Machine learning for placental pathology, why, how, and what now?

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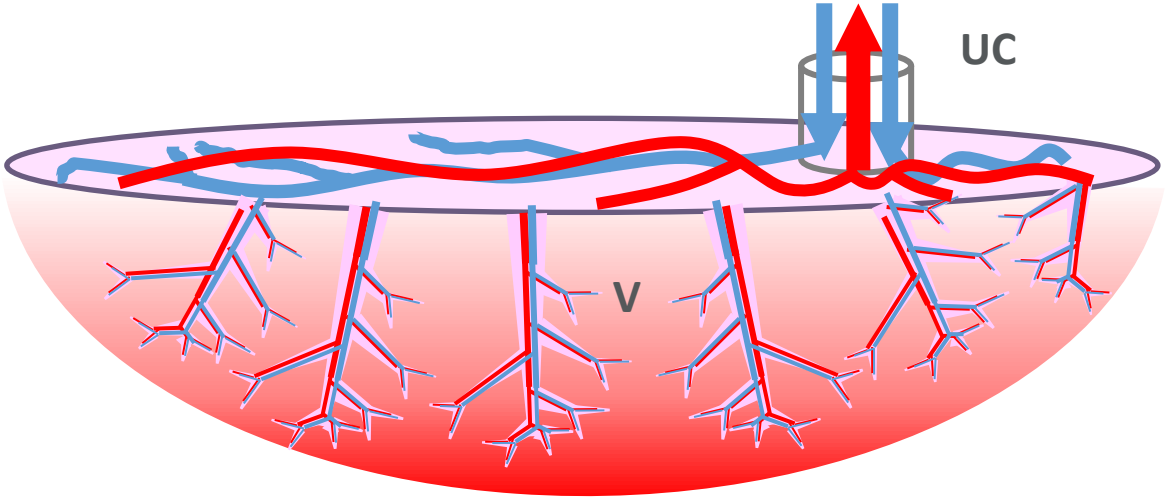
Outline

- Why?
  - Why placenta?
  - Why machine learning?
- How?
  - The task – estimation of gestational age
  - Practicalities
  - Results
- What now?
  - Placenta
  - Pathology
  - Machine learning

The placenta

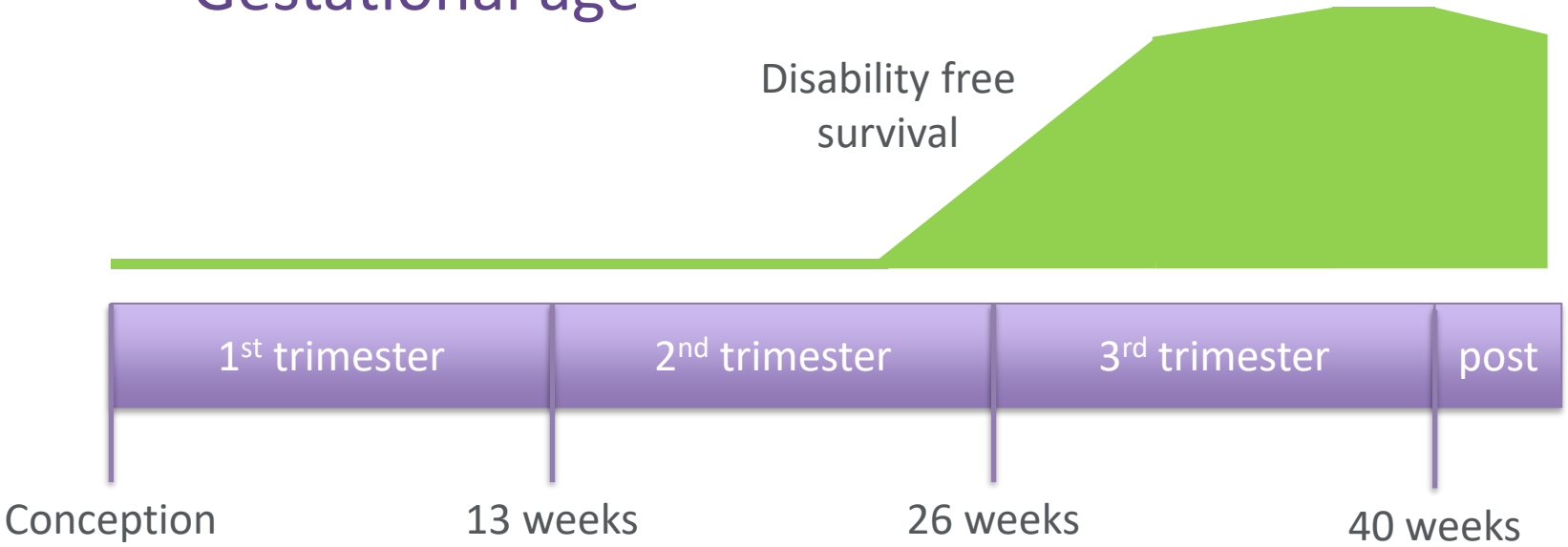
- First organ to form
- Source of fetal O2 + nutrients
- Endocrine, immune, barrier, excretion functions
- Causes or reflects most diseases in pregnancy
- Branching structure:
  - UC->Capillaries
  - Capillaries -> UC



