Biomedical Engineering Focus Areas: An Introduction

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What do biomedical engineers do? BME Focus Areas [Slide 4]

- If the general Biomedical Engineering Introduction module has been presented before this, remind students that they've already heard some information about various BME Focus Areas
- The field of medicine is big, so it follows that the field of biomedical engineering is also big. To narrow the scope, BME is often split into focus areas. Example focus areas (and the ones that Carnegie Mellon University focuses on most are)
  1. biomechanics,
  2. biomaterials & tissue engineering,
  3. biomedical devices,
  4. bioimaging & signal processing,
  5. cellular and molecular biotechnology,
  6. neuroengineering.

- While these focus areas can be useful for identifying specific parts of the field that you're interested in, any one BME solution often incorporates techniques from multiple focus areas. So don't be surprised if more than one of these fields sounds interesting to you -- BME is notoriously multidisciplinary, with lots of passionate people coming together to improve health.
- The goal of today's presentation is to further explore each of these focus areas through their definitions, applications, and case studies. Along the way, we'll spotlight CMU faculty research to highlight research at the cutting edge.

Image Citations

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Definition & Scope: Biomechanics [Slide 6]

- As a reminder: Biomechanics is focused on the mechanics of living structures. In this field, you'll primarily study the mechanical properties of tissues, both on the macro and microscopic levels. Common classes in this area include micromechanics, solid mechanics, viscoelasticity, fluid mechanics, and the study of entropy, diffusion, and osmosis in force generation.

Image Citations

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Applications: Biomechanics [Slide 7]

- Biomechanics has several applications to the medical field. For example, biomechanics is responsible for learning how the cardiovascular system pumps fluid through your body, as well as understanding the mechanics of cells and biological materials. Biomechanics may also look at the way different biological solids and fluids act when under stress.

Image Citations

1. "Studying Blood Flow Dynamics to Identify the Heart of Vessel Failure." *DAIC*, Diagnostic and Interventional Cardiology, 16 Aug. 2016, https://www.dicardiology.com/content/studying-blood-flow-dynamics-identify-heart-vessel-failure.
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Example 1: Cardiovascular Mechanics [Slide 8]

- Stuart Campbell, assistant BME professor at Yale
- Funded by NIH: Exploratory/Developmental Research Grant, $400,00 in funding
- Growing cardiac tissue for diagnosis, specifically for characterizing thickening of heart muscle
    - Thickening caused by excessive stretching of heart walls over time → ventricle enlarges, so each heart cell gets bigger
- Use human cells to grow realistic human heart tissue on a new scaffolding
    - 1) cells drawn from blood sample
    - 2) cells seeded onto scaffold to form tissue sample that is easy to manipulate
    - 3) observe tissue contractions under microscope to see if there are any abnormalities (mathematically determined)
- Goal: make a linear piece of heart tissue that is easy to grab on to and manipulate → Good for lab observation and repeatability of diagnostic experiments
- Future goal: "In the future, I hope to be able to take a patient's blood sample, and in six months, come back and say 'this is our recommendation for your treatment'" → future goal is individualized diagnosis

Content Citations

1. "With Lab-Grown Tissue, an Engineer May Prevent Unexpected Heart Problems." *Yale School of Engineering & Applied Science*, Yale University, 11 Jan. 2015, https://seas.yale.edu/news-events/news/lab-grown-tissue-engineer-may-prevent-unexpected-heart-problems.
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Image Citation

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Example 2: Cellular Biomechanics [Slide 9]

- Specifically focused on deformation of cells and cell adhesion studies
- Cellular Biomechanics Lab at Penn State University BME Department (run by Professor Cheng Dong)
- Want to see cellular interaction with vascular wall → lab has created in vitro side-view flow chamber that makes it possible observe side of cell's contact with adhesive surfaces under dynamic flow
    - Usually, imaging is top down; this allows for a side view rather than a top view
- Structure: two rectangular glass tubes or "microslides"
    - Smaller microslide inserted into larger, creates flow channel w/ flat surface
        - Cells can be grown on this
    - Light source: two chromium optical prisms at 45 degrees, provide light illumination
- Can see side-view images using only light microscope
- Effect: lets us measure effects of flow on cell-surface adhesion, can also closely observe cell deformation and adhesive contact in shear flow
- Specific use: investigating mechanics of white blood cells, how they deform
    - Also investigating how adhesion molecules do in dynamic shear flow

Content Citation

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Image Citation

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CMU Connection: Natural Environment Biomechanics (Musculoskeletal Biomechanics lab) [Slide 10]

- Musculoskeletal Biomechanics Lab here at CMU, Mechanical Engineering Department (Assistant professor Eni Halilaj)
- Studying human musculoskeletal system, which supports voluntary movement, in context of injury and disease

- Tools for investigation: motion capture, medical imaging, computational modeling, and machine learning
    - Note the interdisciplinarity here
- Overall goal of lab: develop rehabilitation strategies that help restore and preserve pain-free movement and mobility in patients
- Project featured on slide (Natural Environment Biomechanics): create new motion capture system to track clinical outcomes using both sensors and video
    - Motivation: traditional motion capture systems are expensive to operate → not often used in the clinical setting
    - What we're fixing: effectiveness of computer vision and wearable sensing when detecting movement biomechanics must produce errors that are small enough to be clinically tolerable
    - "The operational cost associated with traditional motion capture systems has inhibited clinical translation and discouraged large movement analysis studies. Recent advances in computer vision and wearable sensing offer untapped potential for movement analysis in natural environments, but the effectiveness of these technologies in estimating movement biomechanics within clinically tolerable errors is still limited. To address the shortfalls of current algorithms, we are working on new approaches for estimation of clinically relevant outcomes from wearable sensors and video."
- Other projects
    - Role of Mechanics in Osteoarthritis: study interactions between mechanical and biological factors in osteoarthritis development; specifically, evaluate cartilage response to mechanical stimuli (natural loading, ligament tears, assistive devices, etc.) using medical imaging tech
        - "Joint mechanics is a major contributor in the development of osteoarthritis and eventual joint failure, but this effect is highly variable across individuals given interactions between mechanical and biological factors. We study these interactions by evaluating cartilage response to different types of mechanical stimuli (e.g., natural loading, ligament tears, use of assistive devices) via medical imaging technologies. Findings from these studies should form the scientific basis of patient-tailored osteoarthritis prevention and rehabilitation strategies that are more effective than the current standard of care."
    - Precision Rehabilitation: design personalized disease-modifying interventions by using portable technologies and determine how effective they are at targeting a biomechanical outcome → do these technologies modify disease or improve rehabilitation?
        - "Injury prevention programs, disease-modifying interventions, and rehabilitation in orthopedics currently require significant time investment

from patients and medical staff, yet are not tailored to each patient. Our goal is to use insights gained from experimental and computational studies to design personalized interventions assisted by portable technologies and evaluate both their effectiveness in targeting a biomechanical outcome of interest in natural environments and their efficacy in modifying disease/improving rehabilitation. In this direction, we are collaborating with experts in sensing and haptics"

Image & Content Citation

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Definition & Scope: Biomaterials and Tissue Engineering [Slide 12]

- As a reminder: "Biomaterials and tissue engineering is the area of study that creates man-made materials for medical treatment and produces living functional tissue. These materials and tissues can be used both as disease models and as replacements for damaged tissue in the body. As a biomedical engineer focused on biomaterials and tissue engineering, you'll likely study the interactions between materials, cells, and tissues and how these interactions can affect both the body and the materials involved. You'll also study the major responses of the body, including wound healing, the immune response, and the foreign body response; all of these can help you determine how to best design a material depending on how it needs to be incorporated into the body. You'll also characterize different types of biomaterials, such as metals, ceramics and polymers, and you'll look at natural and synthetic materials. Finally, you're likely to spend much of your time culturing cells and determining the biocompatibility of a material."

