COMP 448/548: Medical Image Analysis

Overview of imaging modalities

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Last Lecture

- We need computer help for medical image analysis since
  - There are *too many images* to be analyzed
  - Some tasks are easy for human observers but *time-consuming*
  - Some tasks are not that easy and heavily rely on human interpretations, which may lead to *intra- and inter-observer variability*
  - Analyses mostly rely on qualitative visual analyses but quantitative metrics are useful
- Computational tools facilitate rapid analyses with better reproducibility
- **The goal is to go from medical images to understanding**

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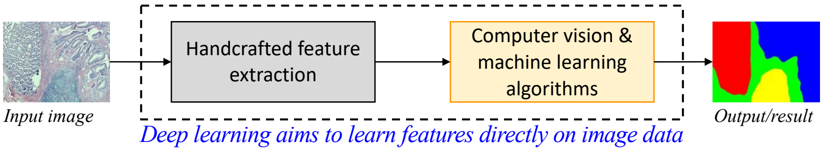
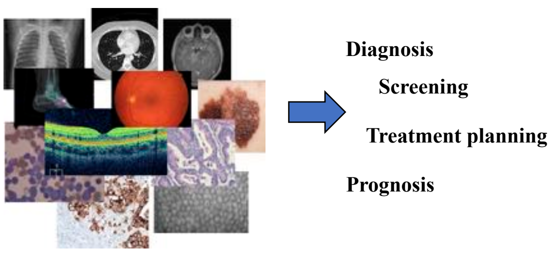
Last Lecture

- For computers to understand medical images, they must
  - Represent an image with mathematical features and
  - Use these features in the design of their algorithms
- Most commonly studied algorithms are for ***segmentation and classification***



Medical imaging is broad

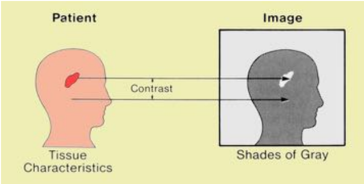
- These algorithms can be designed for different imaging modalities used in
  - Pathology
  - Radiology
  - Nuclear medicine
  - Ophthalmology
  - Dermatology
  - …



- Defining a "*medically meaningful*" problem requires knowledge specific to the domain and the imaging modality that it uses
- Although these algorithms share many common aspects, you need to know the domain and the imaging modality to more wisely design an algorithm

Medical imaging is the process of …

- … converting tissue characteristics into a visual image



- Different medical imaging modalities reveal different characteristics of the human body
  - No medical image (or no medical imaging modality) reveals everything
  - Visibility of specific features depends on the characteristics of the imaging modality and the manner it is operated

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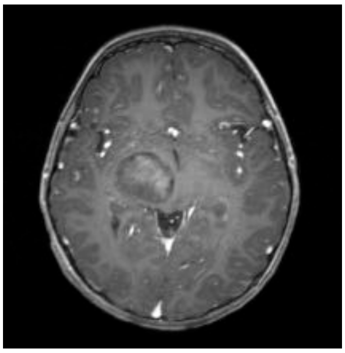
Contrast Resolution and Spatial Resolution

- For a tissue to be seen by a human or a computer, the imaging modality should have sufficient
  - **Contrast resolution:** ability to distinguish intensity differences between this tissue and its surrounding tissues
  - **Spatial resolution:** ability to visualize small enough tissues
- These vary with the imaging modality and the manner it is operated



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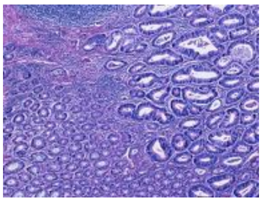
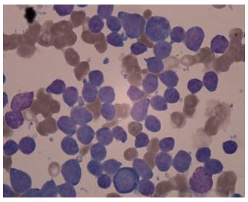
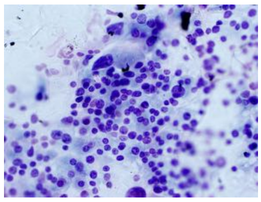
Pathology

- Pathology involves the study and diagnosis of a disease through the examination of surgically removed organs, tissues (biopsy samples), and bodily fluids
- This examination is based on gross macroscopic and microscopic observations