Perinatal origins of disease and the placenta

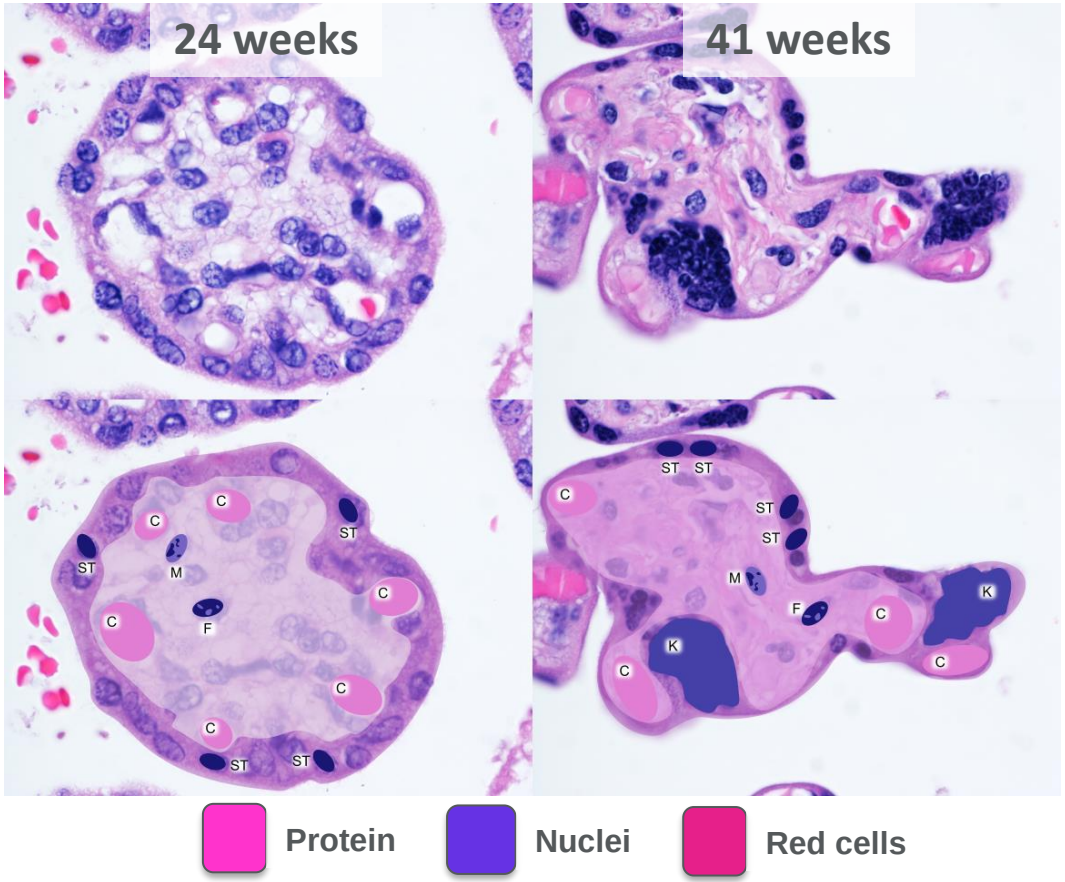
Event	Risk factor for	Citation
In utero for 1918-19 flu	Cardiovascular morbidity, lower income	10.3386/w27673
More ovoid placenta	Colorectal carcinoma	26428494
Histiologic chorioamnionitis	Asthma	10.1001/archpediatrics.2009.238
Decidual arteriopathy	Maternal atherosclerosis	10.1016/j.placenta.2018.12.008
Prematurity	Chronic lung disease	10.1056/NEJMra067279

Gestational age

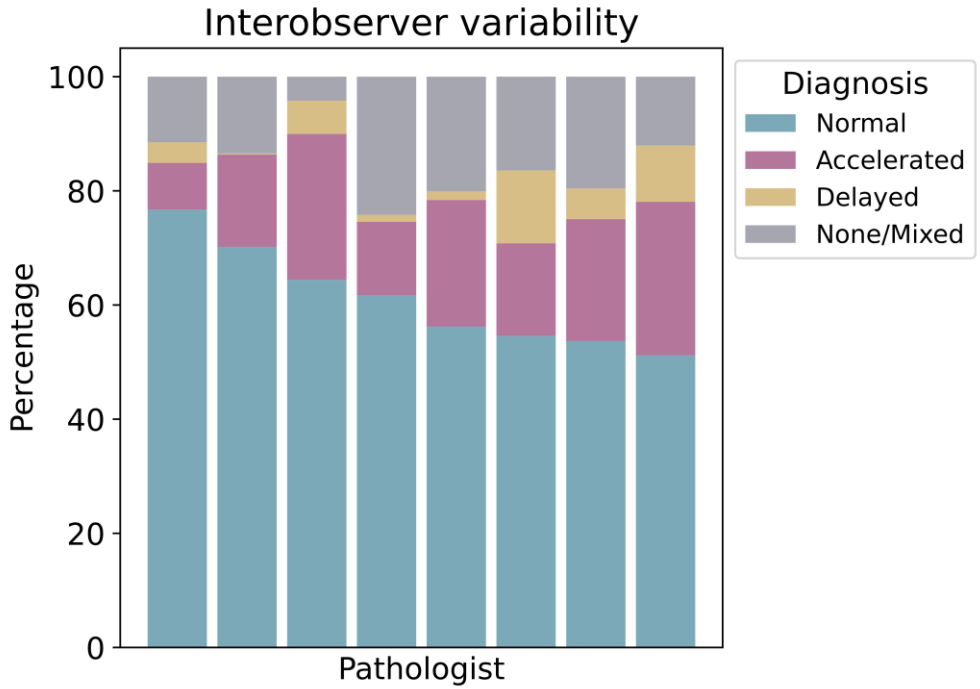


Placenta 24-41 weeks

- Placenta 4x size, increased efficiency
- Maturation – reproducible pattern
  - Villi – thinner
  - Stroma - fewer cells, denser
  - Capillaries – under surface
  - Knots
- Abnormalities
  - Accelerated – hypertension; preeclampsia
  - Delayed – gestational diabetes
- 36k fields, 500k cells on one slide -->
  - **Gestalt across criteria + fields**



