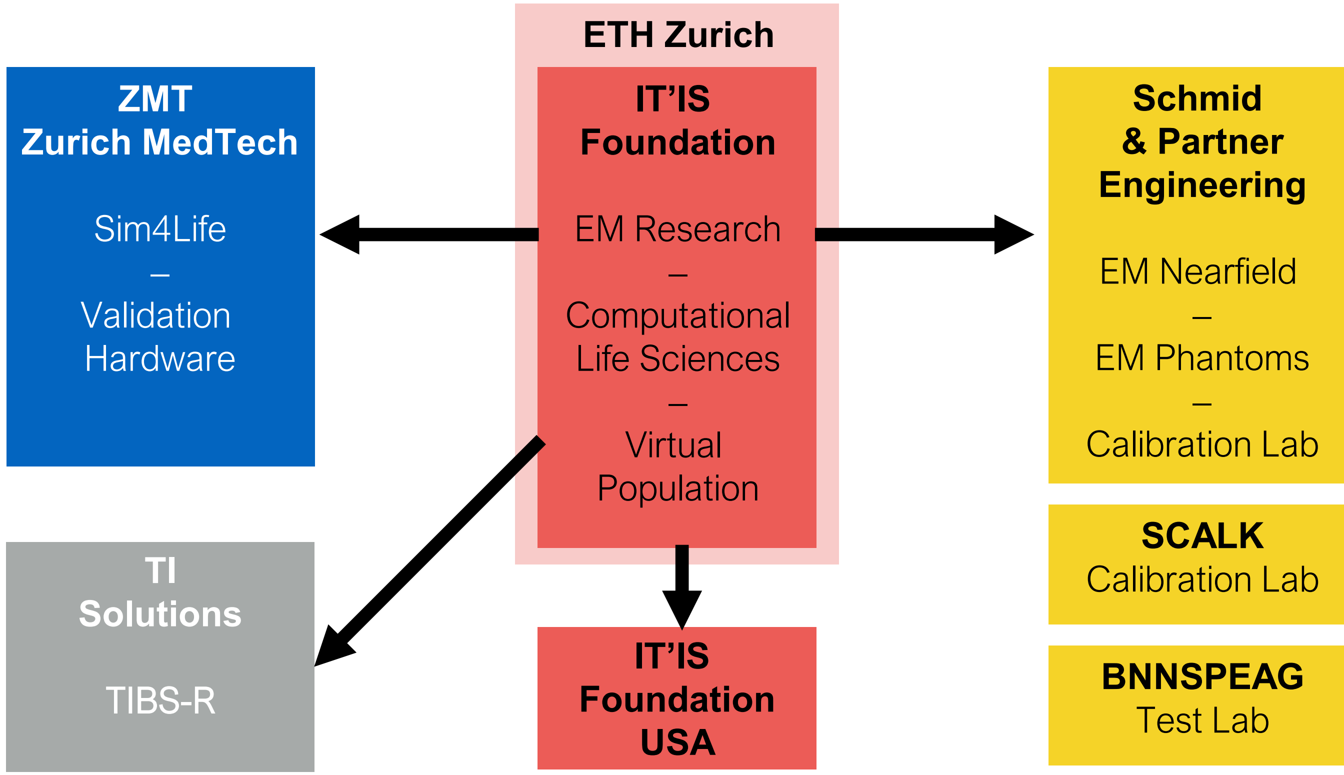
How It Started

- Original mission: EM safety of wireless devices (SAR dosimetry)
- Developed exposure systems for the U.S. NTP carcinogenicity study
- Created the Virtual Population (ViP) anatomical models with U.S. FDA — used by >1,000 research groups, >150 regulatory submissions, >3,000 citations

Key Platforms

- Sim4Life: multiphysics/multiscale simulation from physics to physiological impact
- o^{2}S^{2}PARC: online-accessible, reproducible, FAIR, cloud-based pipelines (NIH SPARC)

IT'IS Foundation & Zurich43 Alliance



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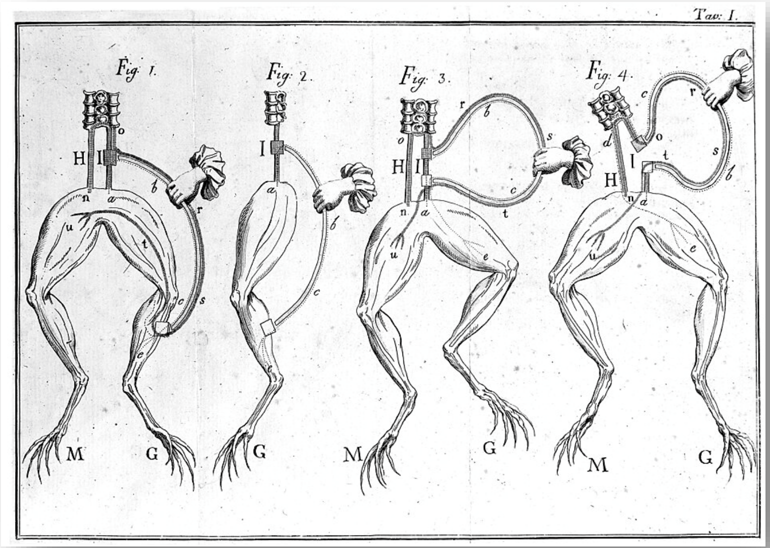
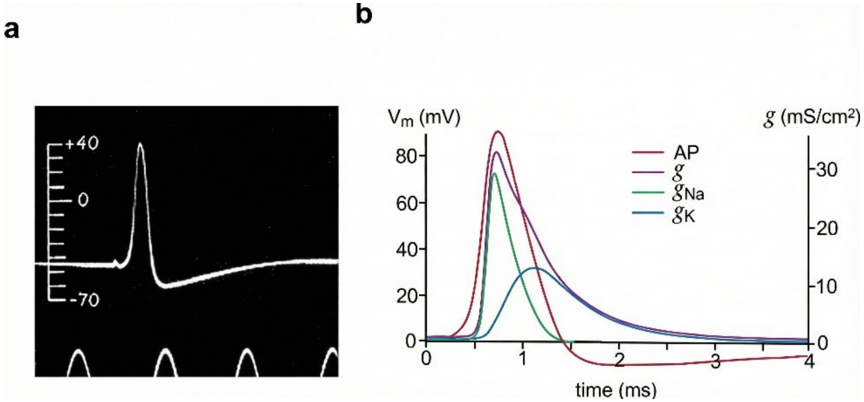
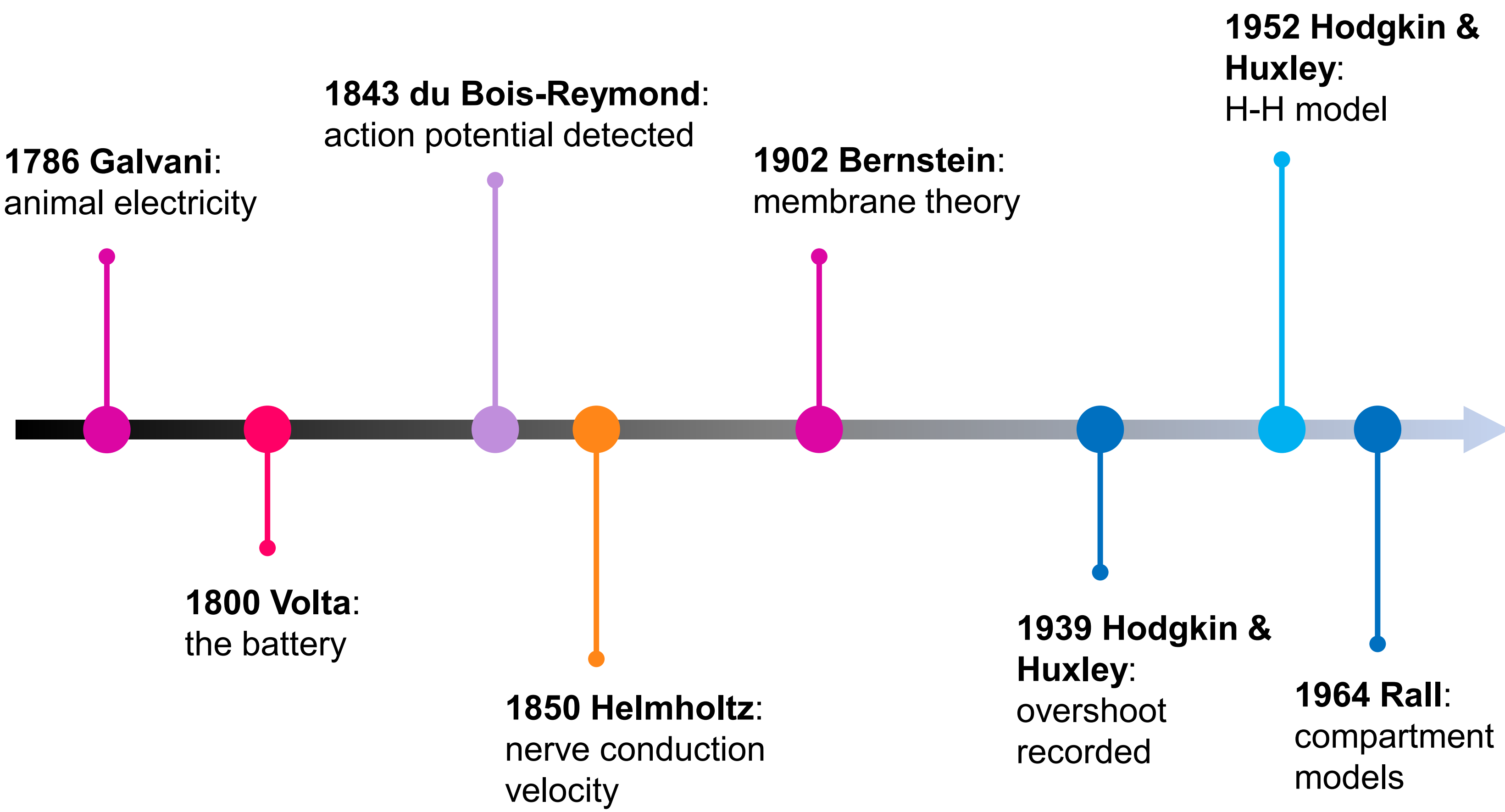
From Frog Legs to Firing Equations:
Two Centuries of Bioelectric Discovery





Images: [1,2]

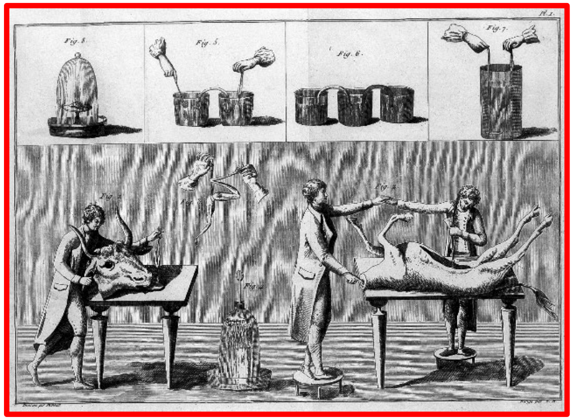
The Big Arc



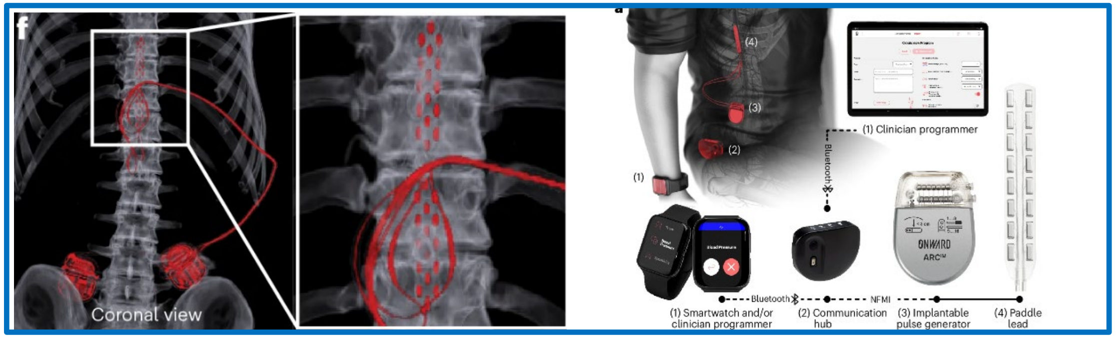
Every neural interface, deep brain stimulator, and brain model descends from these discoveries…

What History Tells Us

Observations → Equations → Devices



$$\nabla \cdot \mathbf{D} = \rho$$
$$\nabla \cdot \mathbf{B} = 0$$
$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t}$$
$$\nabla \times \mathbf{H} = \mathbf{J} + \frac{\partial \mathbf{D}}{\partial t}$$



By the end of Part II, you will know:

1. Where the **cable equation** comes from (distributed parameters)
2. What Hodgkin-Huxley added (nonlinear, **voltage-dependent** conductances)

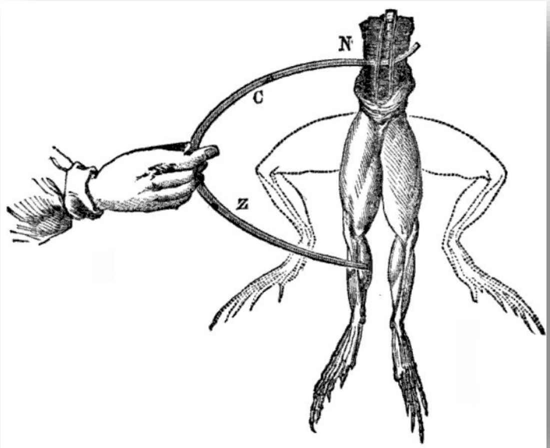
In depth: **Lectures 2 & 3**

Images: [3, 4, 5]

A Progression of Models

The story unfolds over three interlocking developments:

1. **Phenomena**: twitches, "negative variation"
2. **Electrical circuits & fields**: telegraph/cables, Maxwell → Poisson/Laplace)
3. **Membranes & conductances:** Bernstein → voltage clamp → Hodgkin–Huxley



Images: [6, 7, 8]

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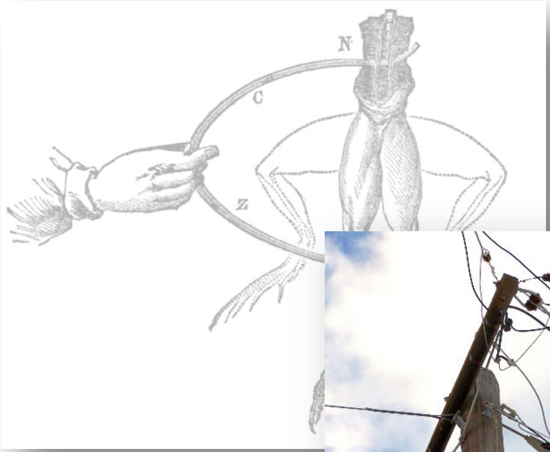