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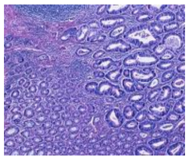
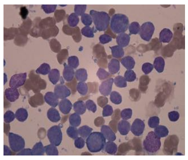
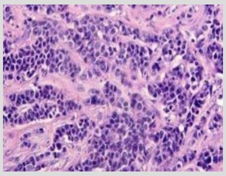
Pathology

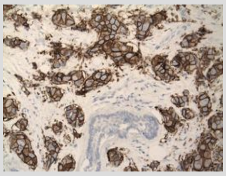
- Microscopic analysis includes examining a tissue (fluid) sample under a microscope in order to identify changes in cell morphologies and tissue architectures observed as a result of a disease
  - Histopathological analysis vs cytological analysis
- In this analysis
  - Contrast resolution is based on differences in tissue staining
  - Spatial resolution is based on both the resolution and magnification of a microscope



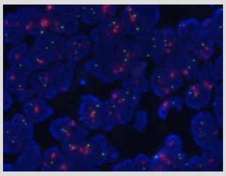




HE staining



IHC (Ki-67) staining



HER2 gene amplification tested by FISH. Red signals: HER2 gene copies, green signals: chromosome enumeration probe 17 copies

HER2 (human epidermal growth factor receptor 2) is a gene that can play a role in the development of breast cancer. This gene is overexpressed for invasive breast cancers. Thus, it has prognostic and predictive implications.

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Histopathological Examination

- It requires mounting thin sections of tissues on glass slides
- Since a fresh tissue is very delicate and easily distorted, it is impossible to prepare thin sections (4-5 μm) from the fresh tissue unless it is chemically preserved or “fixed”
  - Frozen sections: freeze the tissue and keep it frozen while cutting
  - Paraffin sections: infiltrate the tissue with a liquid agent (paraffin wax) that can be converted into a solid then cut thin sections from this solid
- At the end, dissected tissues are stained with either chemicals or antibodies to enhance visualization (*contrast resolution*)

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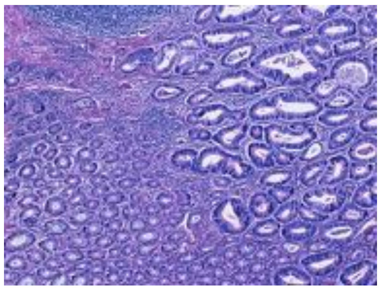
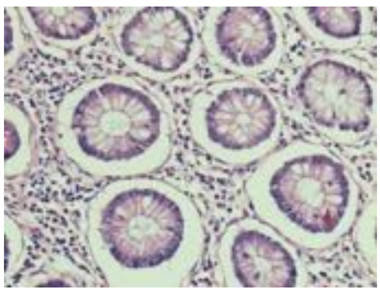
Histopathological Examination

Two commonly used staining techniques are:

1. Hematoxylin-eosin (HE) staining:
   - Hematoxylin stains cell nuclei blue and eosin stains extracellular matrix and cell cytoplasm pink; non-tissues remain white
   - This staining is to visualize the general layout and distribution of cells over a tissue
   - Routinely used technique





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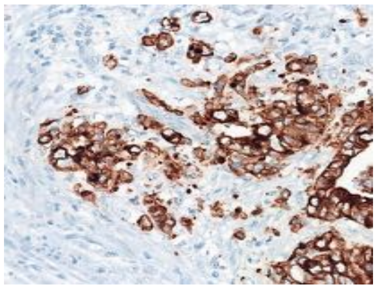
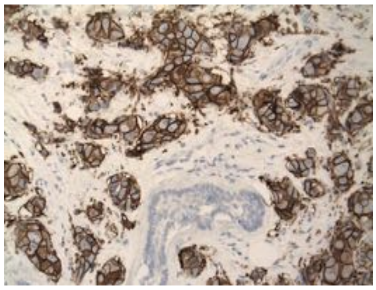
Histopathological Examination