Content Citation

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Applications: Biomaterials and Tissue Engineering [Slide 13]

- Applications of this focus area include the development of artificial organs and bioscaffolds, along with improving the wound healing process. You may also create collagen substitutes or study how implants fail and how materials react in different environments.

Image Citations

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Example 1: Adipose Microenvironments [Slide 14]

- Abbott Lab at CMU (Dept. of BME and Materials Science)
- Lab Focus: monitor adipose tissues to 1) study normal adipose metabolism, 2) create disease model for obesity and type II diabetes, and 3) replace soft tissue defects
- Develop microenvironments for human adipose tissue and monitor responsiveness to stimuli that is believed to influence disease mechanisms and metabolism
    - Stimuli example: transition of obese tissues to insulin resistant type II diabetic tissues
- Long Term Goal: use adipose tissue systems for preventive and therapeutic applications for patients affected by metabolic syndrome
- Lab integrates both tissue engineering and biomaterial engineering
    - Note focus area trend to put both biomaterials and tissue engineering together; technically they are two separate subfields, but so related that one often comes with the other

Image & Content Citation

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Example 2: Wound-Healing Biomaterials [Slide 15]

- Abstract: "There is a vast number of treatments on the market for the management of wounds and burns, representing a multi-billion dollar industry worldwide. These include conventional wound dressings, dressings that incorporate growth factors to stimulate and facilitate the wound healing process, and skin substitutes that incorporate patient-derived cells. This article will review the more established, and the recent advances in the use of biomaterials for wound healing therapies, and their future direction."
- Many biomaterials therapies that help with treatment of wounds and burns
    - Polymer hydrogels
    - Epidermal substitutes that incorporate keratinocytes (wiki: barrier against environmental damage caused by heat, UV radiation, water loss, bacteria, etc.) and dermal fibroblasts (wiki: generate connective tissue and help skin recover from injury)
- Also different strategies for creating these therapies
    - 3D printing directly onto wound
    - Use of induced pluripotent stem cells
- Figure descriptions
    - Autologous Dermal skin substitutes: hyaluronic acid helps with cell proliferation and the migration of fibroblasts and keratinocytes to injury site
        - These substitutes (Hyalograft 3D and Hyalomatrix) use autologous fibroblasts (i.e., cells taken from patent) → fibroblasts lay down extracellular matrix into wound, which encourages split skin grafting
            - (wiki) ECM: provides structural and biochemical support to surrounding cells
        - Hyalomatrix: additional outer silicone membrane to protect healing skin
        - Advantages of substitute type: cells taken from patient → low immune response when applied to wound
        - Disadvantages: requires suitable donor site to collect cells from patient, in vitro culture takes time to get sufficient numbers of cells for use → takes longer to improve patient healing
    - Allogenic dermal substitutes
        - Use stem cells (neonatal fibroblasts) from non-related donor → not as immunogenic as adult cells (but also not as low immune response as autologous source)
        - Similar to autologous substitutes: secrete ECM and growth factors to speed up repair process
        - Types; TransCyte, Dermagraft
            - TransCyte: collagen-coated nylon w/ outer silicon film that is seeded with human neonatal fibroblasts → specifically used for burns (partial + full-thickness)

        - Dermagraft: bioresorbable polyglactin scaffold with human neonatal fibroblasts → used for burns and chronic wounds
    - Avantage: allogenic, can be applied immediately (don't need to wait for culture)
        - Dermagraft: don't need to remove graft from wound → won't rip off layers of newly forming skin underneath dressing
    - Disadvantage: this substitute is expensive (single Dermagraft dressing costs thousands of dollars) → but only one graft needed when substitute is successful
- Epidermal substitute
    - Epidermal keratinocytes: help skin act as barrier to external environment and also help prevent dehydration
    - EpiCel (and other substitutes) give more stable surface for transfer of keratinocytes to burn areas
        - Structure: layer of autologous keratinocytes to mouse fibroblasts + layer of keratinocytes attached to petroleum gauze
        - Add onto wound, remove gauze after 1 week
        - Still fragile when transferring onto wound
    - Primary cell type for re-epithelialization after injury, also have stem cells that can help with regeneration
    - Advantage: can be used to restore skin integrity, can be incorporated into skin for life
    - Disadvantage: incorporation to skin is more difficult when part of patient's dermis is reduced/missing

Content Citation

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CMU Connection: Regenerative Biomaterials and Therapeutics Group [Slide 16]

- Video description: "Adam Feinberg, associate professor of biomedical engineering and materials science and engineering, describes and demonstrates his work in 3-D printing soft materials."
- Specifically focused on printing heart tissue
- Soft material bioprinting by Dr. Adam Feinberg's group at CMU (Biomedical Engineering and Materials Science & Engineering Departments)
- 3D printers that can print soft materials and tissues
- Traditional 3D printers print hard materials → move into soft materials to support printing of living things
- Fill a dish with a support bath material, then print inside of the bath using a syringe, and dissolve the support material by heating up the petri dish to normal body temperature (~97-99 °F) → only the print remains
- This sort of printing can be done layer-by-layer, which makes it more accurate/closer to the object that the print is meant to recreate
- Most soft 3D bioprinting is done by large companies that charge large amounts (in the hundreds of thousands of dollars) for a single print → Feinberg's lab utilizes open source software and hardware (anyone can access the software and edit or modify it)
- Because open-source software can be easily edited, researchers can be specific about the input values they choose (i.e., can be really meticulous about selecting the parameters that enable the best print possible for each specific object/structure) → leads to higher quality results
- Note: we're seeing a general shift towards open source software when possible, as it provides greater access to cutting edge technologies and both supports and encourages collaboration (across labs, companies, countries, etc.) → this means more advancements in the engineering and medical fields
- Feinberg's lab is starting by recreating embryonic heart structures (during earliest stages of heart development) from images → then integrate heart muscle cells into the print material so that the final structures are made from the same material as our hearts
    - This allows for models that more closely approximate the development process → leads to more accurate experiments and a better understanding of embryonic development
- This research combines developmental biology with materials science to give scaffolds made of stem cells → will hopefully lead to 3D-printed functional tissue, so that artificial organs can be made and given to people who need them (heart attack, stroke, etc.)
- Most recent breakthrough from the lab: 3D printing collagen (a biomaterial that makes up every tissue in our body)
    - https://www.youtube.com/watch?v=ivWJOVRA8CQ (an additional video explaining their 2019 research)