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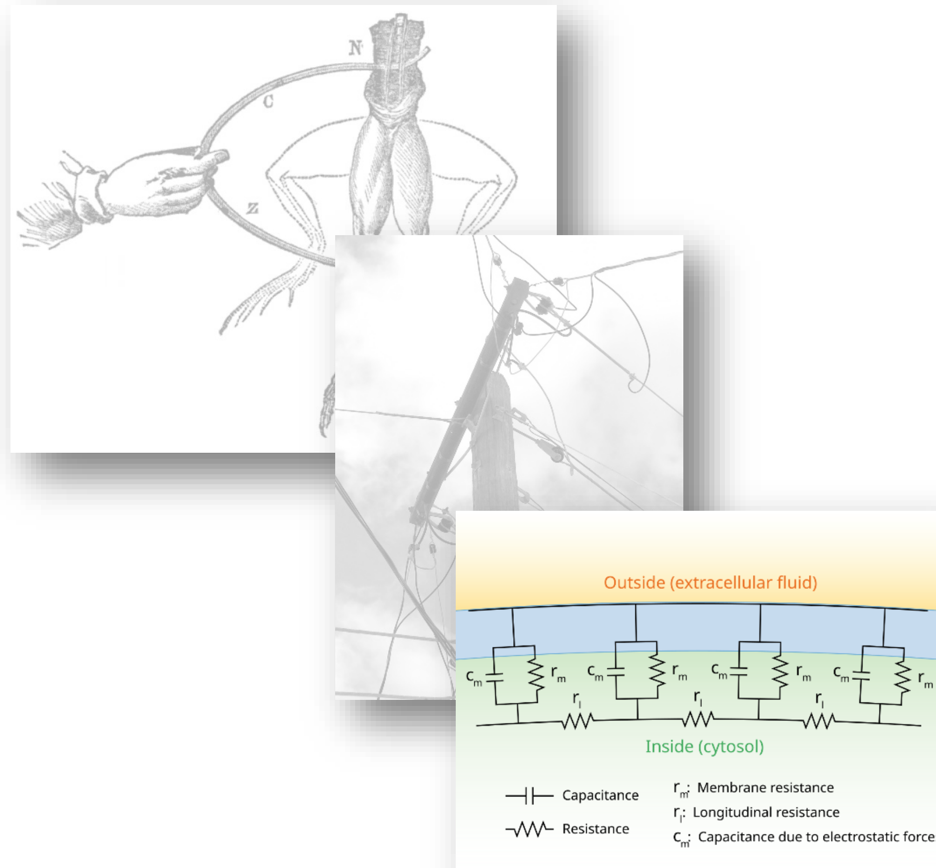
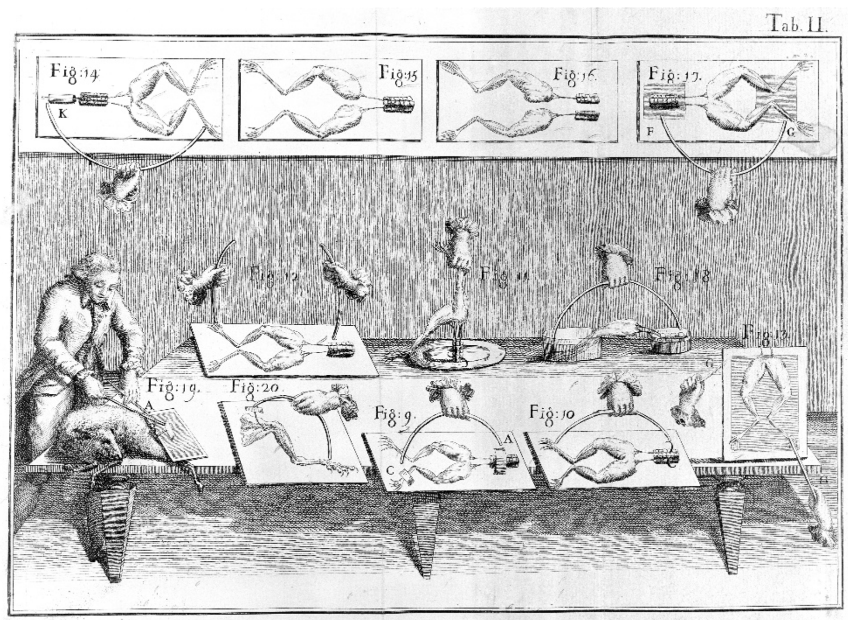


Images: [6, 7, 8]

Galvani’s Frog Legs (Why Europe Cared)

- Dead **frog legs twitch** when brass hooks contact iron — no external machine required
- Systematic experiments began in the early 1780s; decisive observation in Sept 1786
- Galvani proposed intrinsic “animal electricity”: muscles as biological Leyden jars, nerves as conductors
- 1791 treatise (*De Viribus Electricitatis in Motu Musculari*) ignited Europe-wide controversy and reframed “animal spirits” as **measurable electricity**



Bologna!

Images: [9, 10]

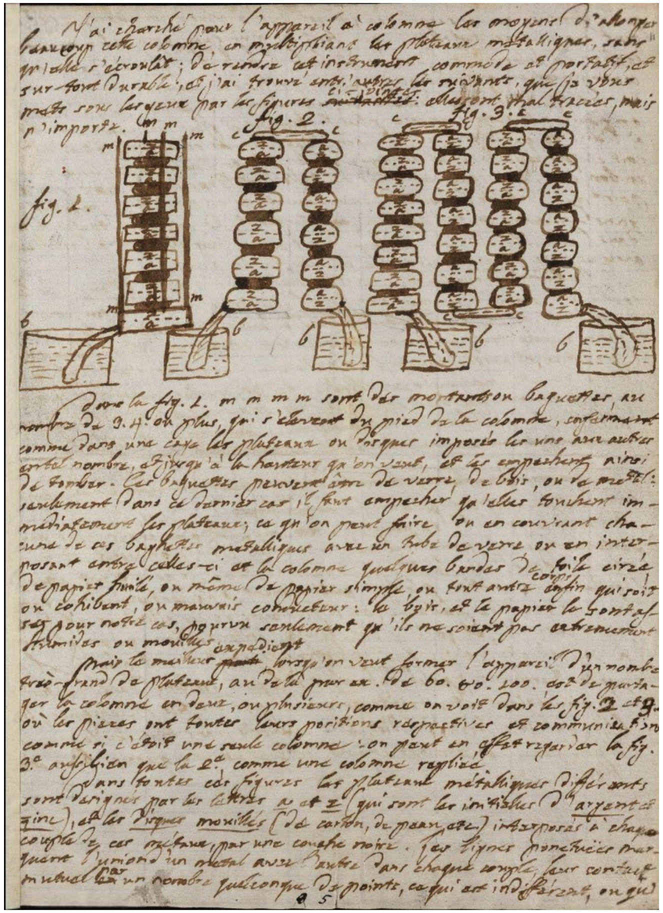
Volta's Challenge!

- Alessandro Volta (Pavia) initially praised Galvani's work as *"one of the most beautiful and most surprising discoveries"*
- By 1792: noticed that Galvani's own setup involved **two different metals** (brass hooks + iron railing) — and contraction strength depended on which pair was used
- Volta tried various metal pairings → consistent ranking ("electromotive series")
- Counter-proposal: **electricity from metal contact**, not the animal — frog merely completes the circuit

Images: [11, 12]

The Voltaic Pile

- Volta announces the voltaic pile to the Royal Society (letter to Joseph Banks)
- Alternating zinc and copper discs, brine-soaked cloth separators
- World's **first continuous electrical current**
- Built specifically to prove electricity needs no animal tissue

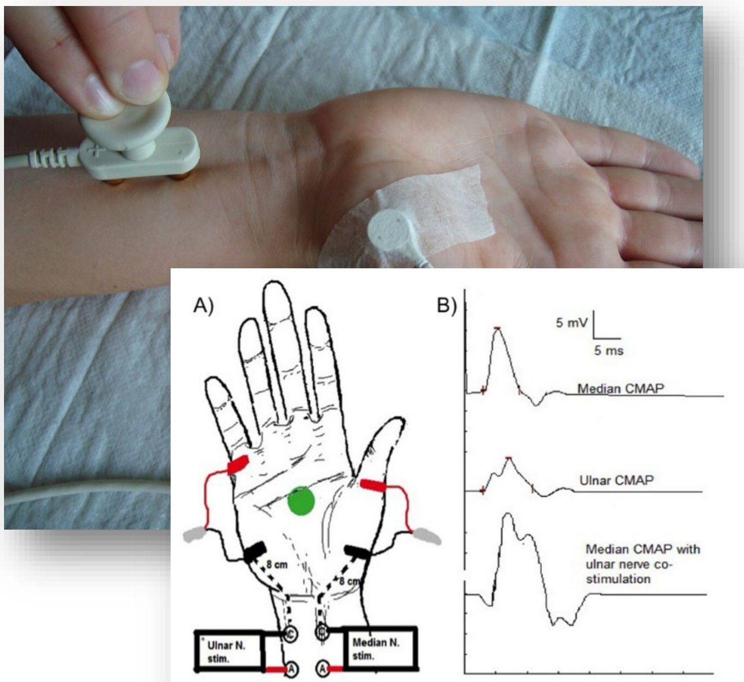


Images: [13, 14]

Oh, The Irony (Pun Intended): *Both Were Right*

Image: [15]

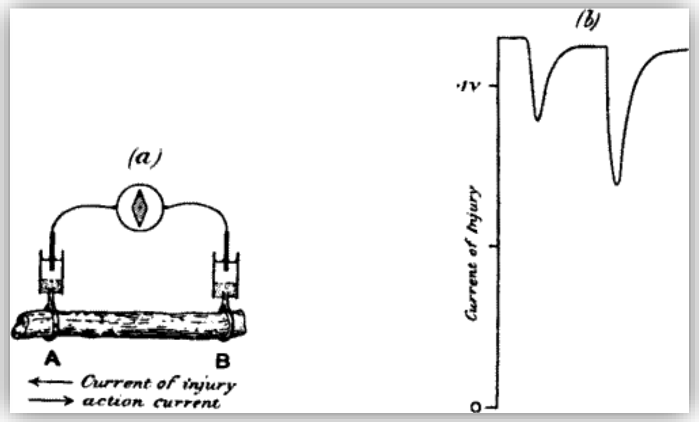
Helmholtz Measures Nerve Velocity
(It Changes Everything)

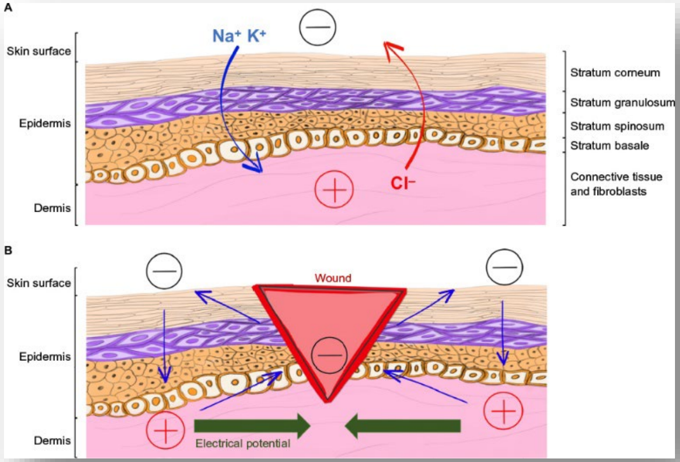


- Johannes Müller had argued nerve velocity might be immeasurable; Helmholtz proves otherwise
- Stimulate frog sciatic nerve at different points; time muscle contraction to infer conduction speed: ~25–40 m/s (order-of-magnitude)
- Why it mattered: measurable delay → **transmission is a physical process**, not instantaneous “vital force”
- Opened the door to quantitative physiology (reaction times, mechanistic models)

Images: [17, 18]

Du Bois-Reymond and the "Negative Variation"





- Key baseline: the injury current — when nerve/muscle is cut, exposed intracellular fluid is negative relative to intact surface → steady current flows from intact tissue toward wound → steady galvanometer deflection
- Galvanometer wound **24,000 times** by hand for sufficient sensitivity
- Du Bois-Reymond's breakthrough: detected a **brief dip** in this steady injury current when the nerve was stimulated — the "negative variation"
- Modern interpretation: an action potential (name came later) transiently depolarizes the intact membrane, reducing the voltage difference → injury current briefly decreases

Images: [19, 20, 21]

Bernstein's Membrane Theory… and Its Hidden Contradiction

- Bernstein framed the resting potential via selective permeability and ionic gradients (Nernst/Goldman logic in embryo)
- Predicted the action potential as a loss of selectivity driving Vm toward ~0 mV
- Key snag: experimental traces sometimes show an **overshoot** (Vm > 0) — Bernstein saw it as an artifact because it contradicted his theory
- Set the stage for the next leap: measuring and explaining the overshoot mechanistically