2. Immunohistochemistry (IHC) staining:

- It uses antibodies to detect an antigen (a specific protein)
- Brown indicates the presence of the target antigen and blue provides a contrast for visualizing the underlying tissue structure
- Amount of staining, staining pattern, and staining location provide diagnostic and prognostic information
- Its major benefit is the ability to provide visualization of the target antigen while maintaining the spatial context and tissue architecture
- Selecting the right antibody is very critical





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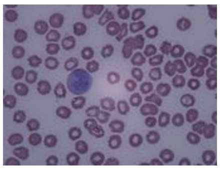
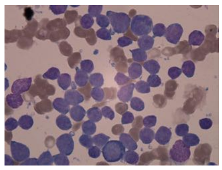
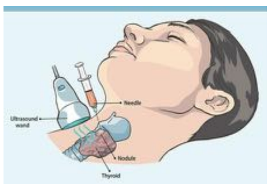
Cytological Examination

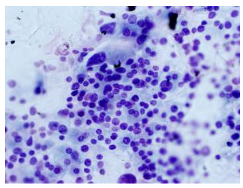
- Examination of free cells or tissue fragments
- Peripheral blood smear is a thin layer of blood smeared on a glass slide
  - For example, to diagnose hematological disorders (e.g., leukemia) and to detect blood parasites (e.g., malaria)





- Fine-needle aspiration withdraws a small amount of tissue or fluid from a suspicious area by a very thin hollow needle
  - After being stained, it is examined under a microscope to see if it contains cancerous cells





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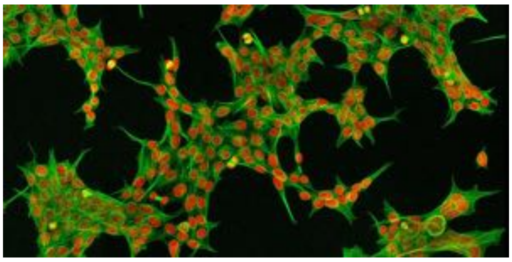
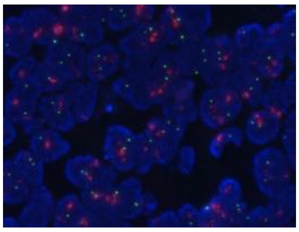
Cytological Examination

- Immunofluorescence staining uses fluorescent antibodies to visualize various cellular antigens
  - These antibodies are detected using a fluorescence microscope
- Fluorescence in situ hybridization (FISH) is a molecular cytogenetic technique that allows detecting presence or absence of specific DNA sequences on chromosomes





HER2 gene amplification tested by FISH. Red signals: HER2 gene copies, green signals: chromosome enumeration probe 17 copies

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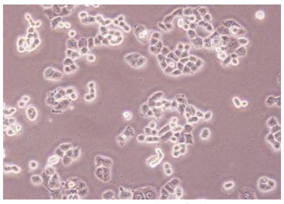
Cell Culture Research

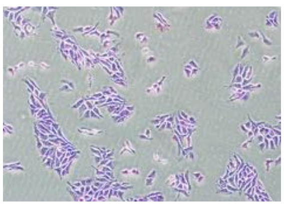
- In vitro experiments, in which cells are grown in a test tube or a culture dish
- They may involve live or stained cells
- For live cells, cell tracking is another common practice

Cell lines are clones of animal or plant cells that can be grown in a culture medium in the laboratory. Each cell line is originated from a single common ancestor cell. They are desirable for repeatable scientific experiments since they allow an analysis repeated many times on genetically identical cells.

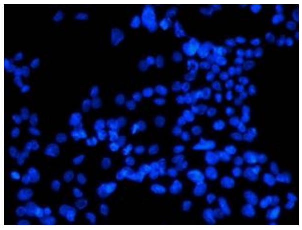
Google "*HeLa cell line conflict*" for an interesting reading on the ethics and policy of collecting biospecimens.