Interobserver variability - maturation



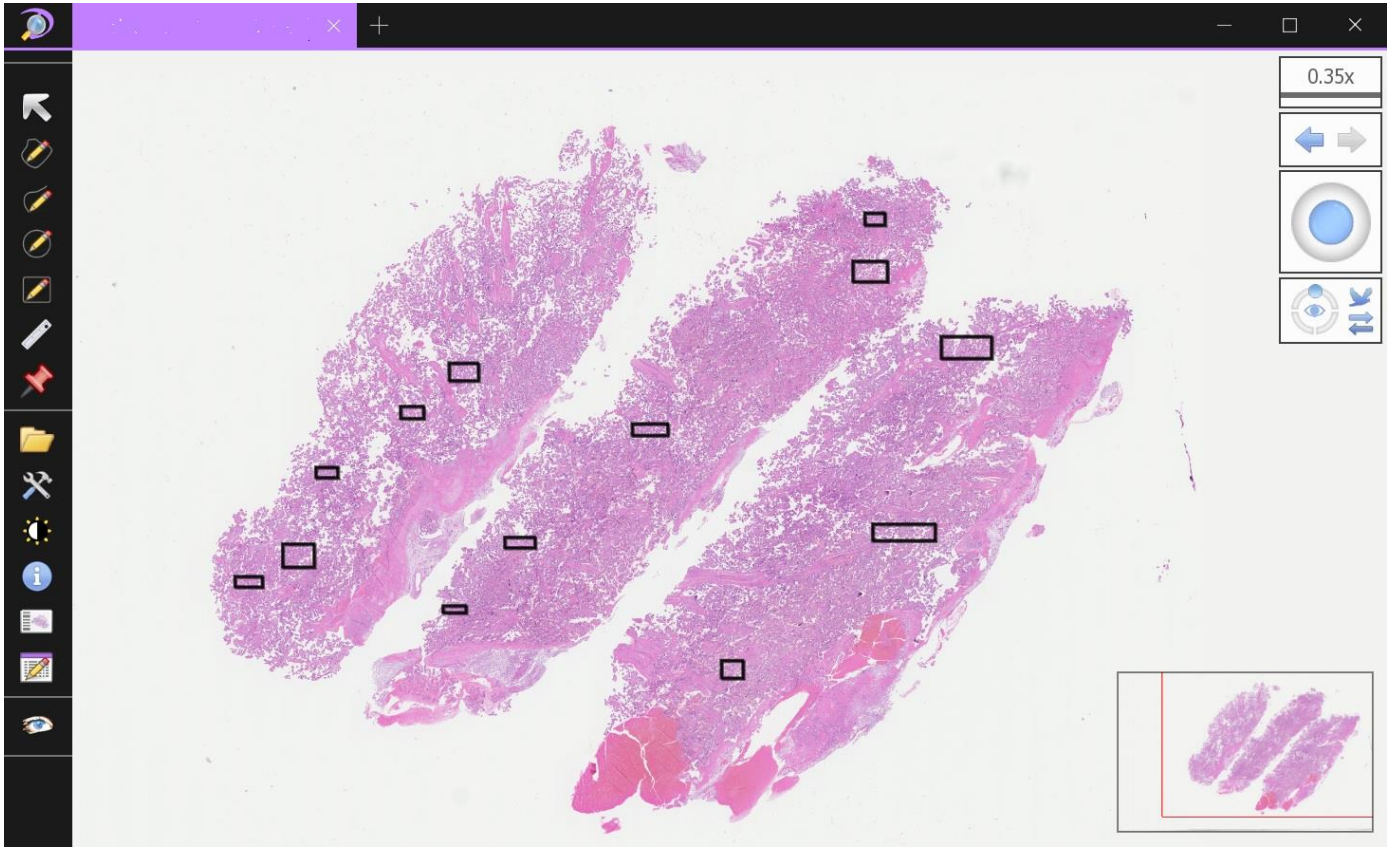
- 8 subspecialty trained perinatal pathologists.
- Routine practice
- Given slides and estimated gestational age, say if the placental maturation is normal, accelerated, delayed, or what.
- Motivation for ML