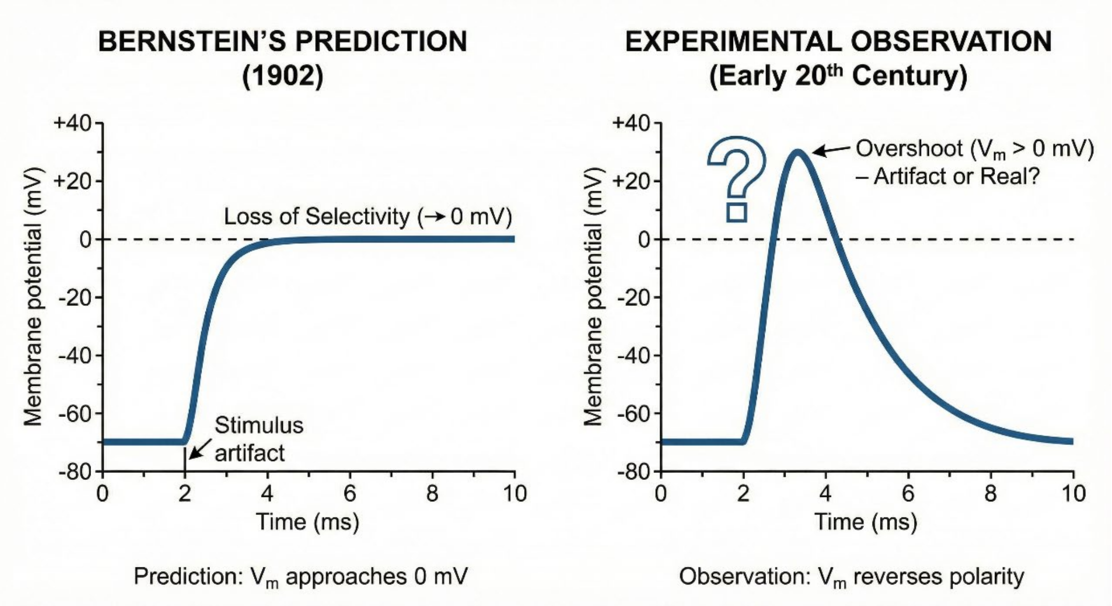
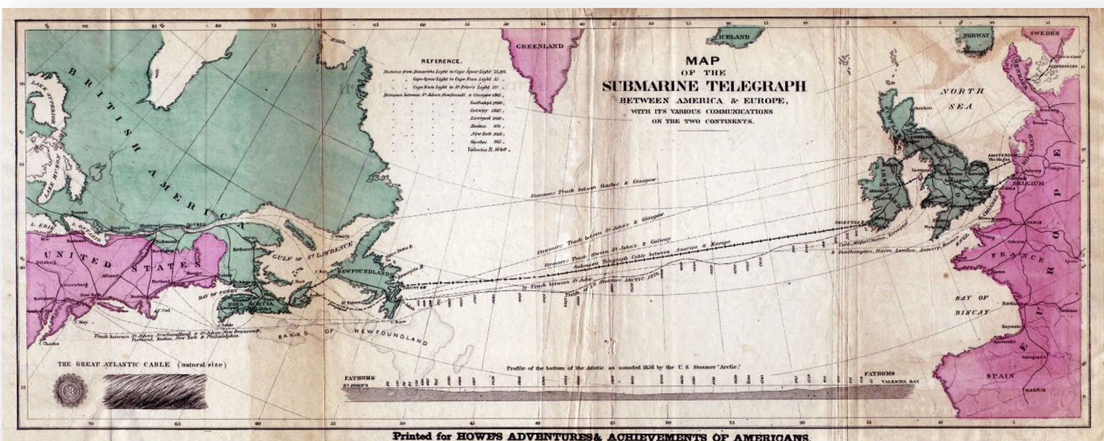
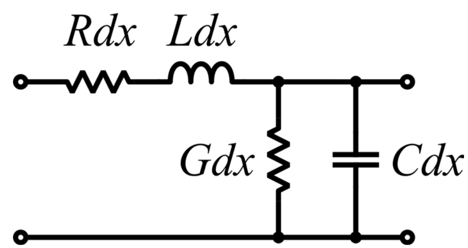


Image: [22]

The Transatlantic Telegraph Problem

- 1858: first transatlantic telegraph cable → **only 0.1 words per minute**!
- William Thomson (Lord Kelvin): treated cable as distributed resistance + capacitance
- Signal retardation grows strongly with cable length
- Thomson's mirror galvanometer enabled the successful 1866 cable

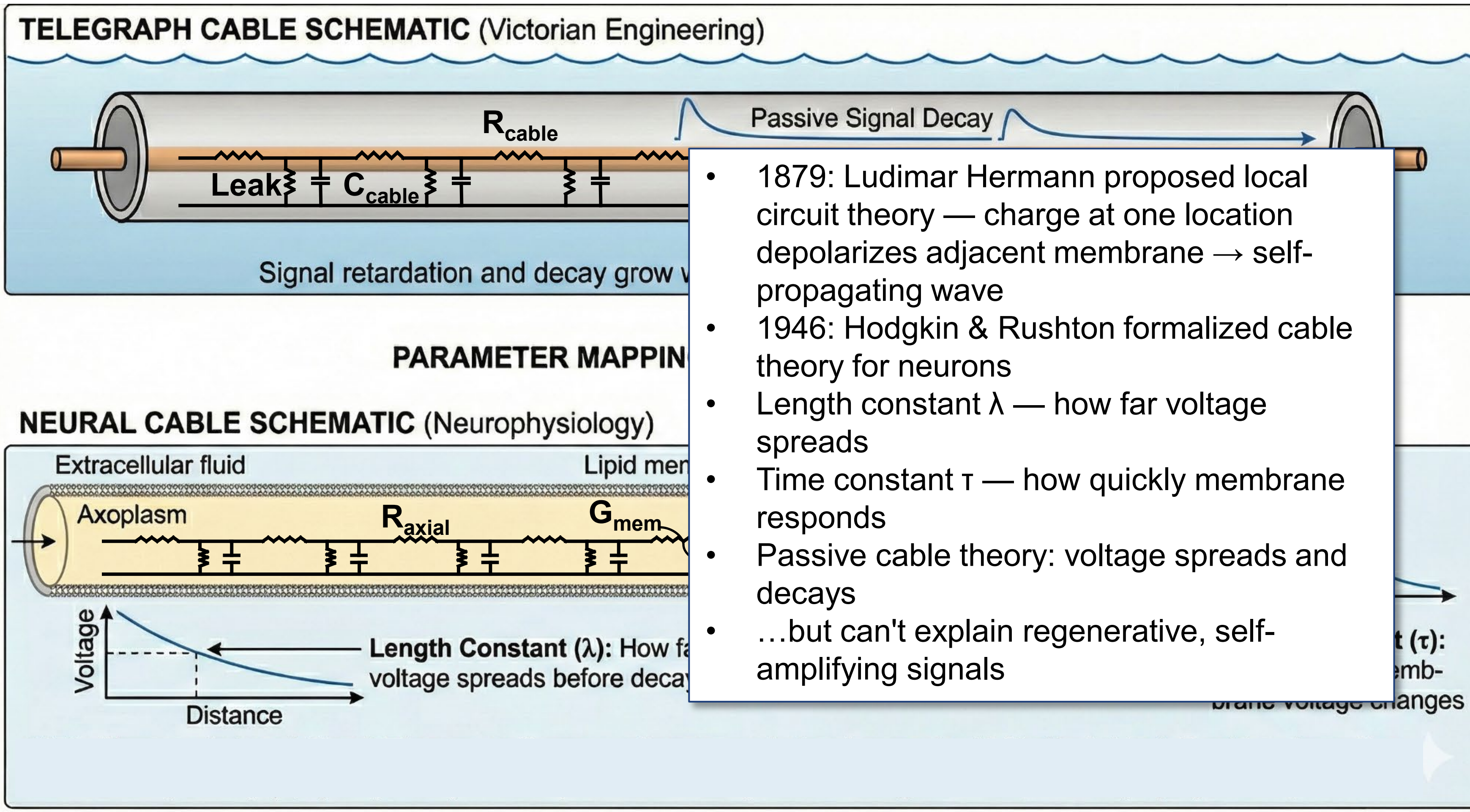




$$\frac{\partial}{\partial x}V(x,t) = -L\,\frac{\partial}{\partial t}I(x,t) - RI(x,t)$$
$$\frac{\partial}{\partial x}I(x,t) = -C\,\frac{\partial}{\partial t}V(x,t) - GV(x,t)$$

Images: [23, 24]

A Mathematical Equivalence



- 1879: Ludimar Hermann proposed local circuit theory — charge at one location depolarizes adjacent membrane → self-propagating wave
- 1946: Hodgkin & Rushton formalized cable theory for neurons
- Length constant λ — how far voltage spreads
- Time constant τ — how quickly membrane responds
- Passive cable theory: voltage spreads and decays
- …but can't explain regenerative, self-amplifying signals

Image: [25]

Cable Equation = 1D Maxwell + Constitutive Relations

- Cable equation: 1D reduction applied to a long, slender, lossy cylinder
- Telegraph engineer's parameters map directly to biophysics:
  - Distributed resistance → axial resistance
  - Distributed capacitance → membrane capacitance
  - Leakage → membrane conductances
- Passive cable theory: spread & decay
- Add nonlinear, voltage-dependent conductances → Hodgkin-Huxley → *excitable, actively propagating system*

Quasi-static: $\nabla\cdot(\sigma\,\nabla\phi) = -I_{\text{source}}$

Current conservation along fibre

$$i_a = -\frac{1}{r_a}\frac{\partial V}{\partial x} \qquad i_m = c_m\frac{\partial V}{\partial t} + g_m(V - E_{\text{rest}}) \qquad -\frac{\partial i_a}{\partial x} = i_m$$

Passive cable equation

$$\lambda^2\,\frac{\partial^2 V}{\partial x^2} = \tau_m\,\frac{\partial V}{\partial t} + V$$

$\lambda = \sqrt{r_m/r_a}$ (length const.) $\tau_m = r_m c_m$ (time const.)

Hodgkin–Huxley: active, excitable cable

$$c_m\frac{\partial V}{\partial t} = \frac{1}{r_a}\frac{\partial^2 V}{\partial x^2} - \bar{g}_{\text{Na}}\,m^3 h\,(V - E_{\text{Na}}) - \bar{g}_{\text{K}}\,n^4\,(V - E_{\text{K}}) - g_L(V - E_L)$$

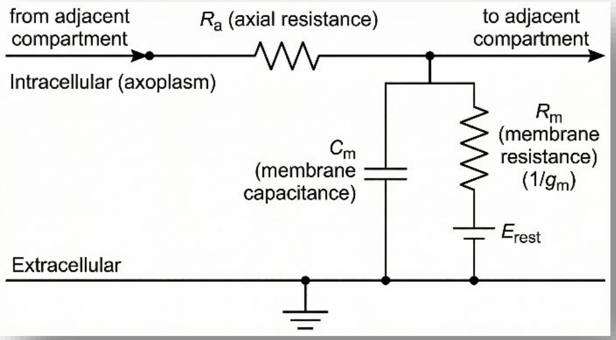
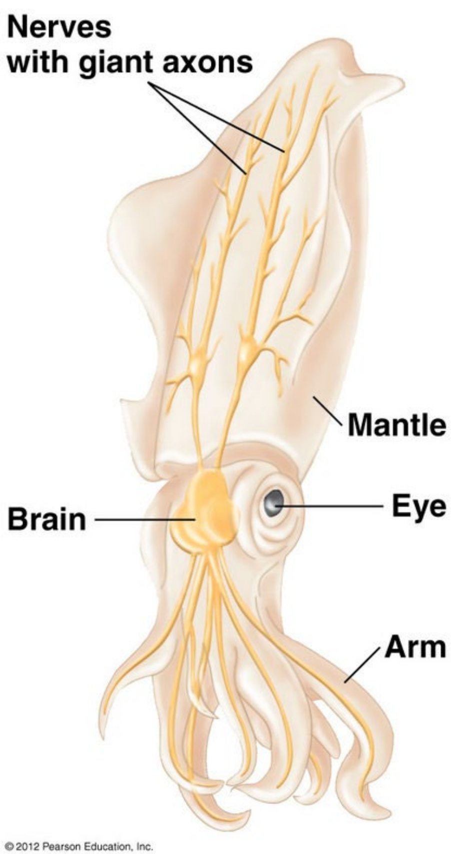


Image: [26]

In depth: **Lectures 2 & 3**

A Zoologist's Linchpin Discovery

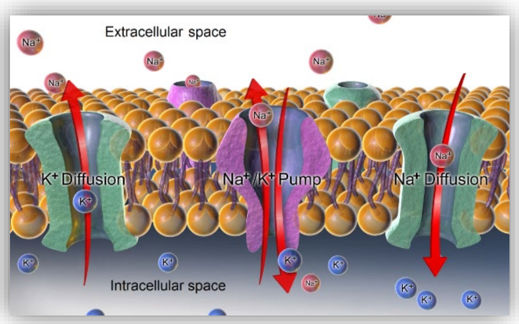


- 1936, Plymouth Marine Lab: J.Z. Young identifies giant nerve fibers in squid mantles
- Up to 1 mm diameter — **100–1,000 × thicker** than mammalian axons
- Why so large?: bigger diameter → faster conduction → rapid escape jet
- Hodgkin: *"[Young]…did more for axonology than any other single advance in technique during the previous 40 years"*
- **Large enough to insert electrodes inside**

Image: [27]

The Sodium Hypothesis

- Hodgkin & Katz (while Huxley was on his honeymoon)
- Hypothesis: overshoot from **selective increase in sodium permeability**
- Test: vary external Na^+ concentration → overshoot tracks sodium equilibrium potential
- Reducing external Na^+ proportionally reduces the overshoot
- Confirmed: the membrane doesn't just "break down" — it specifically opens to Na^+



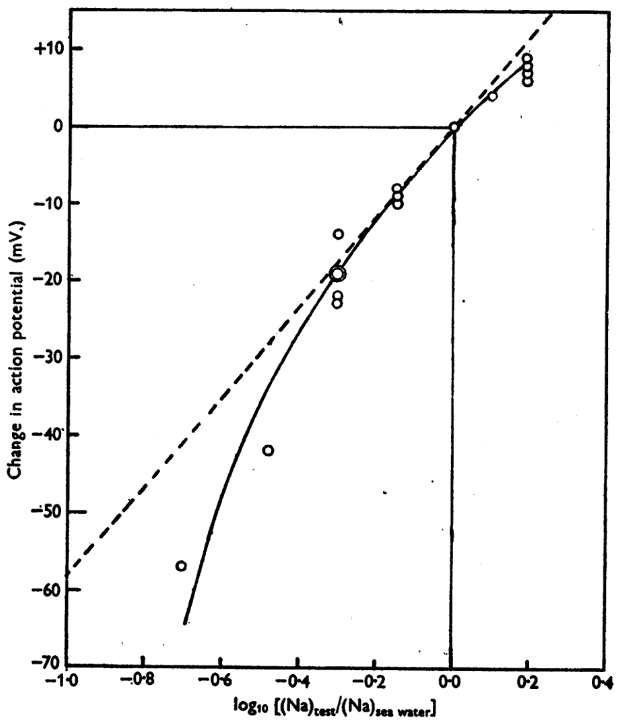


Fig. 6. Change in amplitude of action potential (ordinate) caused by alteration of external sodium concentration (abscissa). The dotted line is drawn through the origin with a slope of 58 mV.