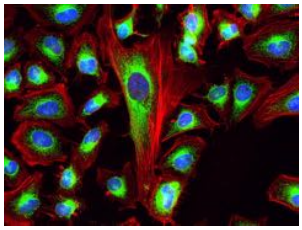
Live (unstained) cells of the MDA-MB-468 human breast cancer cell line



Giemsa stained cells of the Huh7 human hepatocellular carcinoma cell line



Fluorescence (nuclear Hoechst 33258) stained cells of the HepG2 human hepatocellular carcinoma cell line



Fluorescence stained cells of the HeLa human cervical cancer cell line. Cells are stained with three dyes: mitochondria dye (green), F-actin dye (red), and nuclear dye (blue).

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Reflecting on HeLa cells: 70 years on

70 years ago, Henrietta Lacks was treated for cervical cancer at Johns Hopkins Hospital in Baltimore, Maryland. She died mere months later but tumour cells taken from her went on to become the first immortal human cell line. The research breakthroughs this enabled cannot be overstated: 110,000 papers, 11,000 patents and 3 Nobel prizes are just the beginning. While these cells were a boon to research from the start, their use has been followed by questions and controversy. I gave a talk last year on the history and ethics of HeLa cells which included the impact of the Lacks family and the development of informed consent, but that just touched the surface so this blog will cover other aspects of the discussion around their use. In modern society and research, what do HeLa cells represent and what place should they have going forward?

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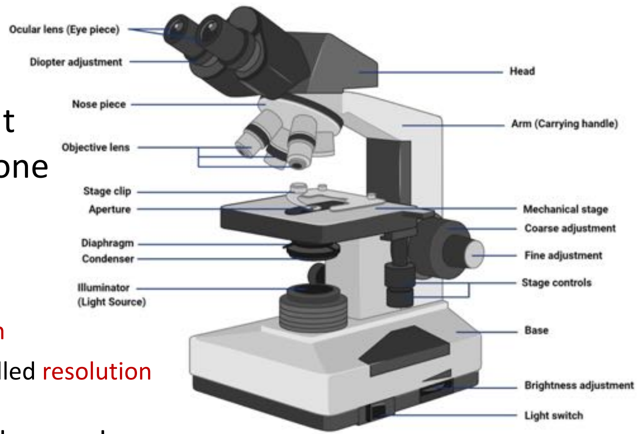
Microscopy Systems



- Brightfield microscope: Simplest but perhaps the most commonly used one
  - Focuses transmitted light onto the specimen to observe its details by enlarging its image
    - Enlarging an image is called magnification
    - Amount of the observed fine details is called resolution
  - Produces a dark image on a bright background
    - This image is magnified by a combination of the objective lens and the eyepiece (ocular lens)
    - A typical eyepiece magnifies images 10 times (10x)
    - Magnification of objective lenses on a rotating nosepiece typically ranges from 4x to 100x
    - The 100x lens is usually an oil-immersion lens (you need to drop an oil onto the slide specimen)

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Microscopy Systems

- Fluorescence microscope:
  - The sample is labeled with fluorophores and illuminated through the lens with a higher photon-energy light source (at shorter wavelength)
  - The illumination light is absorbed by the fluorophores that then emit lower energy photons (at longer wavelength)
  - The emitted light can be separated from surrounding radiation with filters designed for that specific emission wavelength, which allows to observe fluorescent parts

Brightfield microscope

Fluorescence microscope

Note that a brightfield microscope uses visible light to illuminate and produce a magnified image

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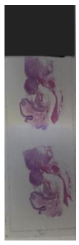
Microscopy Systems

- Digital whole slide scanner:
  - Converts a whole slide into a huge collection of high-resolution digital images
  - Enables to remotely access and view the slides
  - Allows using “smart” computational tools for the quantitative analysis of these slides
- Others: inverted microscopes, confocal microscopes, time-lapse microscopes, transmission electron microscopes, …



Digital pathology emerges as a new field, which is expected to have substantial implications to the current pathology practice