Nuts + Bolts

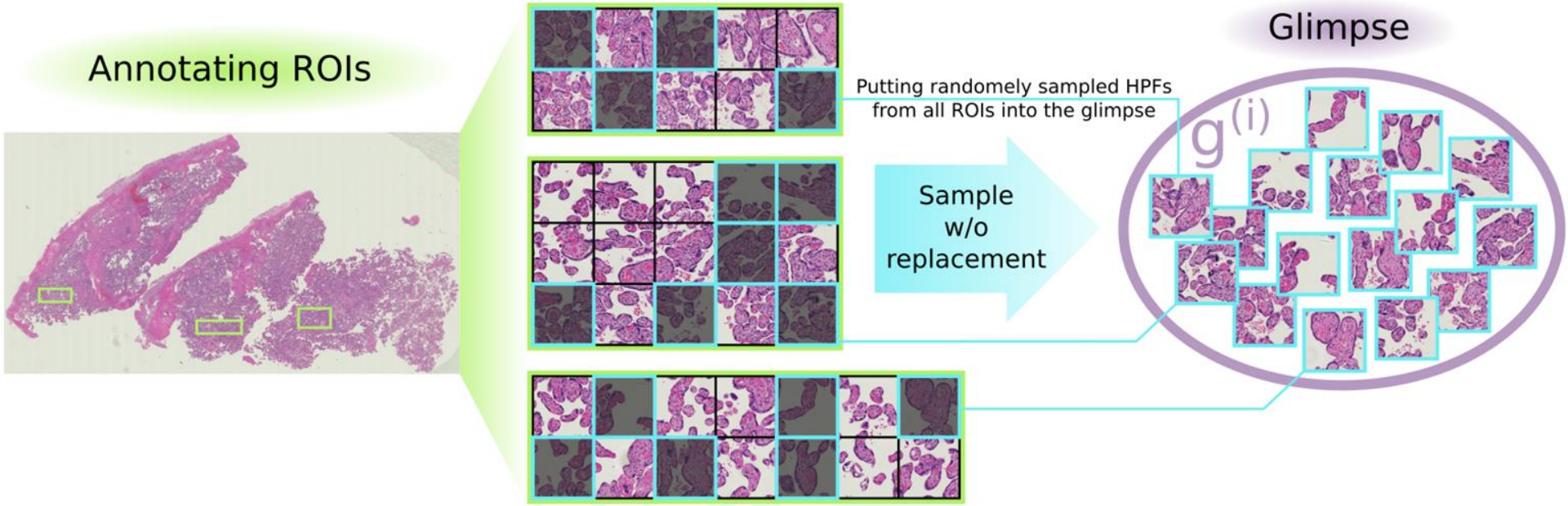
154 patients / slides – 70:15:15 training:validation:test
Whole slide imaging, 20x magnification
Annotation – 10+ regions of interest (ROI) – extract
Macenko color normalization
ROI -> 512 x 512 high power fields, shrunk to 256 x 256 (effective 10x magnification)