- The issue that they've solved: collagen starts as a fluid, so you need a support material when printing it (otherwise, the fluid will just be a puddle on your build platform)
- Builds off o the FRESH 3D bioprinting technique published by Feinberg's group a few years ago
- Can be used to print heart valves, blood vessels, contractile ventricles
- Build multiple functional parts so that we can combine them together → moves beyond functional tissue and into functional organs
- They still haven't printed a whole adult-sized functional heart, but they have taken critical steps towards this reality

Video & Content Citations

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Definition & Scope: Biomedical Devices [Slide 18]

- As a reminder: "Another focus area is biomedical devices, which creates the instruments, machines, implants, and other tools needed for the prevention, diagnosis, treatment, and rehabilitation of illness and disease for humans. Here, you'll learn how to use various research instruments, particularly when taking accurate images and measurements. You'll focus on the difference between diagnostic and therapeutic devices, depending on whether you're helping to identify a disease or get better from it. You'll also learn how to fabricate these devices and look into how your devices will interact with cells, tissues, and organs. Finally, you'll learn how to combine multiple systems together into a single device."

Content Citation

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Applications: Biomedical Devices [Slide 19]

- Common applications include the creation of sensors and actuators, as well as both diagnostic and therapeutic devices. This focus area is responsible for the development of new medical instruments and systems, as well as the software behind each of the devices. As seen in the pictures, some well-known biomedical devices include artificial heart values, insulin pumps, imaging machines, joint replacements, and dialysis machines.

Image Citations

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Example 1: Implantable Heart pump [Slide 20]

- Lead paragraph: "An EU-backed company has developed a novel heart pump that can work in synchrony with the heart without the aid of sensors for over 30 days. This is the first time that a miniaturized pericardial pump has achieved this synchronisation."
- Motivation: heart transplants not common; instead, often use implantable pumps (LVADs) → these have high rate of complications (4 out of 5 patients develop severe complications like bleeding or strokes within 2 years)
    - Complications happen because the pumps can't appropriately reproduce heart's pulsating motion
- CorWave making new membrane pump → reduces complications, improves care
    - Membrane creates undulating movement → generates natural pulse and mimics both blood flow rates and pressure of healthy heart
- Why it's important: first time someone has demonstrated sensorless synchronisation of pericardial pump with native heart for over a month

- Synchronization over span of several million heartbeats
- This synchronization should lower adverse events associated with LVADs, but still lets patients get back to normal daily activities

Content Citations

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Image Citation

1. CorWave. "CorWave LVAD." *YouTube*, research by CorWave company, 6 Dec 2019, https://www.youtube.com/watch?v=OmA9ubj-DUI&t=2s.

Example 2: Lab On a Chip (BioMEMS) [Slide 21]

- BioMEMs are micro-electro-mechanical systems used for biological or medical applications
  - Combination of biology and microtechnology
- MEMs technology is "development od device structures in the micro- or nano-dimensions using a micromachining process," usually on a silicon substrate
- MEMs first created in the late 1980s, then moved to bioMEMS (specific biology applications) primarily because of advances in microfabrication and miniaturization of devices
- Device components are made by adding thin layers of material onto a silicon foundation (also known as a substrate)
- Multiple applications of MEMs technology within biomedical field
  - Diagnostics, Therapeutics, Prosthesis, Surgery
- Diagnostics: pregnancy tests, handheld glucose monitoring systems → in both situations, the bioMEMS devices allow for laboratory-type testing at a miniaturized scale
- One segment of diagnostics is Point of Care Diagnostics, which allows for "more integrated and immediate clinical results"
  - For example, Lab-on-a-Chip devices: treats, separates, and detects different cell types → can recognize a specific disease through multiple tests conducted on a single small chip
  - Many applications: analyzing proteins, DNA, blood, or creation of drug screening systems

- Slide image: shows generalized lab-on-a-chip device and what capabilities it has for molecular diagnostics
    - Sample Preparation: take a biological sample to be analyzed and get it ready for analysis
    - Cell sorting: isolate specific cell type from the overall cell population
        - "Isolation of cells from heterogeneous mixture of cell population"
        - Mechanisms: flow cytometry, dielectrophorosis electrophoresis, electro-magnetic sorting, optical tweezers, micro-filters
    - Cell lysis: lysing breaks down the cell membrane so that the materials inside of the cell can be analyzed by the device (exposes the inner materials of interest for testing)
        - "Disruption of cell membrane for releasing intra cellular material"
        - Mechanisms: thermal, acoustic, mechanical, chemical, electrical
    - Molecular Sensing: the materials of interest are detected and quantified to help with diagnosis
        - "Detecting the presence of analyte molecules such as proteins and nucleic acids"
        - Mechanism: electrical, mechanical, optical, acoustic, magnetic sensing
    - Also an optional purification stage, in order to make sure there's enough material of interest to be efficiently detected by the device
        - "purification /amplification of analytical molecules"
        - Mechanisms: PCR amplification (for nucleic acids), adhesion-based techniques
- Examples of what bioMEMS devices can diagnose:
    - Measurement of certain molecules/compounds in the body (for example, blood gas, glucose, ethanol, cholesterol, pH, etc.)
    - Detection of specific proteins in the body (uses immunochemistry)
    - Characterization of blood components (blood cell counters, whole blood, hemoglobin, blood ketone, etc.)
    - Presence of disease-causing agents (microbes)
    - DNA, RNA, or protein-based diagnostics
- Other bioMEMS diagnostics:
    - Measuring physiological parameters (temperature, pressure, pulse rate)
    - Intraocular and intracranial and cardio-vascular pressure sensors
    - Also used in smart textiles or wearable cardiovascular monitoring systems
- Main issue when creating bioMEMS devices: biocompatibility (whether device uses materials that are compatible with living tissue → no toxic or immune response in body)

Content & Image Citation

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CMU Connection: Ingestible Medical Devices [Slide 22]