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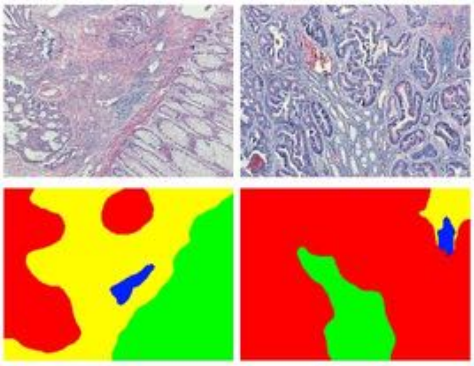
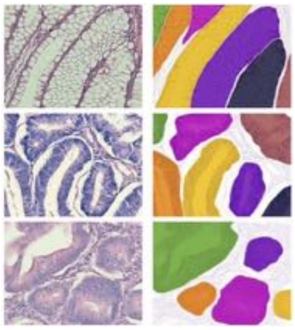
Example Applications

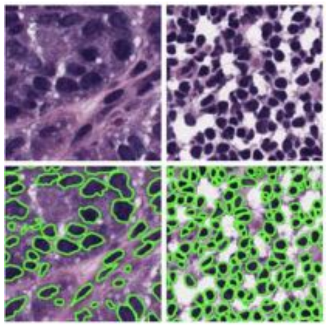


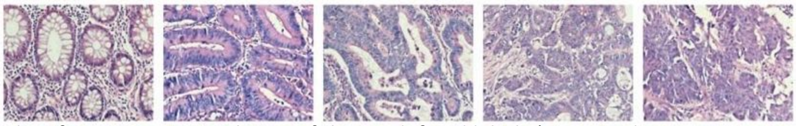
Semantic segmentation to divide an image into its tissue compartments

Instance segmentation for delineating gland boundaries

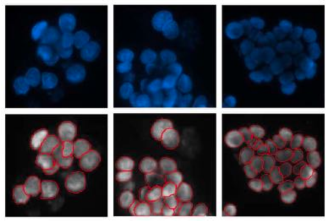


Instance segmentation for delineating nucleus boundaries





Classifying an image with one of the predefined labels (as normal tissue or belonging to one of the four cancer grades)



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Radiology

- Radiology is a medical discipline that diagnoses and treats diseases within the human body based on medical images of organs
- Radiology's imaging modalities include
  - Radiography
  - Computed tomography (CT)
  - Magnetic resonance imaging (MRI)
  - Ultrasound
  - Fluoroscopy
  - Nuclear medicine imaging
  - *Interventional radiology* performs minimally-invasive procedures with the guidance of these imaging technologies (e.g., angioplasty and stent insertion)

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Radiography

- Uses X-rays to produce images of parts inside the human body
  - X-rays of image bones, chest, abdomen, and breast (mammogram)
  - Based on their compositions, tissues absorb X-rays or allow them to pass through
  - *Fluoroscopy* uses X-rays to visualize the real-time movement of a contrast agent through the body (like a X-ray “movie”)
- Contrast resolution is based on differences in X-ray attenuation
  - Differences in atomic number (calcium, iodine, lead) and density/thickness of tissues
  - Bright regions: bone, markers, foreign bodies
  - Dark regions: air/gas
- High spatial resolution

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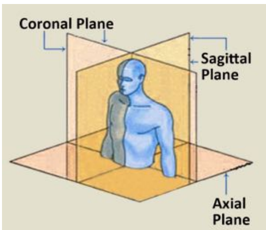
Computed Tomography (CT)

- Multiple X-ray measurements are taken from different angles around the body and cross-sectional image slices are created based on computer calculations
- Similar to radiography, contrast resolution is based on differences in X-ray attenuation and it has high spatial resolution
- But it has much higher contrast resolution



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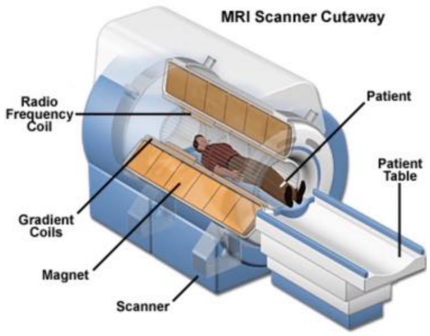
Magnetic Resonance Imaging (MRI)