Annotation

- Hand selected
- ‘Representative’
- ‘Good villi’
- <1% of slide consumed

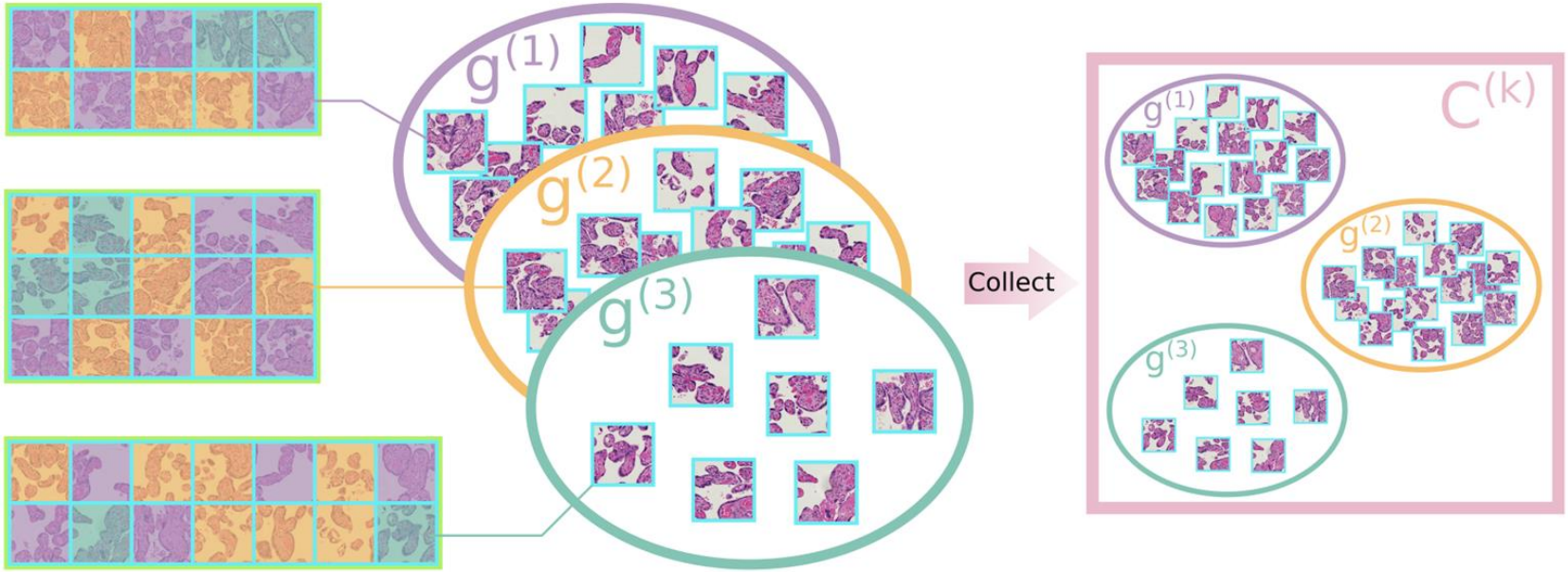


Glimpse for aggregation + attention



Collection formation

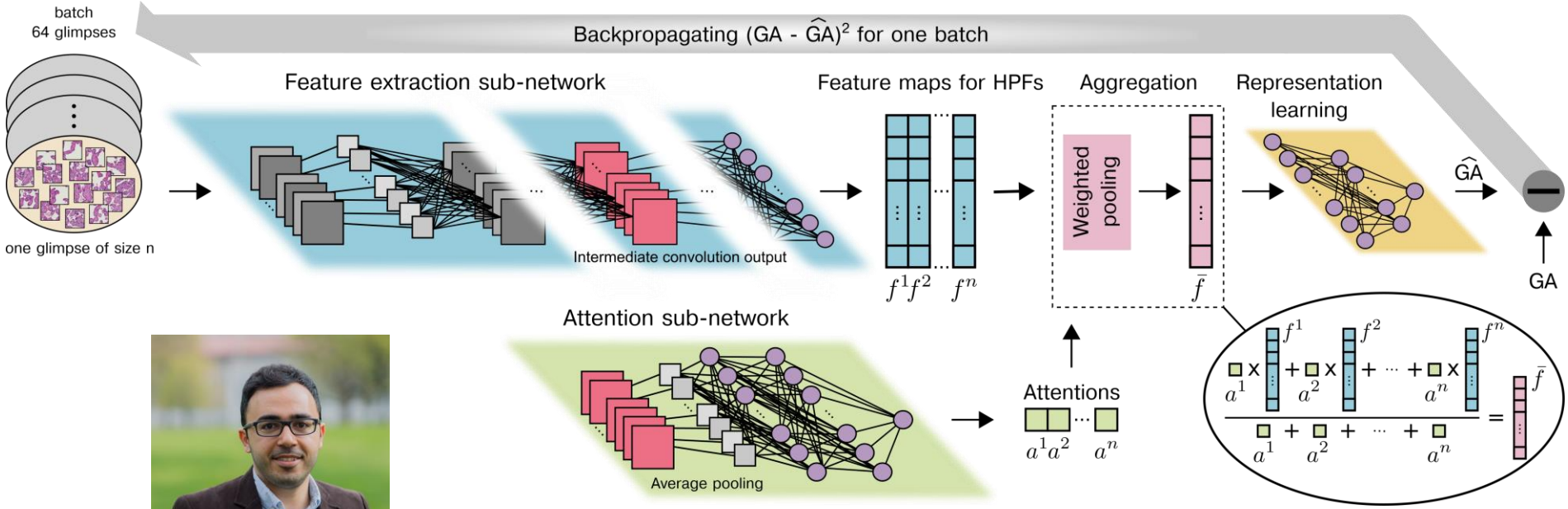
Collecting the glimpses into a Collection



All HPFs are used.

Last glimpse gets the remainder of HPFs.

Model pipeline



Pooya Mobadersany, PhDc

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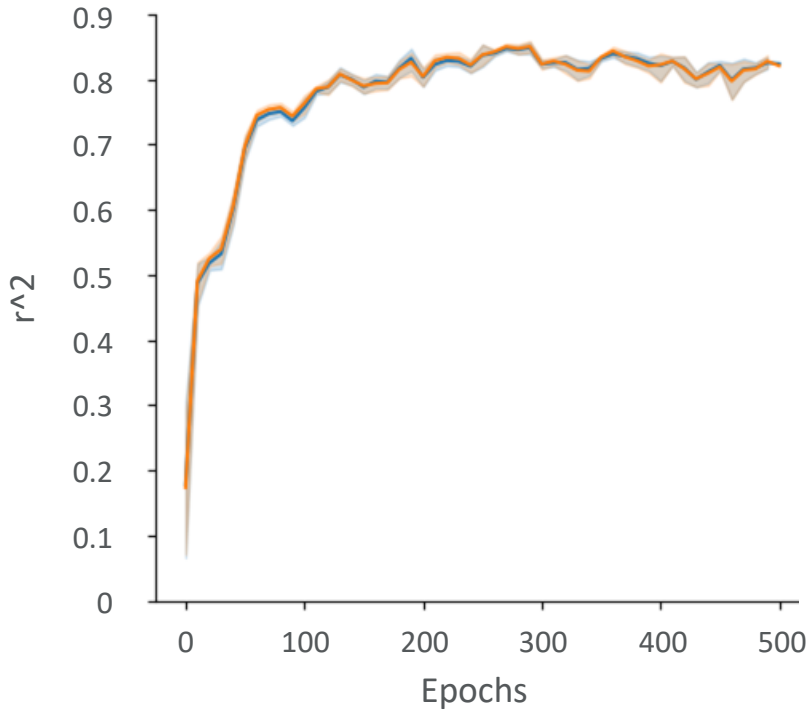
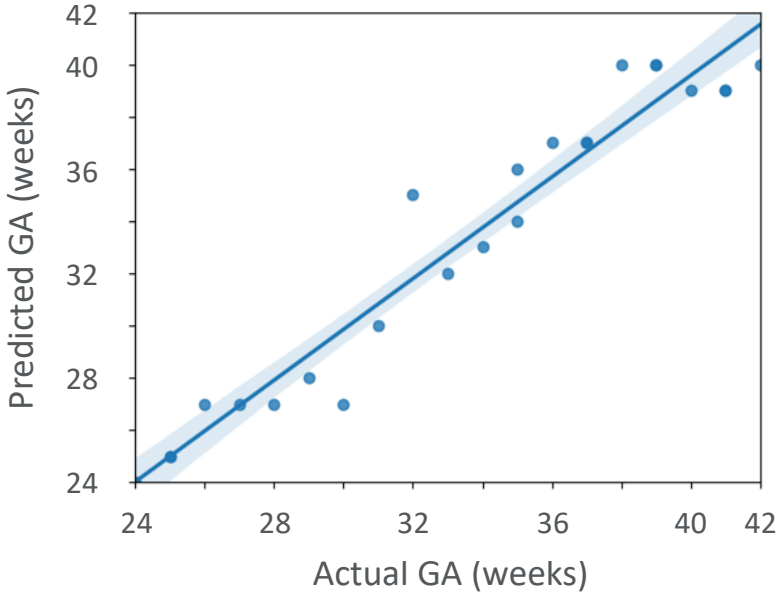
Results - Validation and Test