- Video Description: "Chris Bettinger, assistant professor of biomedical engineering and materials science and engineering at Carnegie Mellon University, discusses edible electronics, a possible less-invasive, future alternative to implants and other medical devices."
- Group wants to work with new materials and microstructures for medical device applications → specifically human-device interfaces
- Goal: "the goal of this protect is to design and engineer sophisticated ingestible electronics that are composed of non-toxic materials and potentially useful in a wide range of diagnostic and therapeutic applications"
- Particularly focused on techniques, materials, and fabrication methods for better interfacing medical devices with the human body
- Most implanted electronic devices (like pacemakers and nerve simulators) can become infected and are expensive and difficult to deploy or use (require surgeons or other medical professionals to ensure that device is interfacing with the body/organ/tissue correctly)
- Goal: take medical implant and condense it down into a device you can eat → avoids problems you see with permanent implants
- Multiple functions (like you can have with permanent implants)
    - Sensing functions
    - Drug delivery
    - Tissue stimulation (in GI tract)
- How do you power these devices? → batteries
    - Group is designing ingestible batteries
    - Inspiration for these batteries: squid ink
        - Squid injects melanin into the water to disguise itself from predators
        - Melanin in eyes, skin, and hair
        - Through electrochemical processing, melanin becomes a battery material that can supply power to ingestible electronics and already exists inside our body
- Advantages of edible electronics:
    - Deployed without medical professional
    - Don't need to be sterilized (less sterilization required for ingestion vs. implantation, won't have as much of an immune response when ingested)
    - More material options→ create better sensing techniques, new battery materials, new structures for ingestible electronics
    - If material gets stuck somewhere, it is biodegradable (mechanical degradation) → different from synthetic materials which may get stuck in GI tract and must be surgically removed
        - Surgery: is painful, risky, and costly

- Melanin electrode batteries, with pectin separating the electrode
    - Cost-effective
    - Nontoxic
    - Same performance as other batteries (10 mW of power, enough to power basically all medical devices on the market)
    - Last ~10-20 hours (which is about how long food stays in your GI tract)
    - Melanins are very stable in acidic environments (so it becomes stable in the stomach)
- Applications of batteries in smart pills: miniature electronic devices that look like pills (pharmaceutical capsules) and are capable of sensing, imaging, or drug delivery
    - Could be used with biosensors, image sensors, pH sensors, chemical sensors
    - Smart pills travel in GI tract to record information (then eliminated from system in same way as other food)
    - Smart pills have future applications in remote patient monitoring, telemedicine, and noninvasive point-of-care testing

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Definition & Scope: Bioimaging and Signal Processing [Slide 24]

- As a reminder: "Bioimaging and Signal Processing study the methods and instruments that we use to acquire, process, and visualize both structural and functional images of living objects or systems both in space and in time. You'll likely study different types and methods of medical imaging, as well as how to process and interpret the signals received from the body. You'll learn how to analyse the images you obtain, as well as the electrical signals from both the brain and heart."

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Applications: Bioimaging and Signal Processing [Slide 25]

- "Common applications of bioimaging and signal processing include electrocardiograms (which characterize your heart beat over time), imaging modalities (such as x-ray, ultrasound, CT, PET, or MRI scans), and looking at both neuron and heart functions in the body. There are also applications in identifying different imaging qualities, such as the contrast, signal, and spatial resolution of an image."

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Example 1: Simultaneous BOLD-fMRI and FDG-PET [Slide 26]

- Based on 2 general imaging techniques; MRI and PET
    - MRI (Magnetic Resonance Imaging)
        - https://www.nibib.nih.gov/science-education/science-topics/magnetic-resonance-imaging-mri
        - 1) your body is placed in a strong magnetic field that causes protons (hydrogen molecules) in your body to align with the field

        - 2) A radiofrequency wave is then sent through the body, which causes the protons to spin and knocks them out of alignment
        - 3) radiofrequency is turned off, and protons start to realign with magnetic field
        - 4) as they realign, they release energy → this energy is detected by the scanner, and we can figure out how long it takes for the protons to get back to their starting position and how much energy was released in order to get there
            - These values (time and energy) help us figure out which tissue types are at which areas in the body
        - Non-invasive technique
        - Creates 3D images of body
        - Used for disease detection, diagnosis, and treatment monitoring
    - PET (Positron Emission Tomography)
        - https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/positron-emission-tomography-pet
        - Scanning device detects photons (light particles) that are emitted by a radioactive molecule that is then processed by the organ or tissue we're trying to image
            - Most common radioactive molecule: fluorodeoxyglucose (FDG): created by applying radioactive atom to glucose (which is a blood sugar) → used by brain for metabolism
        - Measures metabolic activity in cells (usually used in brain, heart, or cancer because it shows biochemical changes in body)
        - Type of nuclear medicine procedure: uses a tiny bit of radioactive substance to help us see how a tissue or organ metabolizes the substance
            - Tells us about the functionality and structure of the organ/tissue
        - 1) radioactive molecule is given to patient through IV
        - 2) the radioactive molecule is broken down in the body, which causes photons to be emitted
        - 3) the photons travel back out of the body to the detectors of the scanner
        - 4) a computer analyzes the photons and makes a map of the organ/tissue
            - More photons emitted = brighter area on image = higher level of organ/tissue function
        - Minimally invasive technique
        - Creates 3D images of the body
- BOLD-fMRI: blood oxygenation level dependent functional magnetic resonance imaging
    - Functional means that the imaging happens at real-time: measures changes in blood flow that occur in the brain

    - Provides information on blood oxygenation→ indirectly provides information on brain function (because amount of oxygen used in brain corresponds with brain activity) → provides map of brain activity
- [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET)
    - Provides information on glucose metabolism → more directly provides information on brain activity (since brain uses glucose in order to initiate functions) → provides map of brain activity
- This paper shows that when the imaging methods are combined, you get better images that are more successfully resolved
    - Give researchers information on both glucose metabolism and blood response (so gives both metabolic and hemodynamic responses)
    - Also helps researchers map out what parts of the brain respond to different tasks → we can start to figure out where different tasks are processed in our brains

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Example 2: ECG Signals [Slide 27]

- Electrocardiogram (ECG): low-cost, portable, non-invasive sensor that measures conduction through heart → tells us about functionality of heart by sensing heartbeat
    - Specifically records the voltage in the heart over time
        - Potential difference between electrodes that are placed on the body → illustrates electrical activity of heart throughout cardiac cycle
    - helps medical professionals diagnose irregularities