- Uses a powerful magnet and radio frequency (RF) pulses to produce detailed cross-sectional images of organs and tissue
  - Magnet produces a strong magnetic field that forces protons in the body to align with that field
  - Short bursts of RF pulses are sent, knocking the protons out of this alignment
  - Then RF pulses are turned off and the protons realign and radiate a radio signal
  - Alignment time and amount of radiated signal depend on tissue characteristics
  - MRI scanner detects these signals and use them to create the organ/tissue images
- Provides better soft tissue contrast than CT



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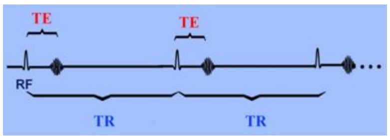
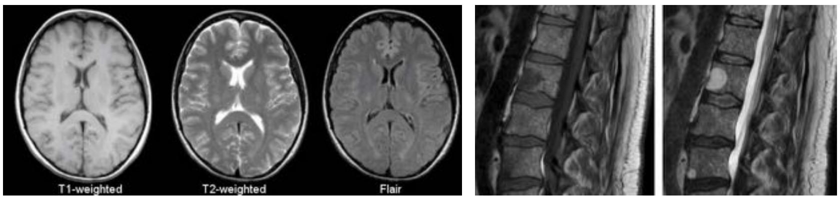
Magnetic Resonance Imaging (MRI)

- Repetition time and echo time are typically used to control image contrast
  - Repetition time (TR): time between successive RF pulses
  - Echo time (TE): time between the delivery of the RF pulse and the receipt of the echo signal



- The most common sequences: T1-weighted and T2-weighted scans



T1-weighted T2-weighted

T1-weighted → short TR and TE
T2-weighted → long TR and TE
Flair → longer TR and TE

- High spatial resolution

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Ultrasound (Sonography)

- Uses high-frequency sound waves and their echoes to create a real-time moving image
- Contrast resolution is based on differences in sound impedance among tissues (how they resist the propagation of ultrasound waves)
  - Bright regions: Tissue interfaces, gas, stones/calcification, heterogeneous tissue
  - Dark regions: Fluid filled structures, homogenous solid organs
- Low spatial resolution

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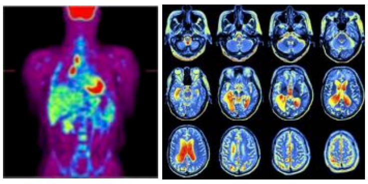
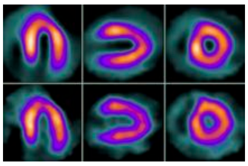
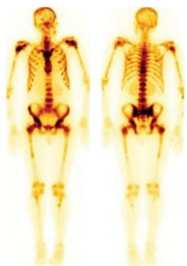
Nuclear Medicine



- Small amounts of radioactive substances (tracers) are injected
- These tracers go to certain parts of the body and go through radioactive (nuclear) decay emitting gamma-ray photons, providing information on organ function and cellular activity



- Radiation is then detected by an external device
  - Gamma camera
  - Positron emission tomography (PET) scanner
  - Single photon emission computed tomography (SPECT) scanner



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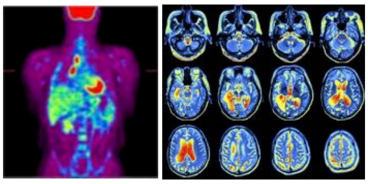
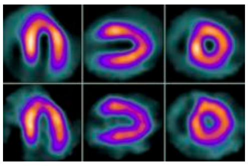
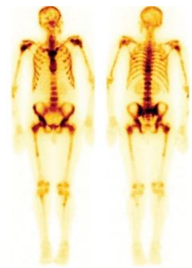
Nuclear Medicine

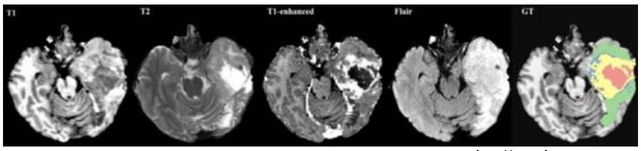




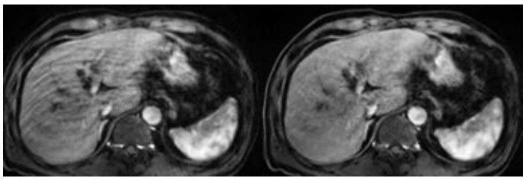


- Examples of nuclear medicine tests
  - PET scan to understand cellular energy need by injecting $^{+18}$FDG glucose
    - To detect cancer and to study brain activities
  - SPECT myocardial perfusion imaging to see how well blood flows through the heart muscle
    - To diagnose coronary artery disease and to find out a previous occurrence of a heart attack
  - Whole body bone scintigraphy (gamma scan) to detect skeletal metastases