R^2	MAE (weeks)	Correct within 3 weeks
0.9444	1.0847	24/24

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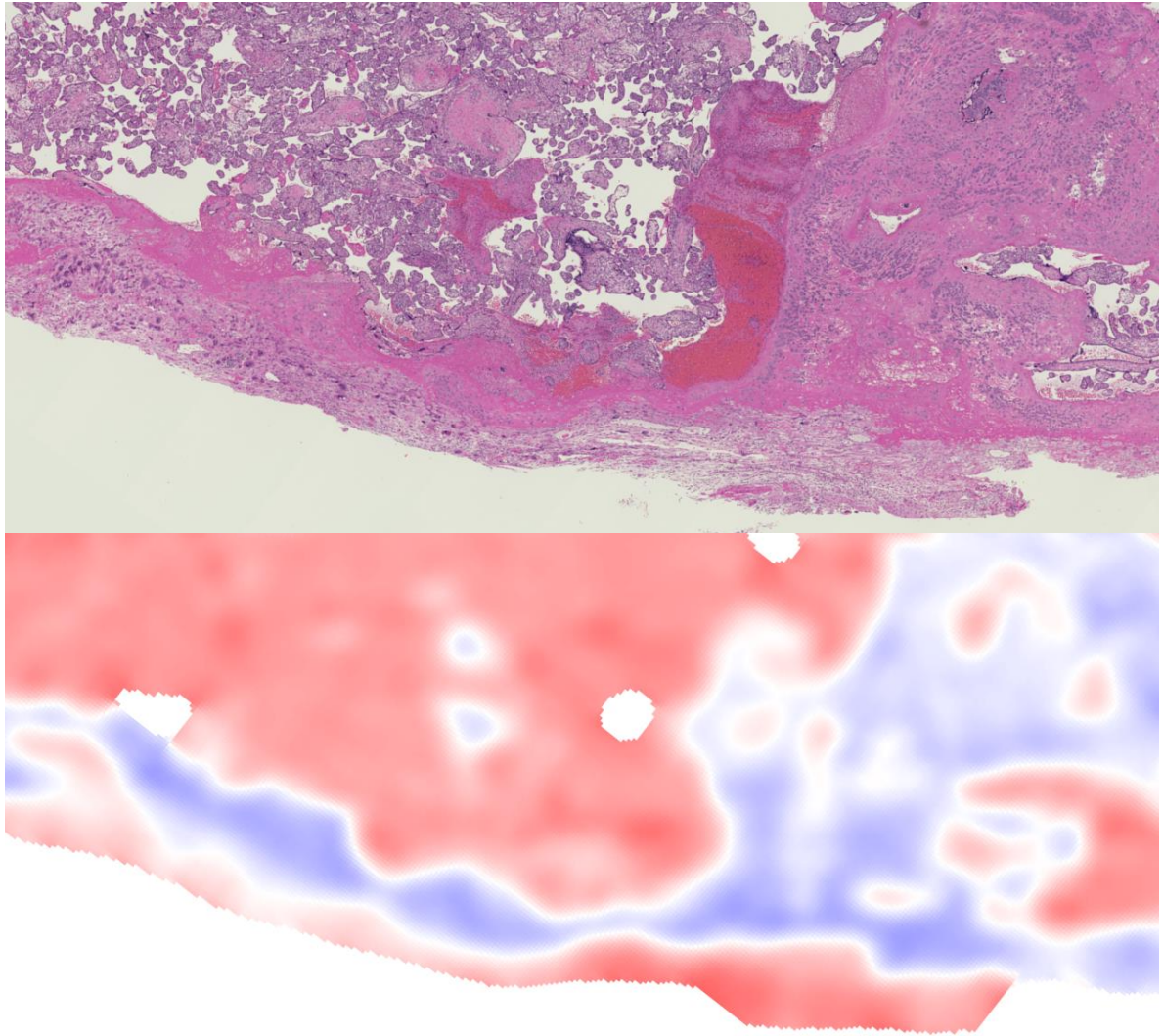
Attention