Images: [30, 31]

Five Papers, One Equation, Three Weeks on a Brunsviga*

- July–August 1949: voltage-clamp recordings separate current into:
- Rapid inward Na^+ current
- Slower outward K^+ current
- Key discovery: **inactivation** — Na^+ channels close despite continued depolarization
- n^4, m^3h: hypothetical charged "particles" in the membrane that independently flip between open/closed positions in response to voltage
- K^+: 4 particles must all be open → n^4; Na^+: 3 activation + 1 inactivation → m^3h
- Later confirmed: K^+ channels are **tetramers** — each subunit has a voltage-sensing domain with charged residues that physically move in the field

Membrane current:

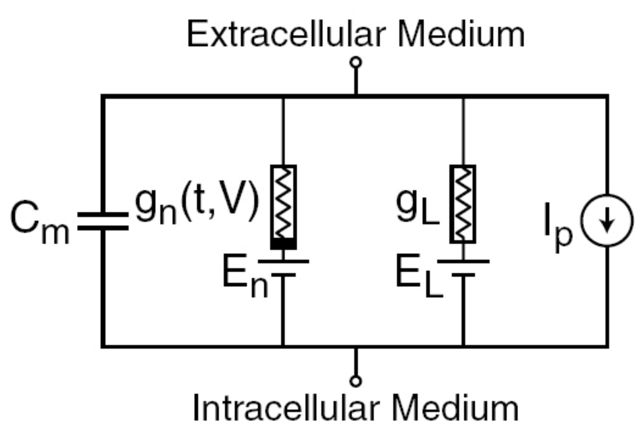
$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + \bar{g}_{\mathrm{K}}\, n^4 (V_m - V_K) + \bar{g}_{\mathrm{Na}}\, m^3 h (V_m - V_{Na}) + \bar{g}_l (V_m - V_l)$$

Gating variables:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = \alpha_n(V_m)\,(1-n) - \beta_n(V_m)\,n$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \alpha_m(V_m)\,(1-m) - \beta_m(V_m)\,m$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = \alpha_h(V_m)\,(1-h) - \beta_h(V_m)\,h$$



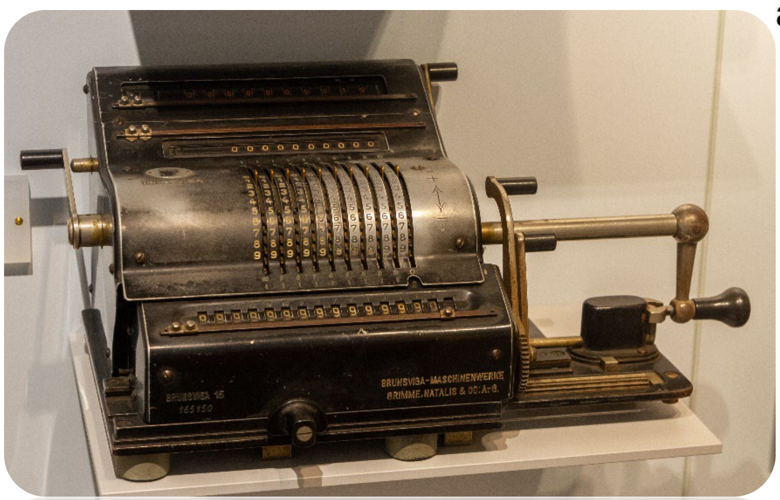
*what the heck is a Brunsviga??

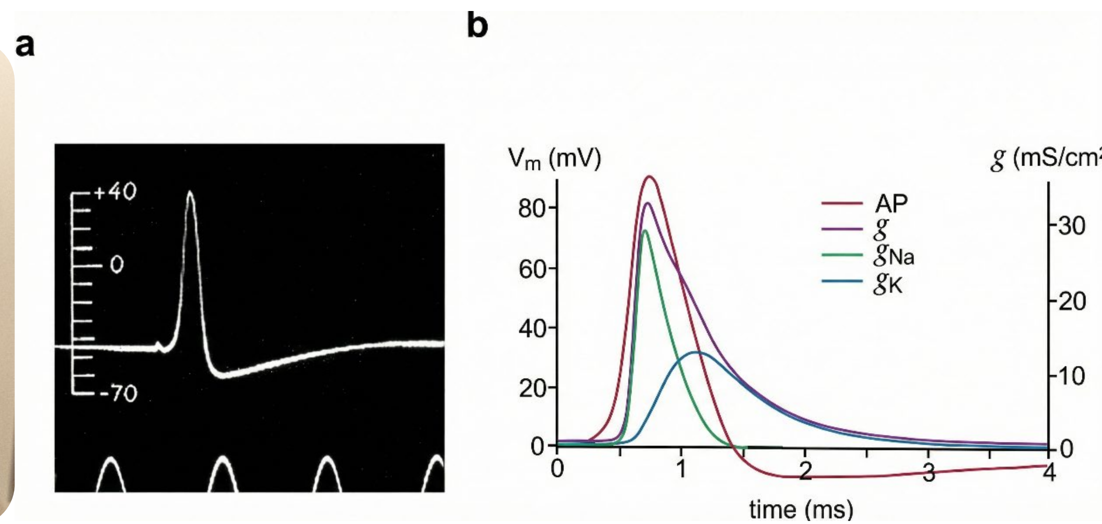
Image: [32]

Computed by Hand: Huxley and the Brunsviga

- To numerically integrate their differential equations and compute the AP waveform, they hoped to use EDSAC (Cambridge's electronic computer) — but it was offline for modifications
- Huxley computed a single propagated AP on a Brunsviga mechanical calculator — a hand-cranked desk machine capable of +, −, ×, ÷, one operation at a time
- **~3 weeks, hundreds of iterations**
- Predicted conduction velocity: **18.8 m/s** vs. measured 21.2 m/s
- Also predicted: threshold behavior, refractory periods, accommodation

- Cole: *"It is hard to believe that this collection will not remain an obvious turning point in electrophysiology."*





Images: [2, 33]

Post-H-H Developments

Denis Noble (Oxford, 1962)

- Adapted HH equations to cardiac **Purkinje** fibers — launched computational cardiac electrophysiology
- Cardiac processes: ms in nerve → hundreds of ms in heart; used an early digital computer for simulations
- Legacy: virtual heart models used in clinical practice today

Wilfrid Rall (NIH, 1957–64)

- Revolutionized **dendrite modeling**: neurons are not point neurons
- Cable theory for branched structures + compartmental modeling: discretize continuous cables into connected compartments for numerical simulation
- Rall & Shepherd (1968): predicted **dendrodendritic synapses in olfactory bulb** → confirmed experimentally — demonstrating predictive power of biophysically detailed modeling

John Eccles (Dunedin, 1951)

- First intracellular recordings from CNS; **EPSPs/IPSPs** with unmistakable time delays
- Proved chemical (not electrical) synaptic transmission — converted by his own data
- 1963 Nobel Prize: Hodgkin, Huxley, and Eccles

Neher & Sakmann (1976; gigaseal 1981)

- **Patch clamp technique**: first single-channel current recordings → provided the conductance values and kinetics that all HH-style models require
- 1991 Nobel Prize in Physiology or Medicine

Rall's Method Needed Software…

- Michael Hines (Duke → Yale): the "Hines method" (1984) — O(n) tree-structured matrix solver for n compartments
- CABLE → **NEURON** simulation environment (with Ted Carnevale, Yale): landmark paper 1997, **NMODL** mechanism language 2000, Python interface 2009, MPI parallelization with Blue Brain 2006
- **ModelDB** (Yale, 1996): >1,800 published models in source code — reproducibility infrastructure
- James Bower & Matt Wilson (Caltech, 1988): **GENESIS** — object-oriented design, The Book of GENESIS used in 26+ countries
- Blue Brain's **CoreNEURON**: GPU-accelerated engine, 4–7 × memory reduction — biophysically detailed simulation at HPC scale

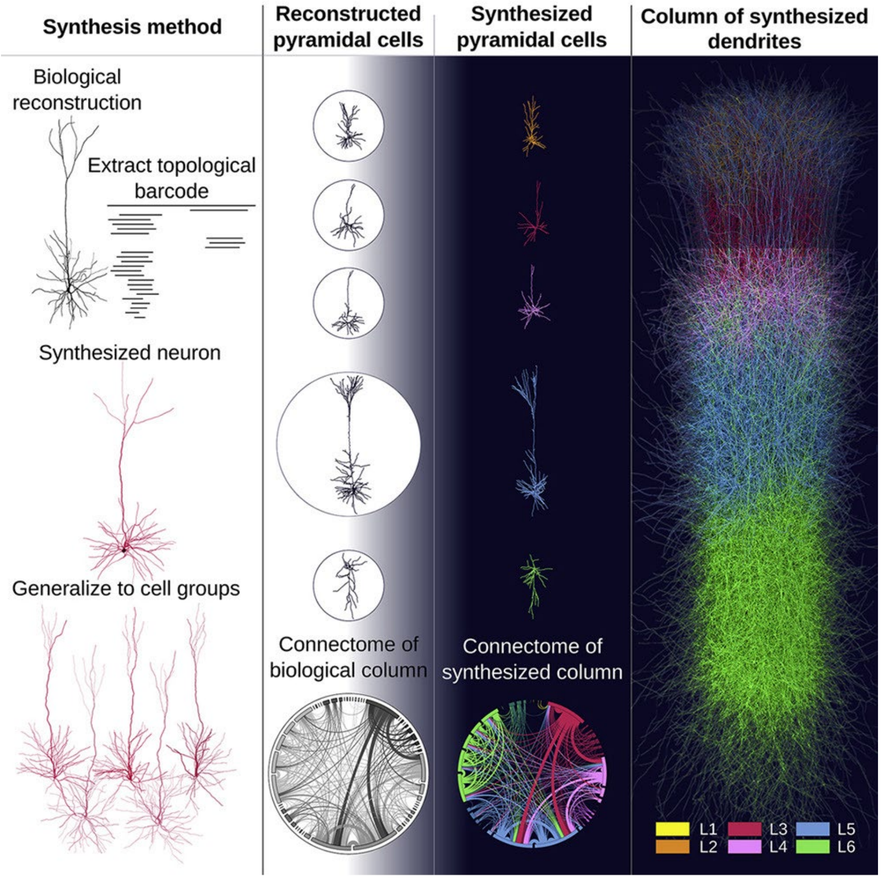
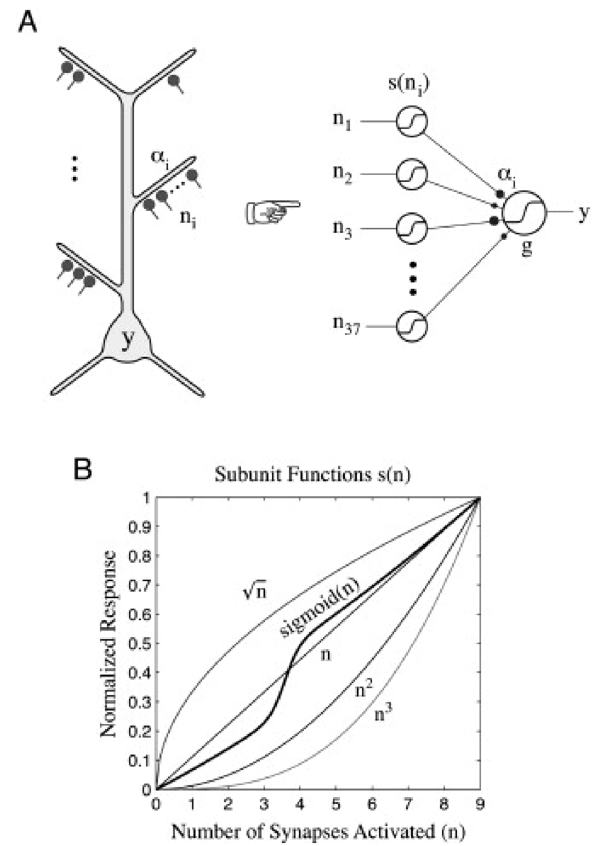


Image: [34]

What Simulators Revealed About Dendrites

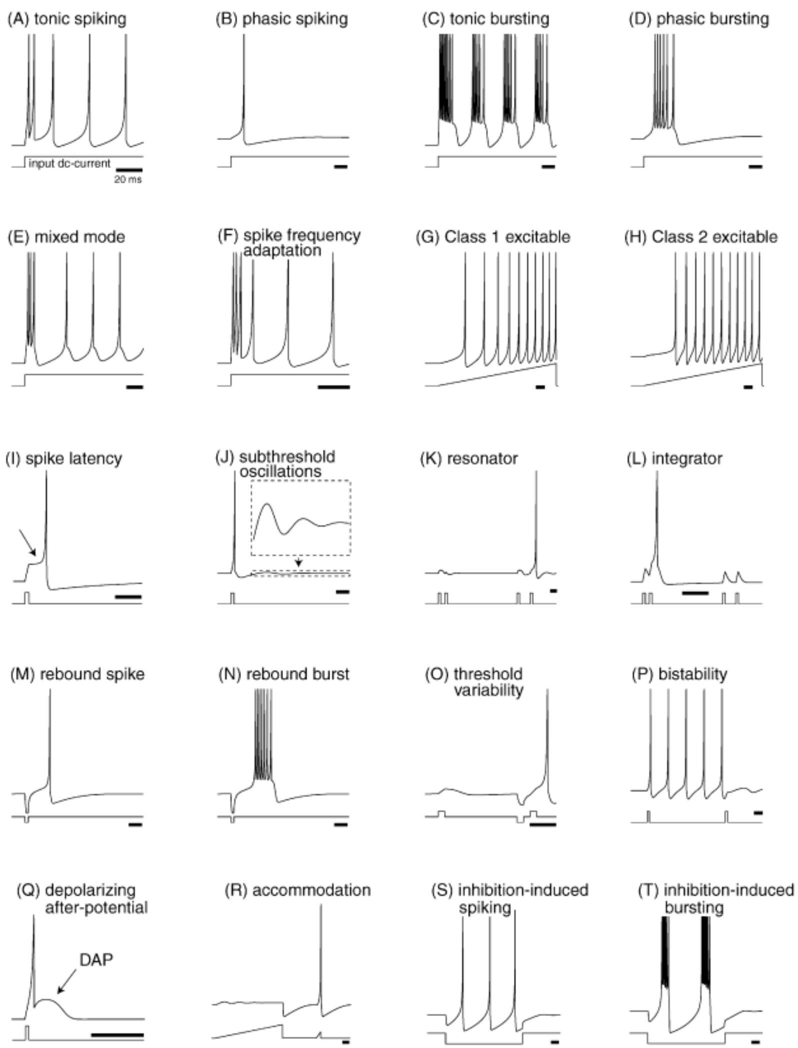
- Poirazi, Brannon & Mel (2003): pyramidal neuron **dendritic tree = two-layer neural network** — branches as independent sigmoidal subunits
- Gidon et al. (Science, 2020): human cortical dendrites generate novel **Ca^{2+} action potentials** → single dendrites classify linearly non-separable inputs



In depth: **Lecture 7**

Image: [35]