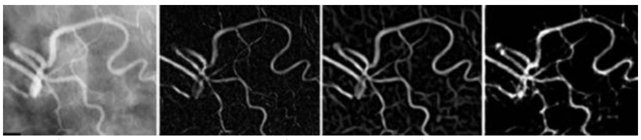
Example Applications



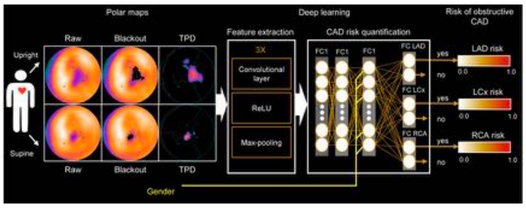
Brain tumor segmentation in MR images: tumor (yellow), necrosis (red), edema (green)



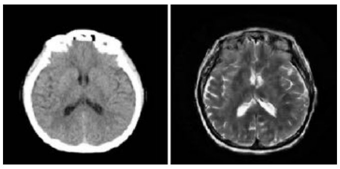
Artifact reduction in MR images



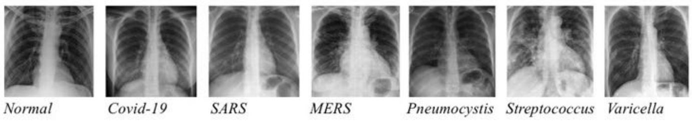
Vessel segmentation in a cardiac angiography image



Diagnosis of a coronary artery disease in SPECT myocardial perfusion imaging



MR image synthesis from a CT image

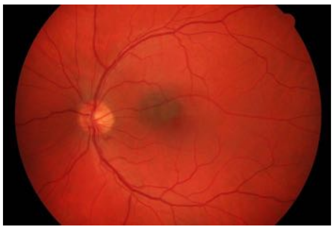


Classifying a chest X-ray for covid-19 detection

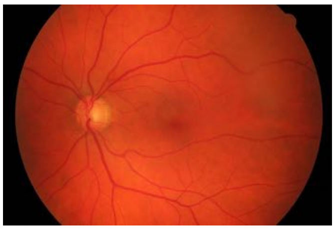
Ophthalmology

- Fundus photography uses a specialized low-power microscope with an attached camera to take a photograph of the interior of the eye (retina, retinal vessels, macula, fundus) through the pupil

Healthy retina



Diabetic retinopathy



Glaucoma

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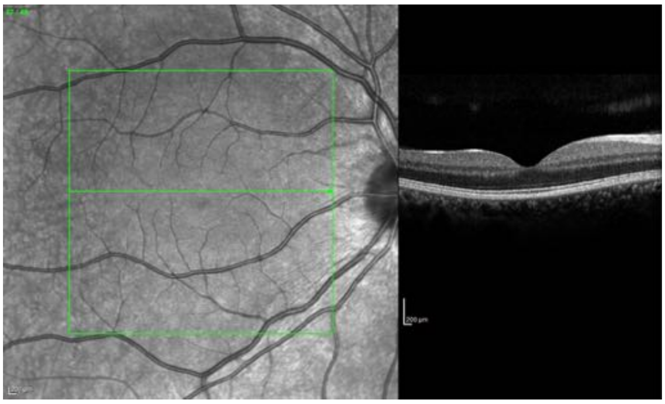
Ophthalmology

- Optical coherence tomography (OCT) emits light into the eye and measures reflectivity of tissues to produce cross-sectional pictures of the retina
- It visualizes the retina's distinctive layers and allows measuring their thickness