    - Low cost + portability means you can measure/analyze physiologic signals even in remote or low-resource settings → good for global health
- Cardiac cycle
    - Two phases: diastole (heart muscle relaxes and fills with blood) and systole (heart muscle contracts and pumps blood)
        - Individual muscle cell contraction initiated by action potential (charge around the membrane of the cell changes enough that ions [specifically Na+, Ca2+, and K+] move across membrane as necessary)
        - Action potential is passed off from one cell to the next → creates a wave across the heart muscle, and this causes the heartbeat
- Electrocardiogram leads
    - To measure potential differences across skin surface, we place electrodes on patient's skin
    - Electrodes: conductive pads attached to skin surface
        - Use a pair of them to measure potential difference between the areas that they're placed on → this pair forms a "lead"
        - We use multiple leads to get a 3D understanding of conduction in the heart
            - Multiple leads gives us information along multiple axes
        - Standard system uses 12 leads, but we only need 2 (modified lead II and V5) to gather the information we need to use algorithms that will determine whether the beat is irregular or not
- Interpreting an ECG
    - PQRST
    - P wave: atrial depolarization → atria contracts
    - QRS complex: ventricular depolarization → ventricles contract (also atrial polarization → atria relax, but this signal is overpowered by the ventricular depolarization signal)
        - Largest feature in an ECG
        - This is usually what beat detectors are analyzing when classifying a patient's beats
    - T wave: ventricular repolarization → ventricles relax
    - Gives information on: rate + rhythm of heartbeats, size and position of heart chambers, presence of damage to heart cells or conduction system
- Many signal processing algorithms have been created to help monitor a patient's ECG recordings (esp. Because ECGs are periodic, which makes frequency analysis possible) → helps patients and clinicians automatically track their heartbeat for irregularities
    - Algorithm also helps filter out any noise (caused by things like breathing, action potentials in other muscles, or the electromagnetic fields of other powerlines) → remove the information we don't care about and keeps the relevant information (PQRST)

    - Can use as an arrhythmia alarm: alarm sounds if an irregular heartbeat is detected, which helps with hospital bedside care
- Using frequency-based analysis, a heartbeat classifier can be created that helps determine regular/irregular heart beats

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CMU Connection: Biomedical Optics [Slide 28]

- Video description: "Assistant Professor of Biomedical Engineering Jana Kainerstorfer has developed a non-invasive, handheld device that uses near-infrared light to monitor breast cancer lesions."
    - Biophotonics lab: focused on creating imaging methods that can improve disease diagnosis and treatment (particularly focused on imaging microvasculature)
        - Wants to create imaging methods that can be used both in a clinical and home setting
    - Specific goal: create handheld device for breast cancer imaging
- Shine near-infrared light on the human body to image and monitor changes in hemoglobin in microvasculature
    - Hemoglobin is used because it's involved in and is altered by many diseases → by monitoring hemoglobin, it's possible to monitor the disease impacting it
    - Breast cancer is highly vascularized, so by imaging the vascularization, we can determine the disease state
        - Vasculature of breast tumors is different from healthy tissue
- Hemoglobin
    - Protein in red blood cells that carries oxygen in the bloodstream
    - Contains iron - specifically, heme groups of hemoglobin "pick up" oxygen and carry it through the body via the bloodstream → makes sure that the blood oxygenated in our lungs gets to the rest of our body
    - Hemoglobin also the dominant absorber of light within the body in the near-infrared light range
- Microvasculature
    - The network/system of the smallest blood vessels in the body
    - Focused on smaller tissue areas (rather than full organs)
- Near-infrared light
    - Type of light that we can't see (invisible to the human eye because it has a longer wavelength than visible light)
    - You may have interacted with it when using night vision goggles/devices

    - Used in many medical applications: detects heat loss, illustrates changing blood flow in the skin
- Near-infrared light is completely non-invasive, and the imaging instrumentation is small and portable
    - Non-invasive, so imaging can be performed on patients directly
- One project goal: build at-home imaging instrumentation that uses near-infrared light to image breast tissue and identify or monitor a lesion in women → lets us avoid other imaging techniques such as X-ray mammography which is a form of ionizing radiation and can therefore do a bit of damage with enough exposure time
    - X-ray mammography: type of imaging technique that uses x-rays in low dosages to image tissue (this low dosage is safe when used every so often, but it becomes dangerous if used very frequently) → not a long-term imaging option
        - Small chance of cancer if the body is repeatedly exposed to radiation (but the amount of radiation used in a single image is so small that this shouldn't be a concern unless tissue is being imaged very often)
        - Measures how ionizing radiation (in the form of x-rays) is absorbed by tissue → different tissue types (muscle vs. fat vs. organs, etc.) absorb x-rays differently, often based on their density
        - Therefore, different tissue types will show up as a different color on the image, allowing imaging specialists to map out different objects or tissue areas within the body
    - Near-infrared light is not dangerous (no ionizing radiation), therefore it can be used as a long-term imaging option (won't damage tissue if used frequently)
- This near-infrared light based instrumentation can then be used at home by a woman to monitor the lesion herself rather than having to go to a professional imaging facility every time
    - Works by shining near-infrared light onto tissue and measuring how deeply it travels into the skin (depending on how deeply it travels, we can determine properties of the tissue and figure out what might be beneath the skin without cutting into the body)
    - Helps map out vascular changes in the breast
        - When breast cancer is present, new blood vessels form (via angiogenesis) in order to provide oxygen to the new tissue → we can monitor cancer progression by seeing how formed these tiny blood vessels are
            - This new vasculature is one indication of potential breast cancer/lesions
    - This will help guide treatment, which can save lives by giving earlier information about disease progression
        - Tracks progress/regression of tumor in response to chemotherapy

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Definition & Scope: Cellular and Molecular Biotechnology [Slide 30]

- As a reminder: "Cellular and molecular biotechnology focuses on the practical application of both cellular and molecular knowledge. This focus area aims to enhance and improve the production of cells and molecules in both cell cultures and microorganisms. You'll likely study biological regulation at the body, organ, and system level. You'll also learn how to culture cells to create different cell types, as well as seeing how changing different culture conditions influences the size and shape of the cells that grow. You may also look into the impacts of genetics on cell development, as well as the diffusion, transport, and delivery of cells and molecules to the body for different medications."

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Applications: Cellular and Molecular Biotechnology [Slide 31]

- "Common applications of this field include the manufacturing of proteins and viruses, as well as the development of pharmaceuticals. Cellular and molecular biotechnology also has an influence on the study of genetic engineering and can help create vaccines, bioreactors, and microfluidic devices."