Scaling Up: Points Neurons & Spiking Networks



In depth: **Lectures 2 & 7**

Image: [36]

Trading Detail for Scale

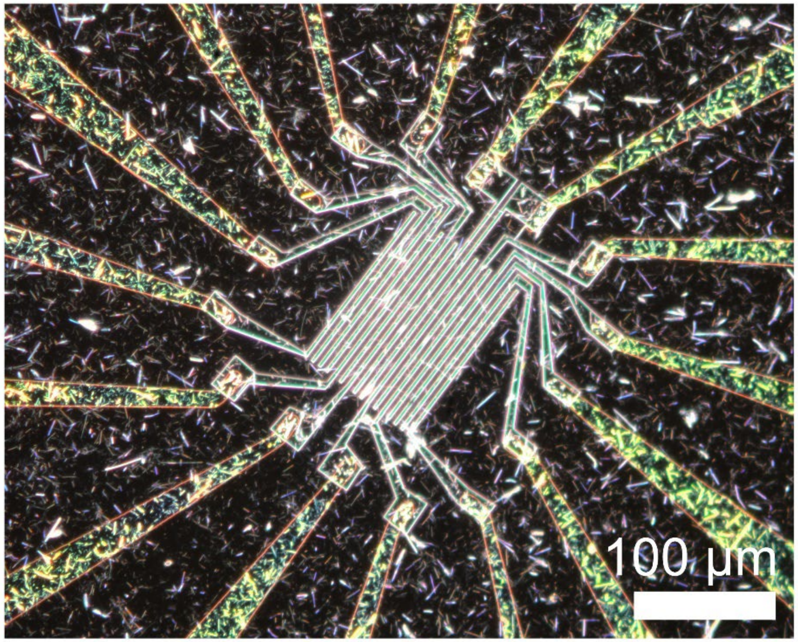
- Lapicque (1907): **integrate-and-fire** — the original "**point neuron**“
- FitzHugh (1961) / Nagumo (1962): collapsed HH to 2 variables → canonical excitable system for phase-plane analysis
- Izhikevich (2003): 2 ODEs, 4 parameters, 13 FLOPs/ms (vs. ~1,200 for HH) — reproduces 20+ cortical firing patterns (*left*)
- AdEx model (Brette & Gerstner, EPFL, 2005): exponential spike + adaptation, ~96% spike-time accuracy vs. detailed HH

Network Simulators

- **NEST** (Diesmann & Gewaltig, 1993/2004, Jülich): millions of neurons on supercomputers via MPI/thread parallelism
- **Brian** (Goodman & Brette, 2008): equation-oriented, code generation for C++/GPU
- **GeNN** (Nowotny, Sussex, 2016): up to 200 × speedup for million-neuron HH networks on GPU
- **PyNN** (Davison et al., 2009): simulator-independent Python API — same code on NEURON, NEST, Brian, or neuromorphic hardware

Learning Rules & Neuromorphic HW

- **Spike time-dependent plasticity (STDP)** (Markram 1997; Bi & Poo 1998): biologically plausible, temporally precise synaptic learning
- IBM **TrueNorth** (2014): 1M neurons, 256M synapses, ~65 mW
- Intel **Loihi** (2018): 130K neurons with on-chip learning
- **SpiNNaker** (Furber, Manchester): engineered for real-time simulation at extreme scale using ARM cores
- → Ultra-low-power platforms for closed-loop bioelectronic devices



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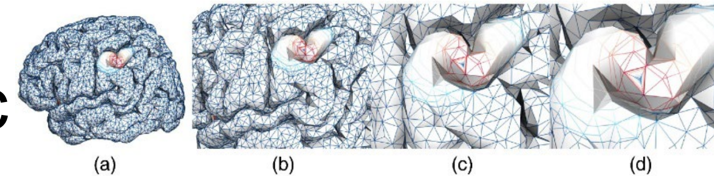
Whole-Brain Simulation: From Neural Masses to the Clinic



Population-Level Dynamics

- Wilson & Cowan (1972): excitatory–inhibitory population model → bistability, oscillations, epileptic wave propagation
- Freeman (1975): "neural mass" coined; deterministic chaos in mesoscopic olfactory dynamics
- Jansen & Rit (1995): three-population cortical column (pyramidal, excitatory interneurons, inhibitory interneurons) — 6 coupled ODEs reproduce realistic alpha oscillations → standard EEG simulation model

The Virtual Brain (TVB)

- Jirsa (CNRS/Aix-Marseille), Ritter (Charité), McIntosh (Toronto), ~2008
- Patient-specific: structural MRI + diffusion-weighted imaging (white matter connectivity with weights + conduction delays) + neural mass model per region
- Now the principal whole-brain simulator on EBRAINS

THEVIRTUALBRAIN.

From Simulation to Surgery

- Epileptor model (Jirsa, *Brain* 2014): bifurcation theory for seizure dynamics, 5 state variables
- Virtual Epileptic Patient pipeline: anatomy + connectivity + stereo-EEG → epileptogenic zone identification
- Wang et al. (*Science Translational Medicine*, 2023): 53 patients, mean 5.6 mm from clinical ground truth
- EPINOV trial (NCT03643016): 356 patients, 11 French centers — prospective randomized trial of TVB-guided surgery

In depth: **Lecture 8**

Image: [38]

Building Digital Brain Tissue

Biophysically Detailed Reconstructions

- **Blue Brain Project** (Markram, EPFL, 2005–2024): *Cell* 2015 — 31,000 neurons, 55 morpho-electrical types, 8M synapses in rat somatosensory cortex; whole mouse neocortex model (10M neurons, 88B synapses); resources → Open Brain Institute (March 2025)
- **Human Brain Project** (EU €1B Flagship, 2013–2023): restructured 2015; delivered EBRAINS, BigBrain atlas, Julich cytoarchitectonic atlas, neuromorphic platforms (SpiNNaker, BrainScaleS), 3,000+ publications

Experimental Ground Truth

- **Allen Institute** (Paul Allen, 2003, Seattle): Mouse Brain Atlas, Cell Types Database, GLIF & biophysically detailed models per cell type
- **MICrONS** (IARPA, ~2016–2025): 1 mm³ mouse visual cortex at synaptic resolution — 200,000+ cells, ~500M synapses; *Nature* 2025, 10-paper suite
- Connectomics arc: *C. elegans* (White et al., 1986: 302 neurons, 7K connections) → *Drosophila* brain (**FlyWire**, Oct 2024: 139,255 neurons, 50M+ synapses)

Standardization

- **NeuroML** (v2 + LEMS, Gleeson & Silver, UCL): machine-readable ion channels, synapses, morphologies, networks → Open Source Brain platform
- **SONATA** (Allen + Blue Brain, 2020): HDF5/JSON for large-scale network storage

Image: [39]

Part II:
Summary & Key Takeaways

Summary & Key Takeaways

1. Measure → Model → Predict

- New instruments revealed facts old theories couldn't explain
- Each cycle forced a better quantitative model

2. Cables are cables are cables

- Telegraph cable → neural cable → HH active cable
- Cable equation = 1D Maxwell under quasi-static assumptions
- HH's addition: nonlinear, voltage-dependent conductances

3. Predictive models → modern engineering

- Brunsviga: 18.8 m/s predicted vs. 21.2 m/s measured
- Threshold, refractoriness, accommodation — predicted for free
- All modern bioelectronic medicine (SCS, DBS, TES etc.) today descends from 1952

4. From 4 equations to clinical instruments

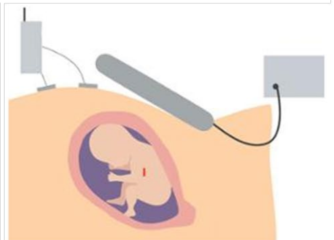
- HH → compartmental models → simulators → patient-specific digital twins
- Abstraction is a design choice: 13 FLOPS (Izhikevich) and 1,200 FLOPS (HH) both serve bioelectronic medicine
- Models now guide surgery (EPINOV), electrode placement (Lead-DBS, STIMO), and regulatory submissions

Outline for Today

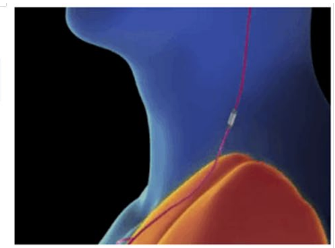
- Part I: Introduction & Course Logistics
- Part II: From Frog Legs to Firing Equations: A Brief History of Bioelectricity
- **Part III: Motivation — Modern Bioelectronics & Neuroprosthetics**

From Brunsviga to Brain-Spine Interfaces:
How Models Became Medicine

Brain and Spine Implants Let a Paralyzed Monkey Walk Again
10 Nov 2016

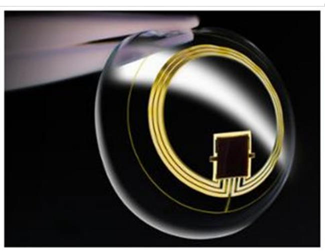


Fetal Pacemaker Ready for Human Trial
11 May

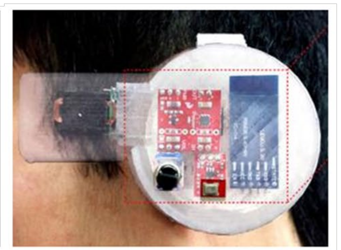


Vagus Nerve Stimulation Fights Rheumatoid Arthritis
25 Jul 2016

AI Can Help Patients Recover Ability to Stand and Walk
19 Jul

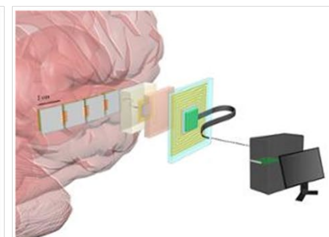


Smart Contact Lenses and Eye Implants Will Give Doctors Medical Insights
25 Jul



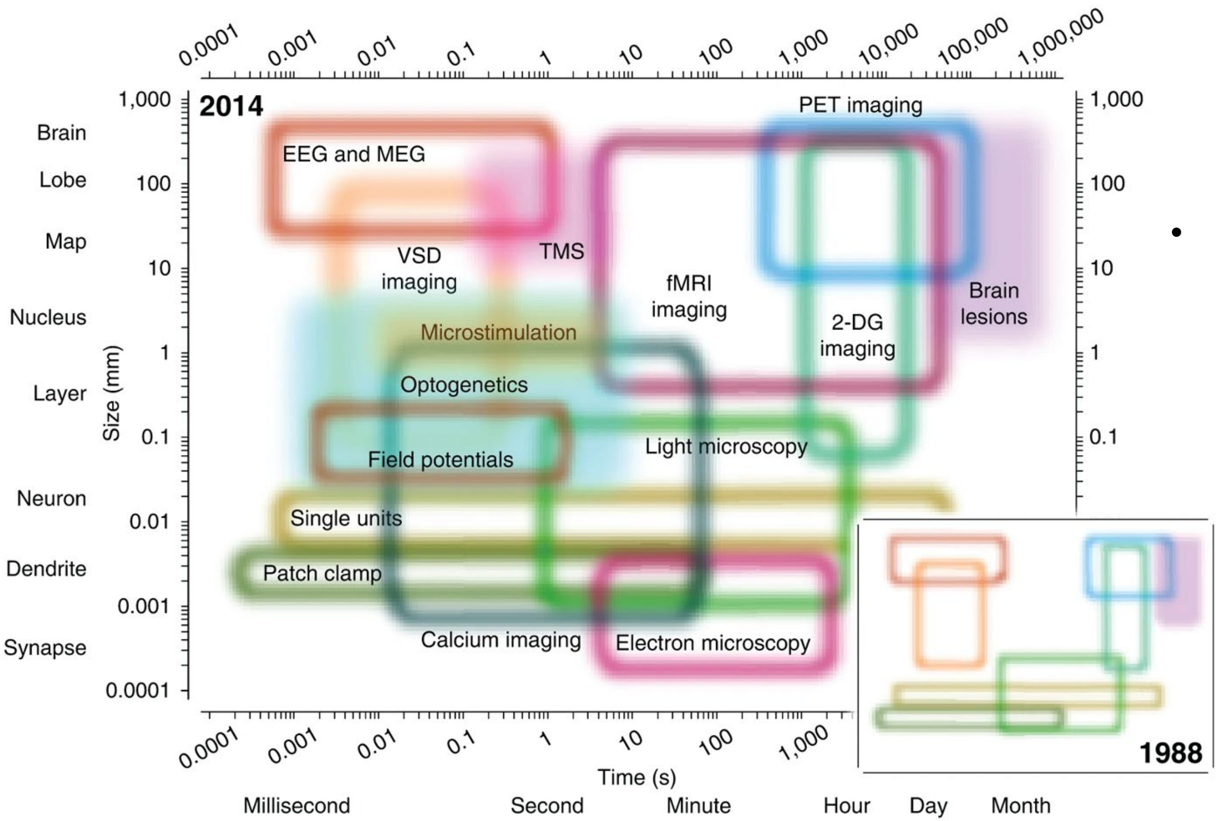
3D-Printed "Earable" Sensor Monitors Vital Signs
27 Jul

Wearable Sensors Give Skin Space to Breathe
20 Jul



DARPA Wants Brain Implants That Record From 1 Million Neurons
10 Jul

Neuroimaging Spatiotemporal Resolution



- Every technique trades spatial resolution for temporal coverage, or vice versa: No single modality spans the full range from synapse to brain, millisecond to month
  - Computational models are the only tool that can bridge these scales (**Week 8**)

- ECoG and field potentials occupy the intermediate "meso-scale" — the target zone for most bioelectronic devices in this course
- Since 1988: The landscape has expanded dramatically — optogenetics, calcium imaging, Neuropixels, and fMRI have filled gaps that did not exist in the original diagram

Image: [41]

DBS: Benabid & Neural Targets

- **Alim-Louis Benabid (Grenoble, 1987)**: First chronic high-frequency stimulation of VIM thalamus for essential tremor
  - STN targeting (1993) addressed all cardinal PD symptoms; 2014 Lasker Award
- **FDA Timeline**: ET 1997 → PD 2002 → dystonia HDE 2003 → OCD HDE 2009 → epilepsy 2018 <u>(>20yrs → comp modeling can greatly accelerate)</u>
- **Directional Leads: Current Steering**: Segmented contacts steer current toward targets, away from side-effect tracts
  - Vercise Cartesia 1-3-3-1 (INTREPID trial, 292 pts, ~49% UPDRS-III improvement); Abbott Infinity; Medtronic SenSight
  - Clinical realization of the electric field shaping predicted by VTA models
- **The Mechanism Debate**: Not simply "inhibition“—informational lesion hypothesis (Grill et al., 2004): DBS disrupts pathological synchrony while permitting information flow
  - Optogenetic dissection (Deisseroth, 2009): Afferent axons, not cell bodies, are key targets