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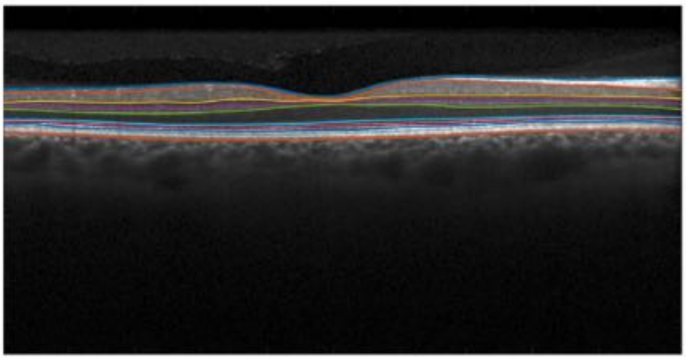

Fig. 1. An example B-scan images, showing the included manual delineations.

Table 2
Manually delineated retina layers.

Layer name	Abbreviation
Retina nerve fiber layer	*RNFL*
Ganglion cell layer and inner plexiform layer	GCL+IPL
Inner nuclear layer	*INL*
Outer plexiform layer	*OPL*
Outer nuclear layer	*ONL*
Inner photoreceptor segments	*IS*
Outer photoreceptor segments	*OS*
Retinal pigment epithelium	*RPE*

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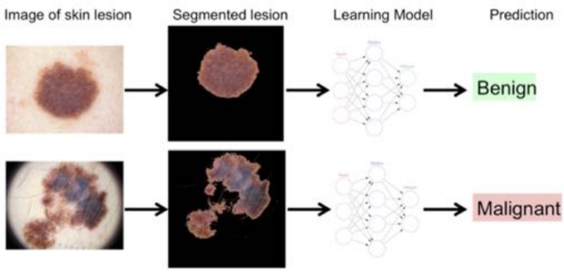
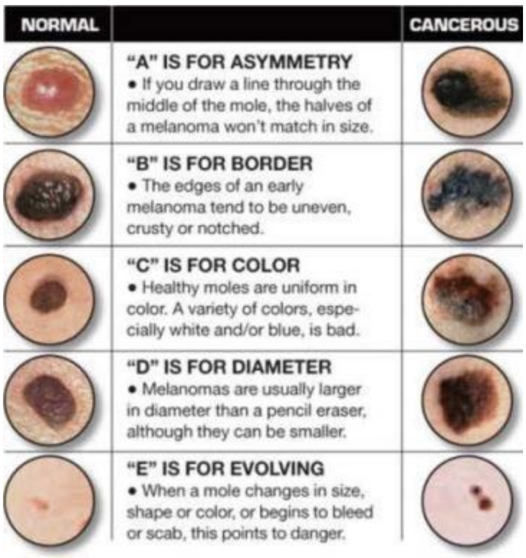
Dermatology





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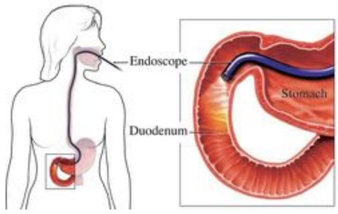
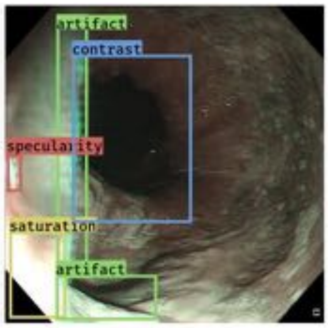
Endoscopy

- Procedure to examine organs inside the human body with an instrument called endoscope
  - Endoscope is a long flexible tube with a light source and a tiny camera at the end





Multiclass artifact detection in video endoscopy

To summarize

- Medical imaging is broad
- There exist many medical imaging modalities
  - We covered some of the widely used ones but there are more
  - Each modality works differently to visualize different features of the human body
  - No imaging modality reveals everything
- Computational analysis tools should be designed taking into account the imaging modality and the manner it is used
  - Although they share many common aspects, you need to know the domain and the imaging modality to more wisely design an algorithm

Thank you!

Next time:

Design pipeline and challenges

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