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Example 1: Vaccine Development [Slide 32]

- Diphtheria, tetanus, pertussis → single, combined vaccine
  - DTaP for childhood vaccine
    - Series of 5 shots (2 months, 4 months, 6 months, 15-18 months, 4-6 years)
  - Tdap for adolescent/adult vaccine
    - Less diphtheria & pertussis proteins than DTaP → less side effects like pain, redness, tenderness
    - Given for people >11 years old
    - Also given to people needing tetanus booster (or people with wounds that can get infected)
  - Td for tetanus booster (no pertussis)
    - Less diphtheria than DTap → Lower side effects
    - Given every 10 years to adults (or people with wounds that can get infected)
- Diphtheria
  - Caused by toxin released by bacteria (Corynebacterium diphtheriae)
  - Causes problems with breathing and swallowing
  - Also affects heart, kidneys, nerves
  - Can be fatal
  - Can lead to death in children and adolescents (common cause of death in 1920s)
  - First vaccine given in 1940s in United States: from 150,000 cases each year at its peak → ~2 cases each year

    - Outbreaks appear in other countries, but higher immunization rates in country → lower outbreak numbers
- Diphtheria vaccine
    - Includes an inactivated version of the diphtheria protein (called a "toxoid")
        - Toxoid triggers immune response to toxin, but can't cause disease
    - Mild side effects: pain, soreness, low-grade fever
- Tetanus
    - Caused by toxin released by bacteria (Clostridium tetani)
    - Usually get the disease when bacteria enter non-sterile punctures/wounds or tissue affected by frostbite, burns, gangrene
        - Common items that cause punctures and have tetanus bacteria on them: nails and glass pieces that were on the ground (bacteria live in soil)
    - Can't catch it from others → no herd immunity protection
    - Once bacteria is under the skin, can't wash or clean it away
    - Causes muscle spasms of the throat and jaw → problems with breathing that can lead to suffocation
    - Also damages heart
    - Primary patient populations: adults with infected wounds and newborns without good sanitation during/after delivery
- Tetanus vaccine
    - Include an inactivated version of diphtheria protein (called a "toxoid")
        - Toxoid triggers immune response to toxin, but can't cause disease
        - Toxin is called tetanospasmin
    - Mild side effects: pain, soreness, low-grade fever
    - Potential allergic reaction (1in a million children)
        - Hives, trouble breathing, lower blood pressure
        - Can be treated with medication
- Pertissus (aka whooping cough)
    - Caused by bacteria (Bordetella pertussis)
    - Very contagious (one of the most contagious diseases)
        - 8/10 non-immune people infected when exposed
    - Can be fatal
    - Causes narrowed windpipe (by mucus production) → uncontrollable coughing and makes it hard to catch your breath
    - Adults can recover, but infants often don't survive
        - Pregnant women can get a Tdap vaccine during third trimester to boost level of pertussis antibodies in baby
    - Can get pertussis more than once
    - Vaccine effects lower over time
        - Need booster doses to maintain immunity

    - Violent cough: breaks blood vessels, cracks ribs, develops hernias, gets nose bleeds, causes vomiting, prevents sleep
    - Also leads to pneumonia, seizures, or apnea (in infants)
    - Children often catch disease from adults
    - Yearly cases are often underrepresented because disease is misdiagnosed
        - Misdiagnosed because bacteria can only be detected in patient at beginning of infection (test may be negative by time diagnosis is sought)
        - CDC reports ~17,500 cases a year, but actual value is likely higher
- Pertussis vaccine
    - Include 2 out of 5 inactivated pertussis proteins (called "toxoid")
        - Toxoid triggers immune response to toxin, but can't cause disease
    - Old vaccine: whole cell (before 1996)
        - Vaccine contained whole cell of killed form of bacteria
        - Side effects: pain, tenderness, fever, drowsiness, fretfulness, high fever, seizure, inconsolable crying in children
    - New vaccine: acellular (after 1996)
        - Whole cell no longer present
        - Possible because of advances in protein chemistry and protein purification
        - Side effects: pain, tenderness
            - sometimes high fever, fever-associated seizures, hypotonic-hyporesponsive syndrome (children are listless and lethargic)
        - Less effective, but booster doses help solve this problem

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Example 2: CRISPR Gene Therapy [Slide 33]

- CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
- Gene therapy: modifies patient's genes in a way that treats or cures a disease
    - Mechanisms include inactivation (inactivating a gene that isn't functioning properly), introduction (adding a new/modified gene to the body), or replacement (replacing the gene with a healthy copy)
    - Can correct genetic defects

        - Like cystic fibrosis, cataracts, Fanconi anemia
    - Can treat and prevent diseases
    - Treats many diseases, like cancer, genetic diseases, infectious diseases
- CRISPR requires two components: guide RNA and Cas9 protein
- CRISPRs: specialized stretches of DNA made of repeated sequences with spacers in between
    - Palindromic repeat segments: rungs of the DNA molecule that can be "read" the same forward and backward (like GATC and CTAG)
    - Spacers: sequences from the viral DNA (tells your body what to "look" for when trying to recognize foreign substances, helps your body identify the virus if it's found in the body)
- Cas9: enzyme that cuts strands of DNA; the "molecular scissors"
    - Cas stands for CRISPR-associated
- CRISPR is revolutionizing the future of gene therapy
    - Traditional approach uses viral vector delivery, which has potential for causing cancer or being toxic to the immune system
    - CRISPR provides alternative that avoids these issues
    - Low cost, easy to use, efficient & precise performance
    - Can alter someone's resistance to a viral attack → helps regulate and support bacterial immunity
- CRISPR lets you "cut and paste" DNA sequences into a gene
    - 1) Determine the sequence of DNA you want to change/modify
        - Target sequence needs to be unique, found only in the targeted gene (nowhere else in genome)
    - 2) Create RNA that matches this sequence and a DNA cutter (Cas9). Combine.
    - 3) Match RNA finds target DNA, DNA cutter cuts the target DNA sequence out
    - 4) The new DNA repairs itself. Two repair mechanisms possible:
        - glue the two cuts back together, but can lead to accidental insertions or deletions → causes gene mutations
        - Fill the break using a short DNA strand
- Can be used as a "live editing tool" for our genome
- Can reverse muscular dystrophy in animals
- Market estimated to be $5.28 billion by end of 2022
- Biggest limitation: not 100% efficient (only a percentage of targeted DNA is successfully edited)
    - Also causes off-target effects if DNA cut at wrong targets → leads to unintended mutations
- Video: "Explore the science of the groundbreaking technology for editing genes, called CRISPR- Cas9, and how the tool could be used to cure diseases."

- https://www.youtube.com/watch?v=6tw_JVz_IEc → Fantastic overview video of how CRISPR works

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CMU Connection: mRNA Drug Delivery [Slide 34]

- Video description: "What if you were holding life-saving medicine ... but had no way to administer it? Zoom down to the nano level with engineer Kathryn A. Whitehead as she gives a breakdown of the little fatty balls (called lipid nanoparticles) perfectly designed to ferry cutting-edge medicines into your body's cells. Learn how her work is already powering mRNA-based COVID-19 vaccines and forging the path for future therapies that could treat Ebola, HIV and even cancer."
- Kathryn Whitehead, Chemical Engineering Associate Professor at CMU
  - Lab focused on genetically engineering breast milk for helping infant disease, oral delivery of insulin, and RNA drug delivery techniques
- mRNA delivery methods used for COVID-19 vaccine
  - Vaccine developed in 11 months with help from long history of researching mRNA delivery methods
  - Biggest problem that they solved: how to get mRNA drugs to the right location in the body
- mRNA injected into muscles or bloodstream → we want it inside of the cells. How do we get it there?
  - Especially difficult because mRNA is fragile → bodies will destroy it if it's unprotected
- Example: think of mRNA as a glass vase you're sending in the mail