Whole slide
Red: +’ve attention – villi
Blue: -’ve – large vessels, basal plate

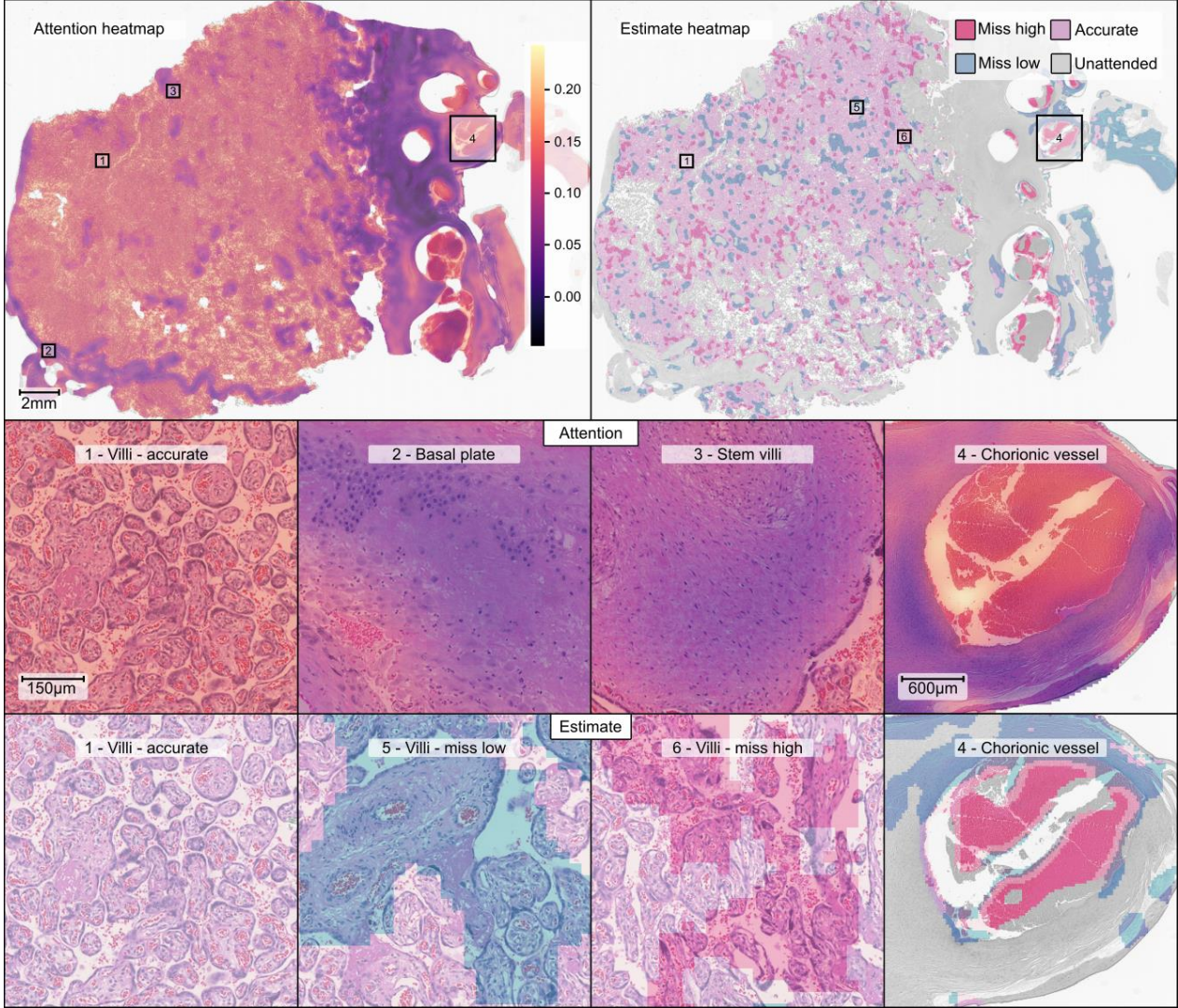
Model implicitly recognizes placental regions: Do we even need ROI?



Whole slide Attention + Estimation

Model implicitly recognizes villi - do we even need ROI? ->
36 new cases, no annotation, whole slide attention + prediction…

R^2	MAE (weeks)	Correct +/- 3 weeks
0.8859	1.3671	34/36



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Summary – gestational age prediction

- Can predict gestational age from microscopic slides with high accuracy
  - Clinical use when GA is unknown
  - Could predict from a single human-selected ROI
  - Quality improvement / improve interobserver variability
  - Utility of Glimpse for aggregation + attention

- Next steps
  - Problems with maturation (preeclampsia, diabetes)
  - Generalizability to different sites
  - Quantitative description of changes during gestation

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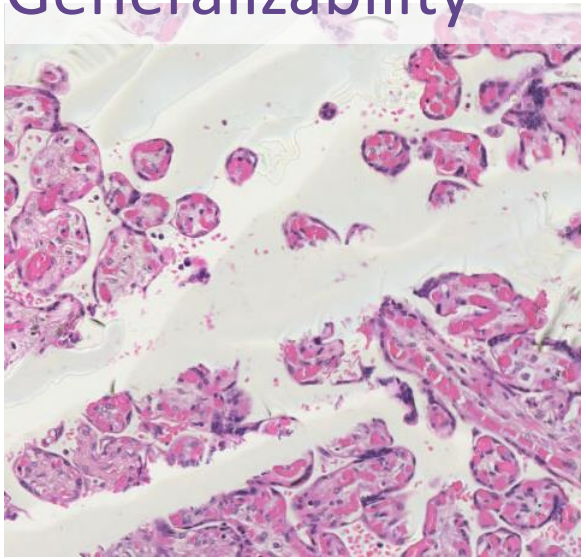
Placenta as a use case