Adaptive DBS: Closing the Loop

- **The β-Oscillation Biomarker (Weeks 8, 10)**: Peter Brown (Oxford): Exaggerated 13–35 Hz LFP power in STN correlates with bradykinesia/rigidity
  - β suppression by levodopa or effective DBS → candidate closed-loop control signal
- **Little et al. (2013):** Closed-loop proof-of-principle: 8 PD patients, 50% blinded motor improvement; 29% better than continuous DBS
  - Simultaneous 56% reduction in total stimulation time
  - Medtronic Percept PC (FDA June 2020): First commercial system with chronic LFP sensing during therapeutic stimulation
  - >40,000 patients worldwide; BrainSense suite for LFP monitoring
- **ADAPT-PD Trial (NCT04547712, 68 patients)**: Reliable LFP control signal in 84.8% of medicated patients
  - Led by Bronte-Stewart (Stanford) and Herrington (MGH/Harvard)
- **BrainSense™ Adaptive DBS** — FDA Approved Feb. 24, 2025: Software update to compatible Percept devices → large commercial BCI deployment

Image: [42]

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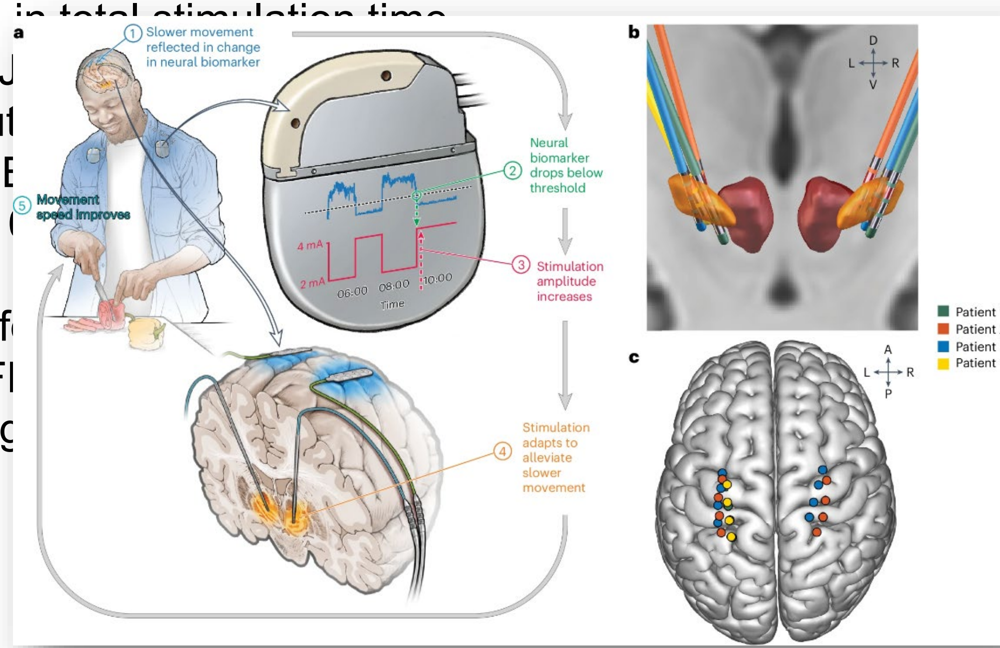

Image: [42]

Psychiatric DBS: Why Personalization Matters

- **Helen Mayberg: Area 25 Hypothesis (2005)**: DBS targeting subcallosal cingulate for treatment-resistant depression
  - First report: 4 of 6 patients responded — promising proof-of-concept
- **The BROADEN Trial Failure**: Planned 200-patient sham-controlled trial (St. Jude/Abbott)
  - Halted after 90 implants: ~20% response in both active and sham groups
  - Failure attributed to standardized targeting missing critical white matter tracts
- **Katherine Scangos (UCSF, 2021): The Personalized Paradigm**: Multi-day intracranial mapping of individual patient's mood circuit
  - Personalized biomarker (amygdala gamma) & individualized stimulation target
  - Closed-loop therapy → rapid, sustained improvement in treatment-resistant patient
- **Key Lesson**: Depression circuits are highly individual → one-size-fits-all targeting fails
  - Same lesson as SCS: Patient-specific computational modeling is essential (**Week 11**)

SCS: From Pain Relief to Locomotor Restoration

- **Foundations: Gate Control → Shealy → 50 Years of Pain SCS**: Melzack & Wall (Science, 1965): Aβ fiber stimulation inhibits nociceptive transmission
  - Shealy (1967): First dorsal column stimulation implant for cancer pain
  - Modern paradigms: Tonic, burst (SUNBURST), HF10 kHz (Nevro SENZA, FDA 2015), DRG (Abbott, FDA 2016)
- **A Different Target: Dorsal Roots, Not Dorsal Columns**: Courtine & Bloch (EPFL/CHUV): Spatiotemporally patterned epidural stimulation
  - Sim4Life models identified proprioceptive afferents in dorsal roots as therapeutic target
  - This explains why 50 years of "dorsal column" pain SCS never restored locomotion
- **STIMO (Wagner et al., Nature 2018)**: 3 chronic SCI participants, walking restored within one week
  - Some voluntary control recovered even without stimulation (neuroplasticity)
- **Rowald et al. (Nature Medicine 2022)**: 3 patients with complete paralysis, motor functions restored within one day (**Lecture 6 & Visitor**)
  - IT'IS Foundation: Patient-specific models (Wagner 2018)

Image: [48]

SCS: From Pain Relief to Locomotor Restoration

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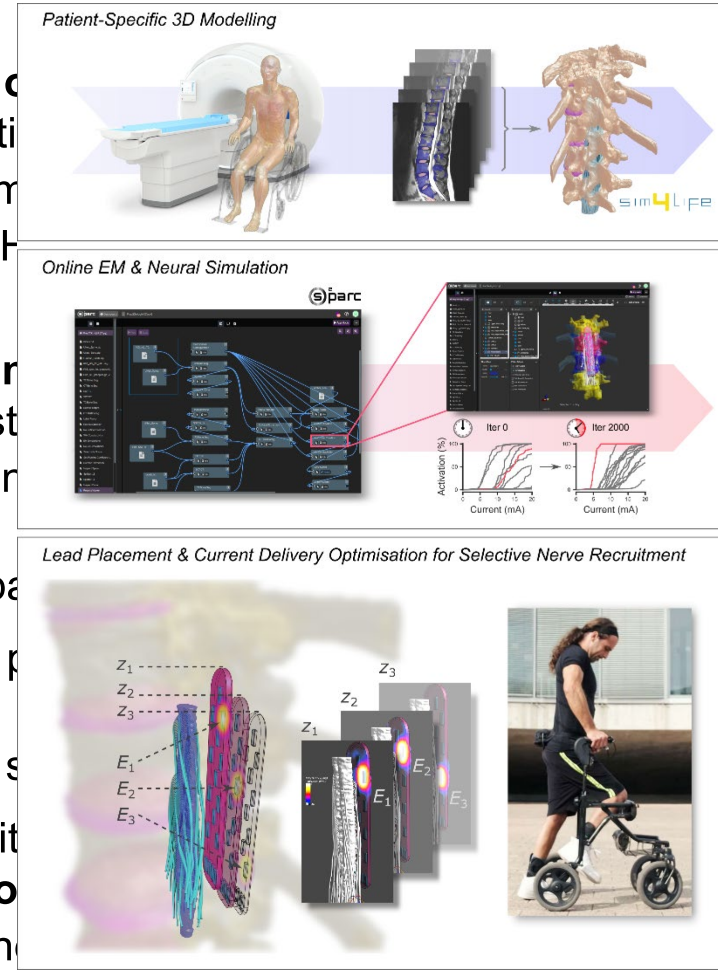

Image: [48]

ONWARD Medical: Commercial Translation

- **From EPFL Spin-off to Public Company**: Co-founded by Courtine & Bloch in 2014 (originally GTX Medical)
  - IPO on Euronext Brussels, 2021
- **ARC-EX: Transcutaneous Spinal Stimulation**: Upper-limb function in incomplete cervical SCI
  - FDA De Novo classification: Dec. 19, 2024
  - CE Mark: Sep. 8, 2025 (clinic & home use)
- **ARC-IM: Implantable System**: Autonomic & mobility indications (blood pressure, locomotion)
  - FDA IDE approval: Aug. 18, 2025 (Empower BP pivotal study)
- **ARC-BCI: Brain-Computer Interface Variant**: Goal — direct cortical control of spinal stimulation for movement restoration

Image: [43]

ONWARD MEDICAL

BCIs: Three Approaches & Speech Decoding

- **BrainGate / Utah Array (Donoghue/Hochberg)**: 96-channel rigid silicon array; first human intracortical BCI (Nagle, 2004)
  - Cathy Hutchinson (2011): First 3D reach-and-grasp; implant functional >5 years

Intravascular Stentrode

- **Synchron Stentrode (Oxley)**: Endovascular: stent-mounted array via jugular vein — no craniotomy
  - SWITCH (Australia, 4 patients): ≥92% click accuracy, 14–20 characters/min
  - COMMAND (U.S., 6 patients): first FDA IDE for permanent BCI; safety endpoints met
- **Neuralink N1 (PRIME Trial, Jan. 2024)**: 1,024 electrodes, 64 flexible threads, robotic insertion; first patient: Noland Arbaugh
  - Thread retraction in first participant → refined; 21 enrolled by Jan. 2026
- **Speech BCIs: Decoding the Voice (UCSF)**: First real-time speech decoding from ECoG in anarthric patient
  - Dual Nature papers (Aug. 2023): Metzger 78 WPM (ECoG); Willett 62 WPM (intracortical, 9.1% WER on 50-word vocab; 23.8% on 125k-word vocab)
  - Natural conversation ~160 WPM — approaching clinical viability

Images: [44, 45]

BCIs: Three Approaches & Speech

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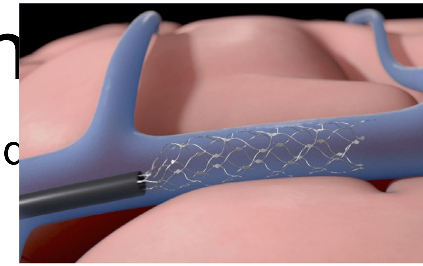
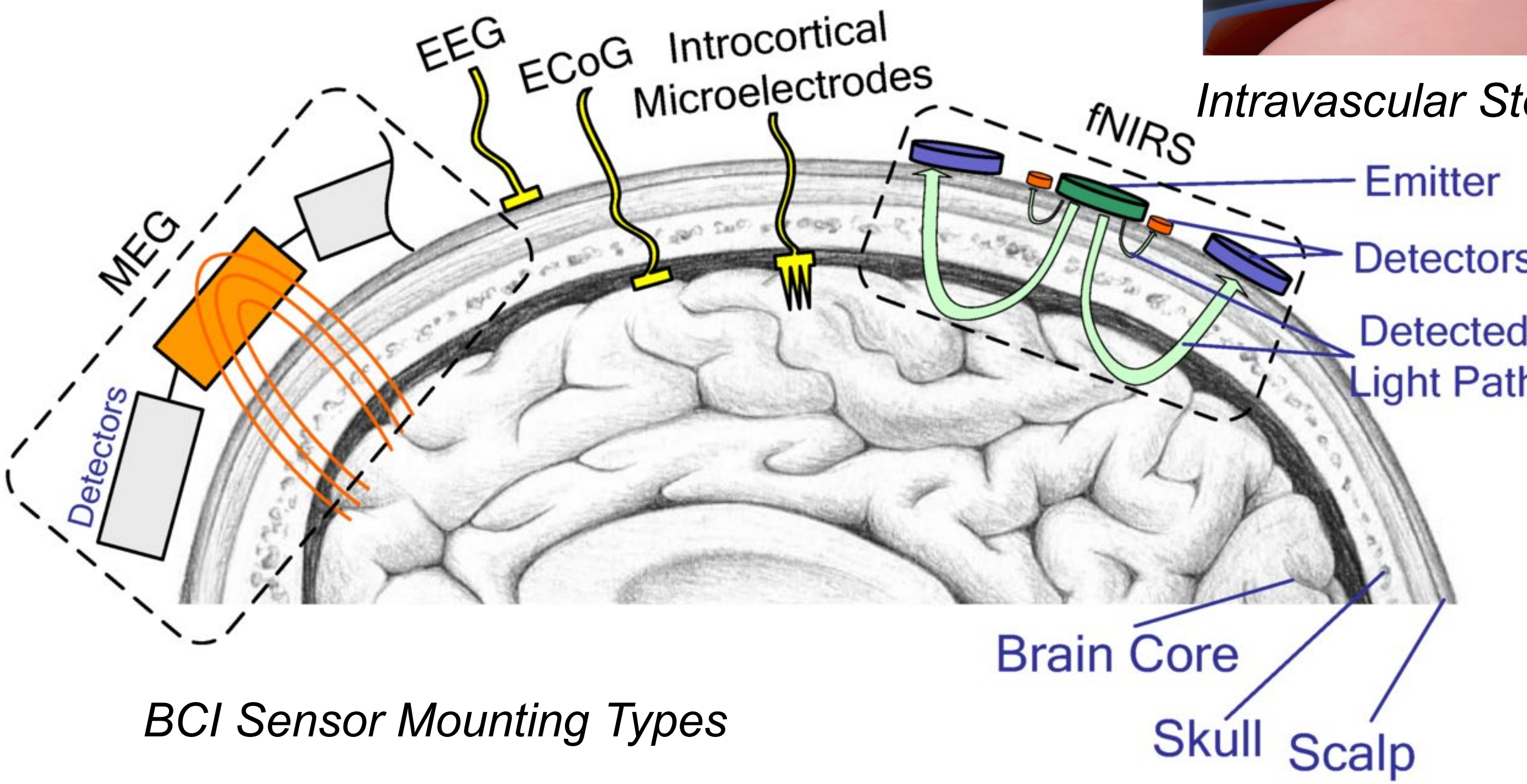


Intravascular Stentrode



BCI Sensor Mounting Types

-
-
-
  - Natural conversation ~160 WPM — approaching clinical viability

Images: [44, 45]