    - Needs a box/bubble wrap to keep it from breaking during delivery
    - Needs an address or it won't be sent to the right place
- To protect the mRNA, we use lipid nanoparticles → act like a "Trojan horse"
    - The nanoparticles look similar enough to cell membranes, so cells don't "think" that the nanoparticles are foreign → cells bring nanoparticle inside, at which point mRNA is delivered/released inside cell
- What lipid nanoparticle is made of
    - Phospholipid: serve as outer "shell" of the nanoparticle, holding all of the other components inside of a lipid bilayer
    - Cholesterol: provides structural support to the "shell", makes sure that the nanoparticle doesn't just fall apart between injection and delivery
    - Ionizable lipid: lipids with a neutral charge when injected into bloodstream → this is safer
        - Switch to positive charge in cells → helps with mRNA release
        - This is the part of the COVID vaccines that varies between companies: Modern and Pfizer, for example, have different ionizable lipids (often proprietary info)
        - But different ionizable lipids aren't that different → don't need to worry about the differences
    - polyethylene glycol (or PEG): holds nanoparticle together
    - If phospholipid, cholesterol, and ionizable lipid are boxes, PEG is packing tape
- Why mRNA?
    - mRNA is like an instruction manual for our cells: tells the cells to make proteins (like coronavirus spike protein)
    - Once you introduce the proteins to the body, immune cells will remember these proteins and attack them if they return (aka when infection occurs)
    - Useful for viral variants as well: the same lipid nanoparticle packaging can be used, and we just change the specific mRNA loaded into the nanoparticle
- Future of mRNA therapeutics
    - cystic fibrosis, muscular dystrophy, sickle cell anemia
        - All caused by protein mutations → mRNA tells cells to make unmutated proteins
    - Cancer treatment: immune cells identify and kill cancer cells
    - Also fight against malaria, Ebola, HIV
- COVID was good in a way in that it caused lots of innovative work in the field of vaccine development

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Definition & Scope: Neuroengineering [Slide 36]

- As a reminder: "neuroengineering uses engineering technology to study the function of various neural systems. You'll learn different neuroimaging techniques in order to best visualize what's going on in your brain. You'll also be introduced to the anatomy of the brain, both on the tissue and neuron level. Because brain activity is dependent on electrical activity, you'll become more familiar with the action potentials to make it possible for your brain cells to communicate with one another. And you'll also learn how you can change or influence the nervous system to produce desired changes."

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Applications: Neuroengineering [Slide 37]

- "Applications of neuroengineering include the creation of implantable technology and materials, as well as the development of neural prosthetic devices. Such devices include cochlear or vestibular implants (in the ear), retinal implants (in the eye), the restoration of touch, bladder or bowel control, and brain-computer interfaces that make it possible for engineers to interact directly with the brain. Sensor and motor prosthetic devices may also be developed."

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Example 1: Retinal Prostheses [Slide 38]

- Visual implantable prosthesis for the blind
- Required components: circuit, wireless power, data telemetry
- Blindness caused by disease destroying parts of the eye → replaced with electronic implants
    - Electronic implants help patients see lines and basic shapes (not full recreations of the environment)
        - Can help recognize simple everyday objects (forks, knives, etc.)
- Problem with these implants: they can shake loose over time
    - They tack their electronic arrays to the inner surface of the retina using a metal tack → this causes bleeding and can shake loose
- New group (Boston Retinal Implant Project) has created a prototype that doesn't fall out due to daily use
    - Specs:
        - 3 x 3.1 mm
        - 38 x 40 array of 1500 micro photodiodes → detect light and control output of pulsed electrical current
        - Brighter light → stronger current
        - Microphotodiodes mimic photoreceptor cells, as they turn light into electrical impulses (that can be sent through optic nerve)
        - Requires intact eyeball, retina, and optic nerve; also functioning bipolar cells

    - Tiny array of electrodes that slide just under the retina, held in place by natural suction
        - Retina: layer of nerve tissue at back of eyeball; sensitive to light, sends visual information through the optic nerve → brain processes the information and a visual image is formed
    - Electrodes help the remaining, undamaged retinal cells transmit signals to brain
    - Camera attached to eyeglasses supplies images to implant
    - Specifically helps retinitis pigmentosa and macular degeneration
        - Both diseases that damage photoreceptors (rods and cones) in eye
            - Rods: vision at low light levels
            - Cones: vision at high light levels, color vision
    - Current prototype has been implanted in animals and two people
        - Animals have tolerated the implants well so far, with eye adapting
        - Animal implantation process: rotate eye and make incision at back of eye
            - Difficult because of the blood vessels beneath retina (have to cut through the blood vessels to make contact between prosthesis and nerve tissue)
        - Human implantation process: metal tube inserted into/behind eye, and implant put into place through the tube
            - People can adjust brightness of image
            - One success story: could recognize everyday objects, read clock, and read large print letters
        - Cable provides chip with power (external battery)
    - Photoreceptor cells pass signal on, but also modify it
    - Components: electrode array (under retina), rest of array and titanium case holding the electronics are placed at the back of the eye
    - Limitations: no color, less detail, less resolution, only covers fraction of retinal field, requires external power (patients have to carry battery pack)
- Complete vision is not currently being restored by retinal implants: instead, help people distinguish between light and dark and find edges of objects

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Example 2: Cochlear Implants [Slide 39]

- Cochlear implant: electrical device that helps people who are deaf or hard of hearing, gives them a sense of sound
    - Used when hearing aids don't provide clear enough sound
    - Both internal and external components
        - Internal component is placed under the skin
        - External component is placed behind the ear
    - Implant parts
        - Microphone (external): picks up sound from environment
        - Speech processor (external): filters out background noise and arranges the sound picked up by microphone
        - Transmitter and receiver/stimulator: receive sound sent by the speech processor as signals → converts them into electric impulses
            - Auditory nerve must receive information in the form of electric impulses
        - Electrode array: collects impulses from stimulator, sends them to auditory nerve
    - Sound (in form of signals) is sent to the auditory nerve, which interprets the signals as sound
- Doesn't restore a person's hearing, but recreates it
    - In other words, a user would still struggle to hear using the auditory system as usual
    - The implant bypasses this method of hearing and introduces a new way of understanding the sounds in the environment
- Different from a hearing aid
    - Hearing aid amplifies sounds in the environment, but still uses a normal auditory system (i.e., still uses the parts of the ear that have been damaged)
        - Just makes noise louder, but doesn't improve understanding of the noise
    - Cochlear implant stimulates the auditory nerve (skips most ear parts involved in the auditory system, including the damaged ones)
    - Takes time to learn: because it's a new method of hearing, it takes practice for patients to correctly interpret