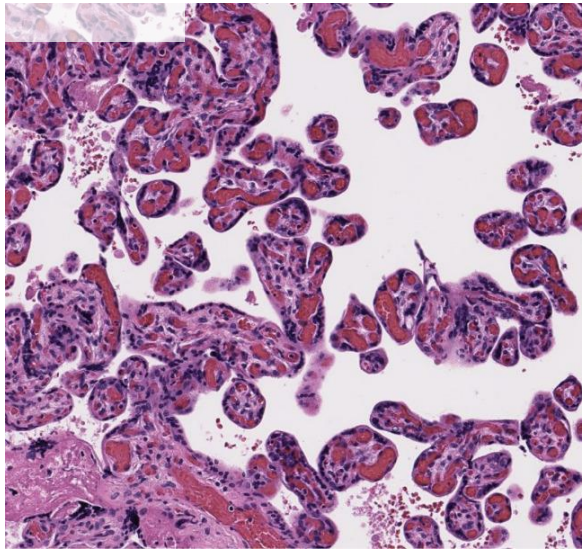
Examining problems in digital pathology and machine learning

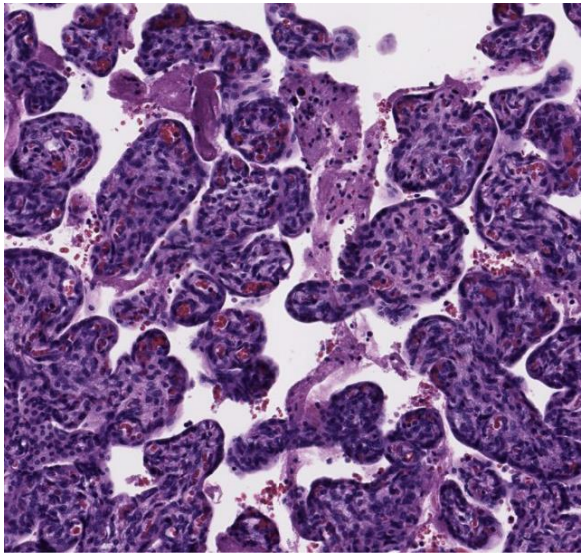
Stress tests

- My data used for training are curated in that
  - All slides from 1 lab
  - Only good quality slides are used
  - “Representative” regions without artifacts are used for analysis
- This won’t hold true for deployment
  - Different labs
  - Different scanners
  - Have to diagnose the slide you have
  - Much interrater disagreement comes from region selection*

Generalizability





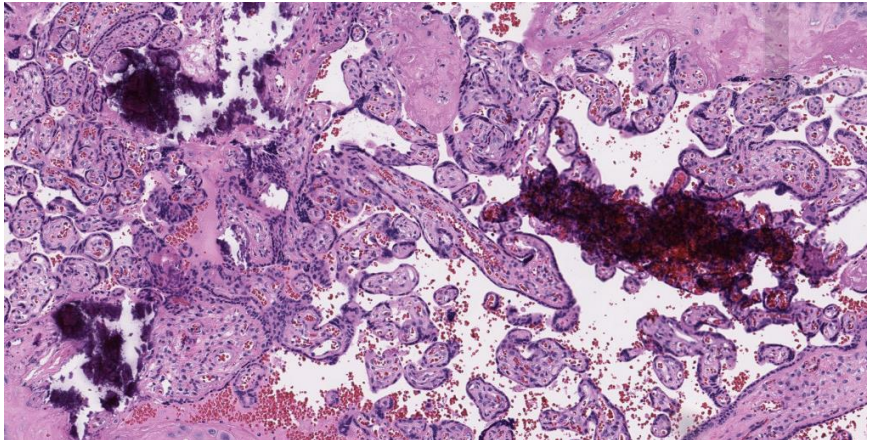


Clockwise from top-left – coverslip wrinkles, tissue scratched; different lab; tissue too thick; tissue folded over, calcifications.

(NU_24_98, CMU_ 14456 A, CMU_ 20838 B, CMU_ 31566 B)

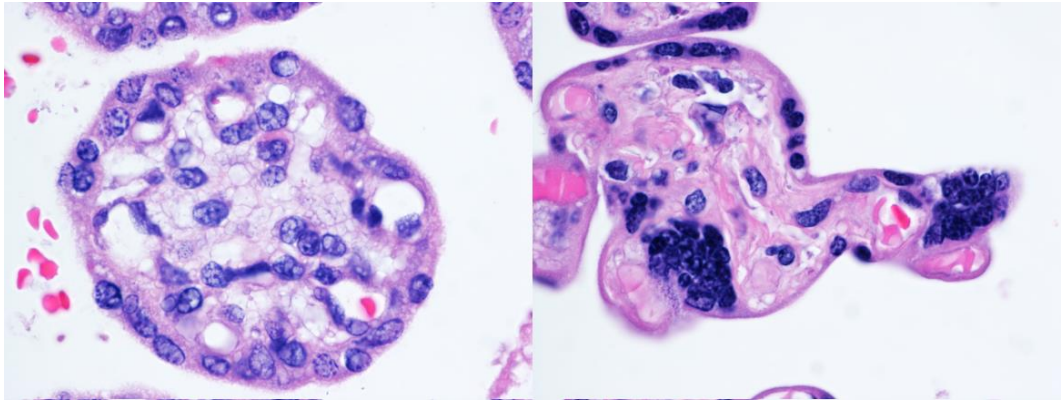
CMU images available from:

(*http://image.upmc.edu:8080/cmu%20placenta%20project/view.apml?*; *Clymer 2020*



Interpretability

- Interpretability (how the model knows what it knows) is not a virtue in medicine
  - Proof – how is hematocrit run?
  - Why not? – test results are always interpreted before diagnosis
  - Human in the loop is standard
- Can these results be made more interpretable?
  - Attention – done – ish
  - Maturation components (knots, stromal density, vessel location etc.)



Acknowledgements

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