Getting Started in Computational Pathology

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Computational Pathology – a definition

• An approach to diagnosis that incorporates multiple sources of raw data (e.g., clinical electronic medical records, laboratory data including “-omics,” and imaging [both radiology and pathology imaging]); 
  extracts biologically and clinically relevant information from these data; uses mathematic models at the molecular, individual, and population levels to generate diagnostic inferences and predictions; and presents this clinically actionable knowledge to customers through dynamic and integrated reports and interfaces, enabling physicians, patients, laboratory personnel, and other health care system stakeholders to make the best possible medical decisions.

• More generally, using computation for the interpretation of multi-parameter data to improve health care.

Computational Pathology – a definition

• An approach to diagnosis that incorporates multiple sources of raw data ...; extracts ...clinically relevant information ..; uses mathematic models ...to generate diagnostic inferences ...enabling physicians to make medical decisions.

Computational Pathology – Why?

- **enabling physicians**, patients, laboratory personnel, and other health care system stakeholders **to make** the best possible **medical decisions**.
  - Reduce inter and intra observer variability
  - Quantitative rather than semi-quantitative measures
Why?

• Efficient and effective Personalized Medicine

Pathologists in Canada 2018 from CMA
Computational Pathology – How?

- extracts biologically and clinically relevant information from these data; uses mathematic models at the molecular, individual, and population levels to generate diagnostic inferences and predictions;

A Suggested Model of the Medical Diagnostic Process

https://www.researchgate.net/publication/239796277_Organizational_Diagnosis_An_Evidence-based_Approach
Models

- Mathematical representations of data showing the relationships between inputs or between inputs and outputs
- Statistics: a branch of mathematics dealing with *data* collection, organization, analysis, interpretation, and presentation (Wikipedia)
- Machine Learning: *algorithms* and statistical models that computer systems use to perform a task without using explicit instructions, using patterns and inference instead (Wikipedia)
- To investigate further: The Close Relationship between applied Statistics and Machine Learning (blog: machinelearningmastery.com)
Statistics vs Machine Learning

Statistics draws population inferences from a sample, and machine learning finds generalizable predictive patterns.

- Inference creates a mathematical model of the data-generation process to formalize understanding

- Prediction aims at forecasting unobserved outcomes or future behavior

Statistics and Machine Learning

- There is a strong argument for using both
- Structured data (tables)
- Unstructured data (images, speech)

Classical ML Applied to Structured Data
Deep Learning Applied to Unstructured Data

Making Models

• Statistical methods with structured data
  • Survival model
  • Hypothesis testing
  • Summary statistics
  • Bayes model
  • Power calculations
  • Linear regression
Making Models

- Statistical methods & classical ML with structured data
  - Support vector machines
  - Decision trees
  - Ensemble methods
  - Logistic regression
  - Multilayer perceptron


https://www.researchgate.net/figure/Graphical-representation-of-an-MLP-or-multi-layer-NN_fig3_279973874

Making Models - Deep Learning

- Can be applied to structured and unstructured data
- The biggest benefit has been seen in the application to unstructured data

Andrew Ng – Coursera Deep Learning Specialization
Deep Learning with Unstructured Data

- **Input data** (aka features) are no longer hand crafted from complex signal spaces such as images.
- NN are very deep & during learning interesting aspects are discovered.
- Moved the effort from crafting of features to data & the design of NN

Computational Pathology – the data

- An approach to diagnosis that incorporates multiple sources of raw data (e.g., clinical electronic medical records, laboratory data including “-omics,” and imaging [both radiology and pathology imaging]); ...
Digital Pathology as a component

- There is a wealth of information on the slide
- Software tools make the extraction of new information tractable, routine information faster and less variable
Beyond Image Sharing

- Many pathology departments already scan slides for education & consult
- What else can be done with the images?
  - Segment
  - Detect
  - Quantify
  - Classify
  - Reconstruct
  - Map
  - Predict

Clinical Tools

Image analysis software is intended to provide quantified or semi-quantified information to provide repeatable data to identify patients who are most likely to respond to a treatment option.

Some examples are Ventana’s Er, Pr, Her2, p53, Ki67 image analysis software.

The Companion Algorithm HER2 (4B5) image analysis software.

*The PATHWAY HER2 (4B5) assay is FDA approved.
Clinical Tools

- Challenges around digital pathology in some markets
  - While DPS use in Canada has largely been at the discretion of pathologists, HC approval has been in place for Omnyx and Leica since 2013 [https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2013-0289-ED](https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2013-0289-ED)

- With digital pathology not available for use in the large US market until recently, there had been reduced incentive for quantitative analysis tools suitable for the clinic
Out-Sourced Tests

- Haliodx (commercially available predictive model)
  - Immunoscore is an in vitro diagnostic test predicting the risk of relapse in early stage colon cancer patients, by measuring the host immune response at the tumor site using image analysis. (CD3+, CD8+ on consecutive slides)

http://www.immunoscore.org/research.shtml
Research Tools

• There are many platforms that allow the researcher to segment images and quantify results
  • inForm
  • Tissue Mark
  • Visiopharm
  • Definiens
  • Indica Labs
Visiopharm – a Typical Workflow

1. Pre-processing
2. Training
3. Segmenting
4. Post-processing
5. Calculating results
Commercial Image Analysis platforms may not suit your needs or may be too expensive.

- Some “bioimage informatics” platforms
  - ImageJ (NIH)
  - Cell Profiler (Broad Institute)
  - Cran R (R Foundation)
  - icy (France-BioImaging)

You may (will) need to do some tweaking to get what you need out of them
DIY- Code

• For the code comfortable or those who wish to partner with engineering/comp. sci./statisticians
  • python libraries
    • Scikit-learn
    • Pandas
    • Keras, tensorflow
    • XGBoost...
  • opencv
  • Cran R – has thousands of packages

• OpenSlide- to be able to deal with the large images
DIY – Computational resources

• This work takes computing power
• Desktop - often good enough for proof of concept
  • May take hours to process a single image – may need to tile images
  • Often a hierarchical approach helps
  • GPUs
• Multiple Computers
  • Cloud services (AWS, Google Cloud)

Some Additional Resources

- http://tissuepathology.com
- https://cran.r-project.org/web/views/MachineLearning.html
- http://www.jpathinformatics.org/
- tyna.hope@gmail.com