    - Hearing aids and cochlear implants can be used simultaneously for less severe cases of hearing loss
        - Cochlear implant is partially inserted
- Cochlear implants work better when implanted at a younger age, as this makes it easier for their brains to incorporate the implant signals into speech and language skill development
- When implanted at an older age, adults learn by association ("this signal corresponds to this sound")
- Word recognition is dependent on biological factors (age at implantation, length of deafness, length of use)

Content & Image Citations

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CMU Connection: Non-Invasive Mind-Control of Robotic Limbs [Slide 40]

- Video description: "Biomedical Engineering Department Head Bin He and his team have developed the first-ever successful non-invasive mind-controlled robotic arm to continuously track a computer cursor."
- Researchers at both CMU and the University of Minnesota
- 2019 breakthrough in field of non-invasive robotic device control
    - First mind-controlled robotic arm capable of continuously tracking a computer sensor
    - Uses a noninvasive brain-computer interface (BCI) to accomplish this
- BCI: "acquire brain signals, analyze them, and translate them into commands that are relayed to output devices that carry out desired actions"
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3497935/
    - These signals are most often acquired by brain implants, as they tend to have less background noise → this makes for easier interpretation, because the signals are clearer
        - Implants are invasive, require medical/surgical expertise to install & operate
        - Also expensive and dangerous to patients (as any surgery presents potential safety concerns)

    - If signals can be precisely interpreted, they can help with many daily tasks for patients with neuromuscular disorders (cerebral palsy, stroke, spinal cord injuries,etc.)
- Overall goal for this field of study: develop noninvasive BCIs so that paralyzed patients can control robotic limbs or environment
- Signals can also be acquired noninvasively, but the signals have more background noise → this means the signals may not be clear enough for BCIs to accurately or quickly determine their "true" meaning
    - This leads to signals that have lower resolution, which in turn leads to users having less precise control over the robotic limbs
- To address this problem, researchers (like Bin He) have turned to neural decoding and machine learning
    - Neural decoding: how to make sense of the information received from neurons (the information is received as electrical activity/action potentials)
        - Specifically try to find patterns within this neural electrical activity to find meaning in the collected signals
        - Helps researchers reconstruct stimuli (for example, you'd know exactly what object the user was looking at from the electrical activity alone)
    - Machine learning: creates computer models that can automatically analyze data to provide useful conclusions
        - These models can learn from the data, so that they get better after training
        - Able to identify patterns without input from humans
- Result: He's lab has created a method of noninvasive signal analysis that can successfully interpret the noisier brain signals without implantation → leads to higher resolution and more accurate movement of the robotic arm
    - Enhanced BCI learning by ~60% for traditional tasks
    - 50% improvement in continuous tracking of computer sensor
    - Done with help of noninvasive neuroimaging (mapping the activity, function, and structure of the brain or nervous system using imaging methods)
        - New neuroimaging methods that have a higher spatial resolution (meaning that the structures and functions can be more finely distinguished between different areas of the brain)
        - Also better training for signal analysis and processing → better spatial resolution of the collected data
    - Also better user training methods, with more active user engagement throughout the tracking task
    - Together, these give continuous 2D control over the robotic device in real time
    - Human subjects can follow cursor continuously

        - Previous tests with older noninvasive BCIs have shown jerky (rather than smooth) robotic limb motions → robotic arm did not move in real time but instead had to "catch up" with the brain's commands
- Team has plans for bringing the technology to market, so that patients can safely control and interact with their environments
    - This work will start with clinical trials
- Ultimate goal: noninvasive BCIs that can be used as a universal assistive technology
    - Will help everyone (not only those with specific disorders)
    - Will be as prominent in our lives as smartphones

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Looking Forward: Unanswered Questions in BME [Slide 42]

- While BME is split into several focus areas, they're generally held together by a few unanswered questions within the field. One of the biggest focuses is how to create technology that supports individual patient care. Right now, we have more general healthcare procedures, with certain treatments or surgeries suggested for single conditions. In the future, however, the goal is to tailor treatment to each individual patient, considering their medical history, comorbidities, genetics, and other specific biological factors. This, in turn, should lead to personalized treatment, diagnosis, and monitoring of diseases, which will place the patient at the center of healthcare.
- Another goal of BME is to create fully functional artificial organs. Right now, we're largely limited by the number of organs donated in a year. The inadequate supply means people can spend the rest of their lives on a waiting list, and because the organs are coming from another person, they're not completely new and can trigger an immune response unless treated. By moving to artificial organs, we can remove our dependency on donated organs. Theoretically, we could create as many organs as we needed, avoiding

waitlists and shortening turnaround times. And because we can potentially use a patient's own cells to create the organ, an immune response is less likely. While we're making advances, there's still work to be done on fully functionalizing the organs we have created.

- As technology advances, we're also likely to focus on incorporating machines with the human body more. By creating human-machine interfaces, we can use bioelectrical signals in our body to potentially control machines around us, which may be useful for health monitoring, medical diagnostics, prosthetics, assistive devices, and more. Researchers are also turning to artificial intelligence for support in diagnostics. AI is capable of processing more data than a single human can, meaning that it may be possible to remove medical professionals from the diagnosis of common diseases or conditions. This will free up doctors and nurses, making them available for cases that are too complex for computers to accurately diagnose.
- Of course, while we've certainly made advances in our understanding of medical conditions, there's still a lot we don't know. As biomedical technologies continue to push what we're capable of, we hope that we'll be able to better understand the root causes behind certain diseases, leading to more targeted treatments that focus on the cause rather than the symptoms. Such work may provide us with answers to some of our more difficult medical conditions like cancer, aging, and Alzheimer's
- And throughout all of this, biomedical engineers continue to grapple with ethical questions. How can new technologies be fairly priced so that patients get the care they need? What's the limit of gene editing: should we only correct fatal conditions? Or should we be able to correct all genes? If we can restore function through prosthetic devices, is it possible and appropriate to provide people with "superhuman" abilities? And as technology becomes more heavily integrated into our bodies, do we remain the same person? Keep the same personality, mood, or mindset? While the field doesn't have a full answer to each question, conversations on the topics are frequent, demonstrating how we as a field consider our purpose and our place within society.

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You may like more than one of these focus areas...and that's okay! [Slide 43]

- With so many focus areas to choose from, you may be feeling a little overwhelmed, but that's okay! Because BME is such a large field, it's inherently interdisciplinary, using talent from multiple focus areas and other STEM fields to approach big problems. Because BME focuses on the entire human body and all of the ways that the human body may function differently than expected, there are numerous specific problems, each potentially requiring specialized solutions. At the same time, it's possible to take different approaches to the same problems. This means that different focus areas can collaborate to create the single best solution, which often leads to more complex or impressive innovations. In fact, most biomedical engineers are interested in at least a couple of focus areas, as many areas are related to each other because they work with similar systems, sciences, or materials. For example, many of the CMU professors featured in this presentation are hosted in multiple STEM departments. So just know that if more than one focus area sounds interesting to you, you're in good company!

Image Citation

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