BCIs: Three Approaches & Speech

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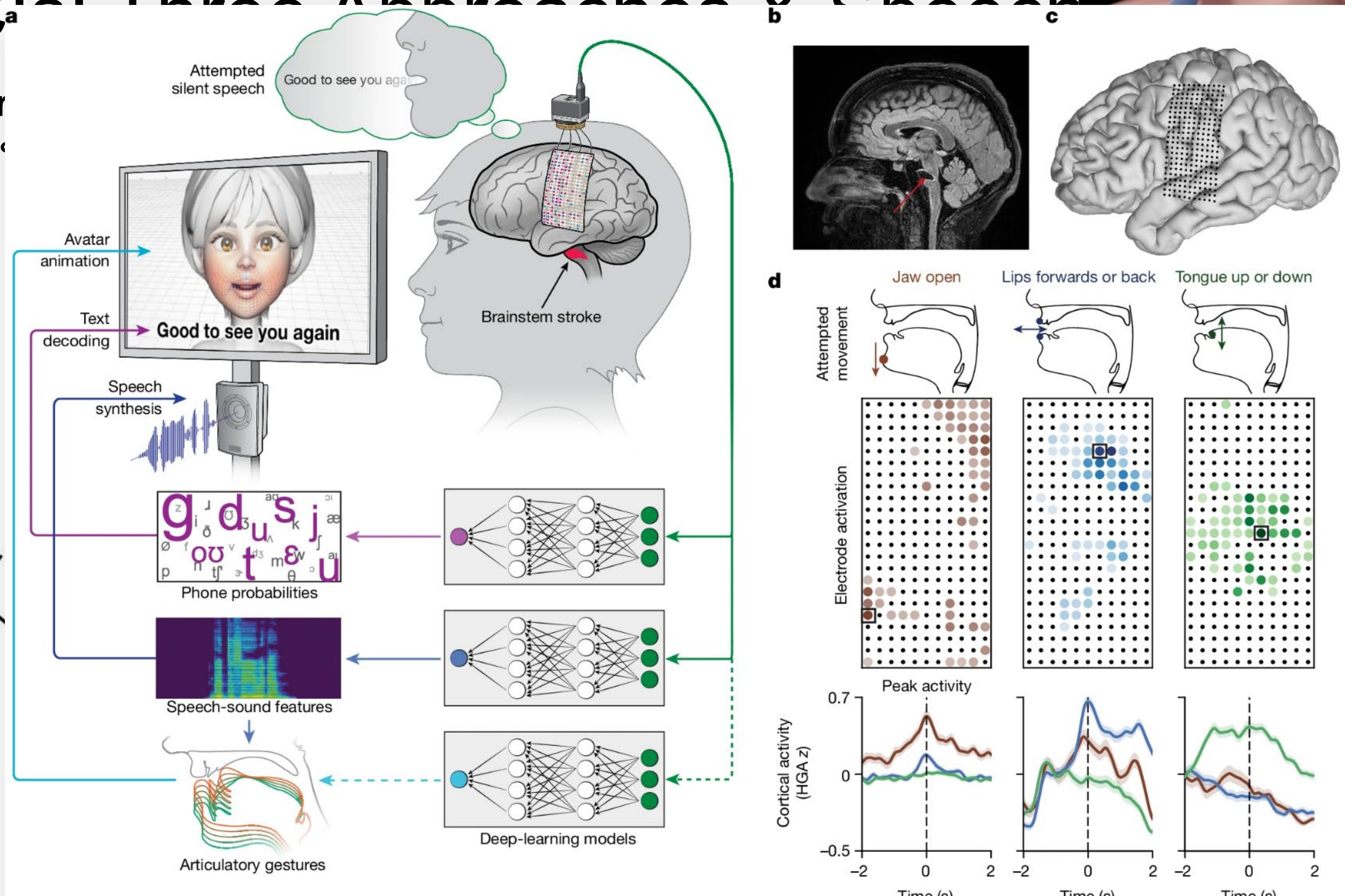


  ○ Natural conversation ~160 WPM — approaching clinical viability

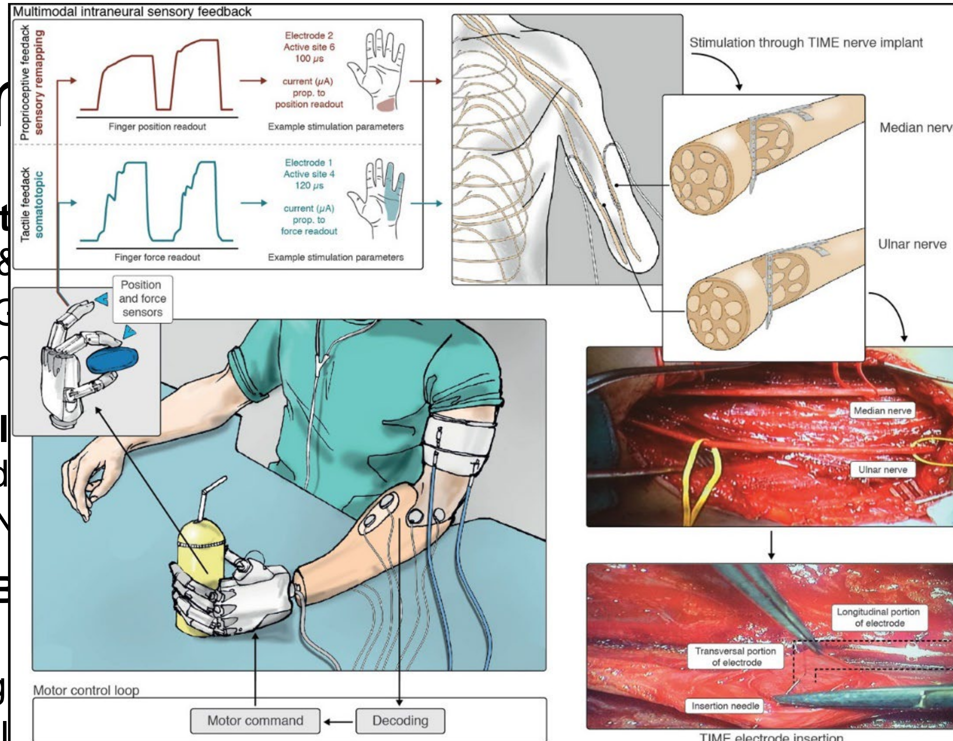
Images: [44, 45]

Brain-Spine Interface & Sensory Feedback

- **Lorach et al. (Nature 2023): A Digital Bridge**: Two WIMAGINE 64-electrode ECoG implants (CEA, Grenoble) & epidural spinal stimulation
  - Participant Gert-Jan Oskam: Walking, stairs, complex terrain restored
  - Calibrated in minutes; stable over one year; neuroplastic recovery even without device
- **Bidirectional BCIs: Closing the Sensory Loop**: Flesher et al. (2021): Somatosensory cortex microstimulation during robotic arm control
  - Participant Nathan Copeland: Tactile feedback → 2× faster object transfer (10.2 vs. 20.9 s)
- **Neural Bypass (Bouton et al., 2016)**: Ian Burkhart (quadriplegic): Cortical decoding → 130-electrode forearm sleeve
  - Isolated finger movements, grasping, credit card swiping — first electronic spinal bypass
  - Bidirectional feedback is essential for dexterous, natural movement
- **Micera Bidirectional Hand Prosthesis (EPFL / Scuola Superiore Sant'Anna)**: Intraneural sensory feedback via peripheral nerve electrodes
  - Raspopovic et al. (Sci. Transl. Med., 2014): TIMEs in median + ulnar nerves restored real-time touch — force modulation and object identification without vision
  - Petrini et al. (Ann. Neurol., 2019): 3 amputees, 6-month trial — stable intraneural feedback, reduced phantom limb pain by up to 70%
  - D'Anna et al. (Sci. Robotics, 2019): among the first demonstrations of simultaneous tactile + proprioceptive feedback in a closed-loop neuroprosthesis

Image: [46]

Brain-Spi… …eedback



- **Lorach et al. (Nat…** …e ECoG implants (CEA, Grenoble) &…
  - Participant G…
  - Calibrated in… …n without device
- **Bidirectional BCI…** …atosensory cortex microstimulation d…
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Image: [46]

Cochlear Implants & Beyond

- **Cochlear Implant: The Original Bioelectronic Success**: Graeme Clark (1978, Melbourne): first multi-channel cochlear implant
  - Sound → spectral decomposition → electrode array in cochlea → auditory nerve stimulation
  - >1 million recipients worldwide — most successful neural prosthetic ever
- **Retinal Prosthetics**: Argus II (Second Sight): 60-electrode epiretinal array for retinitis pigmentosa
  - GenSight PIONEER trial: Optogenetic approach using channelrhodopsin + light goggles
  - Sahel et al. (Nature Medicine 2021): Partial vision recovery in blind patient
- **Computational Modeling Role (Lecture 5)**: Electrode-neuron distance models predict auditory percepts in CI
  - Same FEM + biophysical framework used across all sensory prosthetics

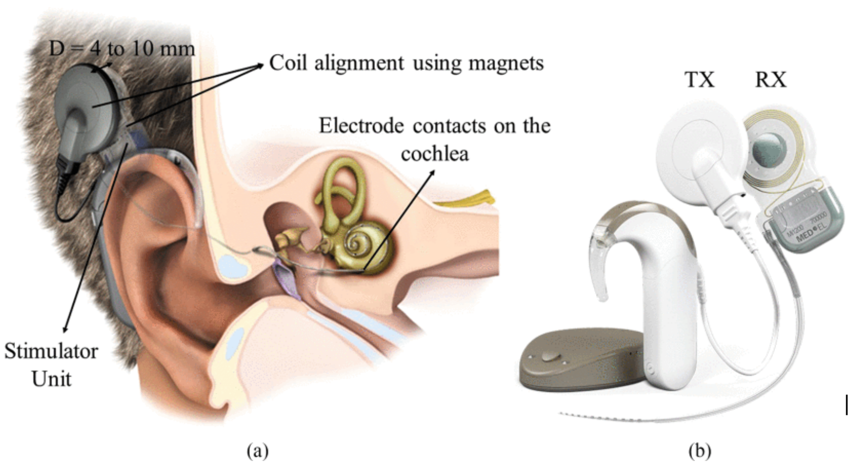

Image: [47]

The Argus II Cautionary Tale

- **Second Sight & the Argus II**: FDA-approved retinal prosthesis (2013) for retinitis pigmentosa; 350+ patients implanted
- **Company Collapse (2019–2020)**: Pivoted to cortical Orion implant; laid off 84/108 staff; near-bankruptcy
  - 2022 merger with Nano Precision Medical — focus shifted entirely from Argus
- **Patients Left in the Dark**: Limited/no repairs, replacements, upgrades
  - Patients learned of abandonment secondhand; some lost vision when hardware failed
  - Defunct implants risk MRI complications; surgical removal non-trivial
- **Ethical Questions for Neuroprosthetics**:
  - What obligations exist when devices become part of someone's nervous system?
  - Informed consent: should patients be warned of business-model risk, not just medical risk?
  - "Bricking" a neuroprosthetic ≠ discontinuing a phone — the device is part of the self

VNS: Epilepsy, Immunology, & Cardiac

- **VNS for Epilepsy (FDA 1997) & Depression (FDA 2005)**: LivaNova: >125,000 patients; gammaCore (electroCore): non-invasive VNS for migraine
- **Tracey's Inflammatory Reflex (2000–2002)**: Vagal efferents → splenic acetylcholine → α7 nicotinic receptors → TNF suppression
  - Founded bioelectronic medicine as a discipline (**Lecture 5**)
- **SetPoint Medical: First FDA-Approved Neuroimmune Modulation Device**: RESET-RA trial (n=242): ACR20 35.2% active vs. 24.2% sham (p=0.0209); 52.8% at 12 mo
  - FDA approval July 2025 for rheumatoid arthritis — a landmark for the field
- **Cardiac VNS: Mixed Results**: INOVATE-HF (707 pts, 2016): Negative — terminated for futility
  - ANTHEM-HF (60 pts, 10 Hz): Positive — LVEF 32→35%, walk distance +59 m
  - NeuHeart (EU Horizon 2020): coupled EM-neuro-cardiovascular regulation (**Lecture 5**)
- **The Selectivity Challenge**:
  - Vagus: so many functions, one nerve (with branches & topographic organization)
  - Cervical vagus: ~100,000 fibers; ASCENT & Sim4Life for selective VNS modeling

TMS, tDCS, tACS: The Clinical Landscape

- **Transcranial Magnetic Stimulation (Barker, Sheffield, 1985)**: Rapidly changing magnetic field (~1 T, ~100 μs) non-invasively activates motor cortex
  - FDA for depression: Oct. 2008 (10 Hz left DLPFC)
  - Brainsway Deep TMS: depression (2013), OCD (2018, first non-invasive), smoking (2020)
- **THREE-D Trial (2018, 414 patients)**: 3-minute iTBS non-inferior to 37.5-minute standard rTMS for depression
  - Dramatically improved clinical throughput → transformative for treatment access
- **tDCS (Nitsche & Paulus, 2000)**: Polarity-specific excitability modulation: anodal increases, cathodal decreases
  - NMDA-receptor-dependent plasticity (Stagg, Oxford)
- **tACS: Oscillation Entrainment**: Entrains endogenous oscillations at stimulation frequency (Herrmann, Oldenburg)
  - Cellular mechanism: Preferential entrainment of fast-spiking interneurons (Fröhlich, UNC)
- **The Personalization Imperative**: Identical montages → different intracranial fields (skull/CSF/cortical variability)
  - Motivates image-based treatment planning (**Lecture 10 & Visitor**) and TI

Image: [50]

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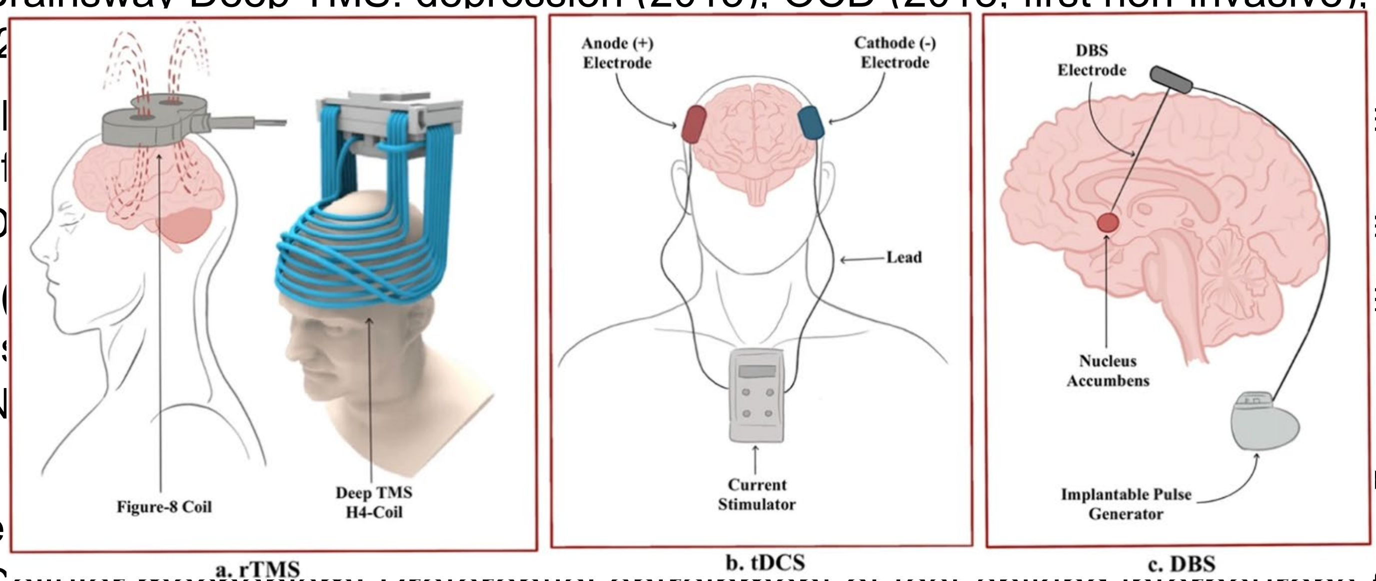

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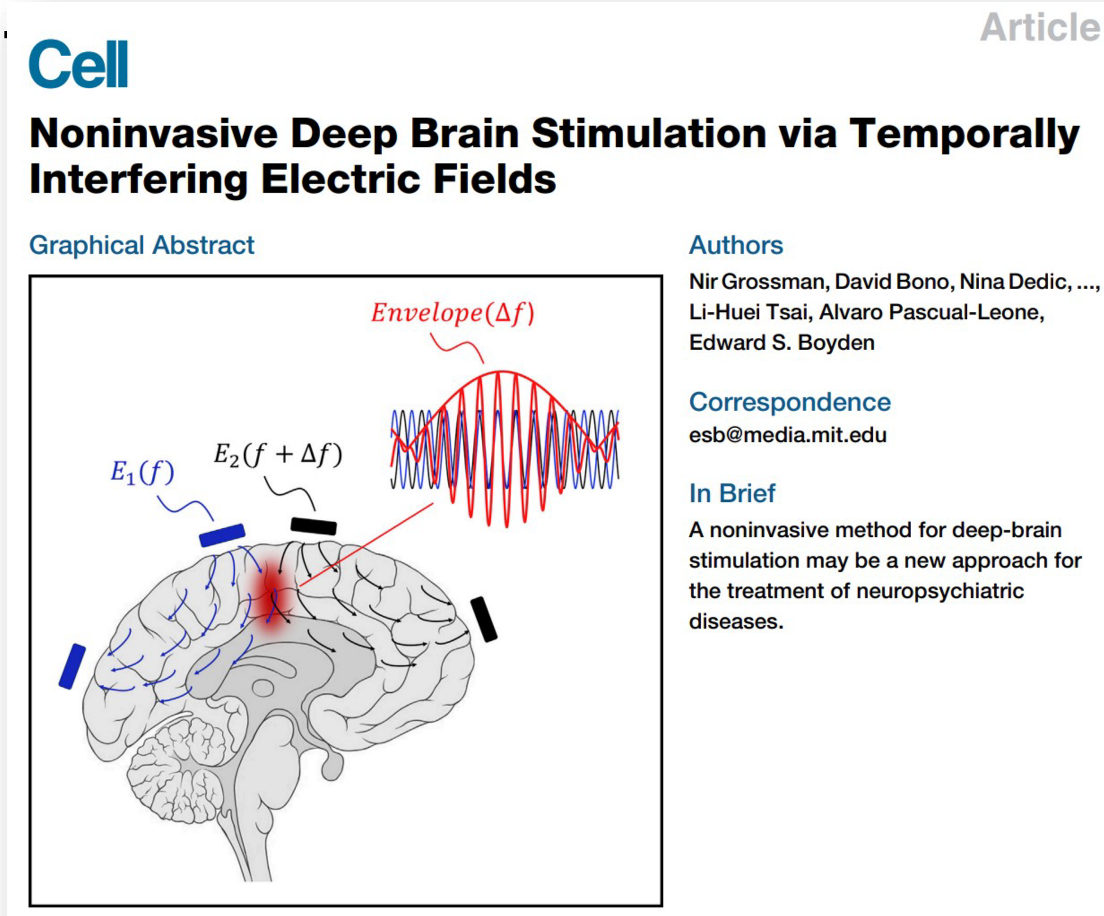
Image: [50]

Temporal Interference & Focused Ultrasound

- **Temporal Interference (Grossman et al., Cell 2017)**: Two high-frequency (kHz) fields → amplitude-modulated envelope at difference freq.
  - Deep brain stimulation without invasive electrodes or surface tissue activation
  - Mechanism: Nonlinear ion-channel rectification?? (Rampersad et al., 2019)
- **TI Solutions AG (IT'IS spin-off, 2019)**: TIBS-R stimulator & TIP planning tool
- **Human Validation**: Violante et al. (Nature Neuroscience 2023): Focal hippocampal modulation via TI-fMRI
- Missey et al. (2025): TI suppressed epileptic biomarkers in stereo-EEG patients — first direct clinical evidence
- **Course connection**: TI modeling in **Week 10**

- **Focused Ultrasound (FUS)**: mechano-electric neuromodulation; excellent focality
  - Exablate Neuro: FDA-approved for ET (2016) and tremor-dominant PD (2018)
  - 5-year data: 73.1% sustained improvement; >22,000 ET patients treated

…used Ultrasound


Article

Cell

Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Graphical Abstract

Authors

Nir Grossman, David Bono, Nina Dedic, ..., Li-Huei Tsai, Alvaro Pascual-Leone, Edward S. Boyden

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In Brief

A noninvasive method for deep-brain stimulation may be a new approach for the treatment of neuropsychiatric diseases.

Two high-frequency (kHz)
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(Rampersad et al., 2019)

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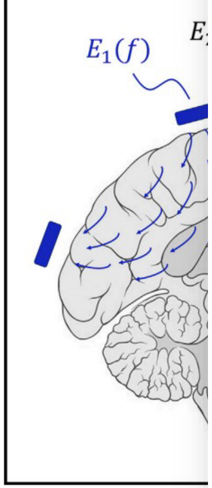
Graphical Abstra...



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Brain Stimulation

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ELSEVIER

Non-invasive temporal interference stimulation of the hippocampus suppresses epileptic biomarkers in patients with Epilepsy: biophysical differences between kilohertz and amplitude modulated stimulation

Florian Missey[a,b,1], Emma Acerbo[c,d,1], Adam S. Dickey[d], Jan Trajlinek[a], Ondřej Studnička[a], Claudia Lubrano[a], Mariane de Araújo e Silva[a], Evan Brady[d], Vit Všianský[e], Johanna Szabo[f], Irena Dolezalova[e], Daniel Fabo[f], Martin Pail[e], Claire-Anne Gutekunst[c], Rosanna Migliore[g], Michele Migliore[g,h], Stanislas Lagarde[b,i], Romain Carron[b,j], Fariba Karimi[k], Raul Castillo Astorga[m], Antonino M. Cassara[k], Niels Kuster[k,l], Esra Neufeld[k], Fabrice Bartolomei[b,i], Nigel P. Pedersen[m], Robert E. Gross[c,n], Viktor Jirsa[b], Daniel L. Drane[d,o,p], Milan Brázdil[e], Adam Williamson[a,q,*]

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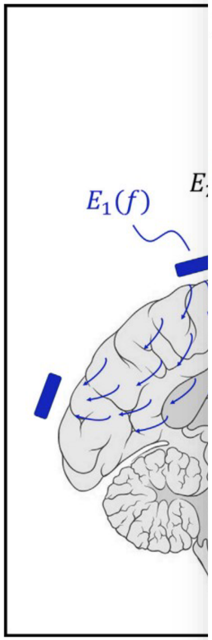
Noninvasive Deep Brain Stimulation via Temporally Interfering Electric Fields

Graphical Abstra...



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Florian Missey [a,b,...]
Claudia Lubrano [a...]
Johanna Szabo [f], ...
Rosanna Migliore...
Fariba Karimi [k], R...
Esra Neufeld [k], Fa...
Daniel L. Drane [d,...]

nature neuroscience
Article
https://doi.org/10.1038/s41593-023-01456-8

Non-invasive temporal interference electrical stimulation of the human hippocampus

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Check for updates

Ines R. Violante [1], Ketevan Alania [2,3], Antonino M. Cassarà [4], Esra Neufeld [4], Emma Acerbo [5,6], Romain Carron [5,7], Adam Williamson [5,8], Danielle L. Kurtin [1], Edward Rhodes [2,3], Adam Hampshire [2], Niels Kuster [4,9], Edward S. Boyden [10,11], Alvaro Pascual-Leone [12,13] & Nir Grossman [2,3]

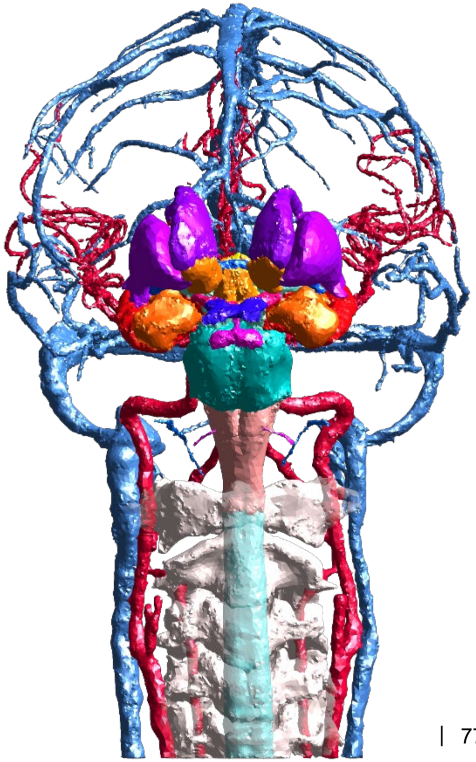
Deep brain stimulation (DBS) via implanted electrodes is used worldwide to treat patients with severe neurological and psychiatric disorders. However,

NeuroPace RNS & Responsive Neuromodulation

- **NeuroPace RNS System (FDA Nov. 14, 2013)**: First closed-loop brain stimulation system approved for drug-resistant epilepsy
  - Detects abnormal ECoG patterns → delivers targeted stimulation to seizure focus
  - >4,000 patients implanted; continuous long-term intracranial EEG data
- **Key Principle: Detect → Respond**: Only stimulate when pathological activity detected → less total energy, fewer side effects
  - Same paradigm as adaptive DBS but for epilepsy
- **Clinical Evidence (Nair et al., Neurology, 2020)**: Pivotal RCT (191 patients): 37.9% active vs. 17.3% sham ($p < 0.001$)
  - 9-year follow-up: Median 75% seizure reduction at 2 years; 82% at ≥3 years
  - 1 in 3 patients achieving >90% reduction; efficacy improves with time
- **Comparison with VNS for Epilepsy**: RNS: focal, closed-loop, intracranial; VNS: Diffuse, open-loop, peripheral

Lead-DBS, MIDA, & Patient-Specific Planning

- **Lead-DBS (Horn & Kühn, 2015; v3 2023)**: Open-source electrode localization, VTA modeling, connectivity mapping
  - Used in 100+ research centers; non-inferior to standard-of-care programming in trials
- **MIDA: Regulatory-Grade Head Model**: IT'IS, ETH, U.S. FDA, & Harvard (2015): 500 µm isotropic, 153 structures
  - Deep brain nuclei, cranial nerves, vasculature — integrating MRI, MRA, DTI
  - Computational phantom for safety/efficacy assessment in Sim4Life Virtual Population
- **Sim4Life Platform (IT'IS / ZMT)**: Coupled EM + neuronal simulation for DBS, SCS, TMS, TI
  - Patient-specific models from MRI; AI-assisted segmentation
  - Surrogate model capabilities for rapid treatment planning
- **Course Connection**: **Week 7** (DBS), **11** (personalized planning)



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Convergence & the Next Decade

- **Three Defining Trends**: Closed-loop adaptive systems: BrainSense aDBS across 40,000+ devices; RNS for epilepsy; brain-spine interface for SCI
  - Patient-specific digital twins: Imaging → segmentation → EM simulation → neuron model → outcome prediction before surgery
  - Target expansion: Movement disorders → inflammation (SetPoint), psychiatry (Scangos), metabolism (Galvani), gene expression (Fussenegger)
- **Unifying Theme**: Computational models are no longer auxiliary to clinical translation — they are integral to it
  - Every major advance documented here used computational modeling as an enabling infrastructure
- **Course Connection**: The methods taught in this course (Rall → FEM solvers → coupled EM-neuro platforms) form the quantitative backbone of these clinical advances

Image Credits

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Exercise Outline

DATE	EXERCISE THEME
19.02	"Hello Neuron": integrate-and-fire in Python/NEURON
26.02	Point neuron phase portrait; basic time integration numerics
05.03	Recruitment prediction for myelinated axon using AF/GAF
12.03	EM (FEM) modeling of transcranial brain stimulation
19.03	Stimulation selectivity and signal content modeling for nerve interfaces
26.03	Guest (SCS – NeuroRestore)
02.04	Mini project work
09.04	No class: Easter break
16.04	Guest (Neuromodulation Spin-Off – Z43)
23.04	Mini project work
30.04	Guest (NIBS – Kinderspital)
07.05	Mini project work
14.05	No class: Ascension Day
21.05	Mini project work
28.05	Project presentations

Room: ETZ E7

13:15-14:00 Lecture

14:00-14:15 Break

14:15-15:00 Lecture

14:00-14:15 Break

15:15-16:00 Exercise

- Quick introduction to o^2S^2PARC (accounts ready)
- Quick introduction to NEURON YALE software. For this session we will only use the NEURON library included in Python.
- Exercises for the session : Single Compartment Neuron Model
  - Task 1: Create neuron with 1 segment and assign membrane properties to match the rat subthalamic nucleus soma
  - Task 2: Exploring Hodgkin–Huxley dynamics in NEURON with I-Clamp
- By the end of this session, you should be able to:
  - Create a point neuron model in Python (leaving only the soma)
  - Assign the Hodgkin Huxley (HH) membrane mechanisms
  - Add a point process (current clamp)
  - Study how the different ion channels evolve for different stimulation patterns
  - Answer all the questions related to the main tasks

➢ We will provide a Jupyter Notebook with all the steps to follow to complete the different tasks.

➢ Make sure you fill in all the blanks as part of the tasks (otherwise the code will not run).