How Much Data Do We Need, and Where Do We Get It?

Joe Deasy, PhD
Department of Medical Physics

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Predictive modeling: inputs

- Image features
- Clinical data
- Dose-volume metrics
- Bioarrays

Predictive modeling process

Predictive modeling sources and outputs

Sources
- Planning dose-volume histograms
- Dose-mapping to identify sensitive regions
- Other planning data e.g., segmented structures
- Clinical variables
- Radiomics from
  - Diagnostic imaging workup
  - Planning/simulation scan
  - Daily setup images
- Genomic data
  - Tumor actionable mutations
  - DNA, RNA, copy number variations
  - Key Genomic mutations: BRCA1, BRCA2
  - Germline genome wide association studies
- Pathology: pathomics

Prediction outputs
- Overall survival
- Local control at a given time point
- Risk of complication (NTCP)
- Likelihood of local control (TCP)
- Genetically stratified risk of complications
- Image segmentation
- Cancer subtype
- Likelihood of response to a given cancer drug
- Likelihood of response to immune therapy
- Risk of developing cancer
- ...

The prediction modeling pipeline

Clinical question: Must be comparable!
How do you keep from fine tuning the model too much in attempting to agree with the input data?

Cross-validation!

Set-aside cross-validation costs data that could be used for fitting: so why do it?

**Rigor:** to convince other people (and yourself) that there has been no cheating (‘information leakage’) that informed the ‘hyper parameter’ choices.

For small-ish datasets you can use leave-one-out cross validation as the only validation method.

**Warning:** The entire **supervised** component of the modeling process must be contained within the LOOCV loop, with no prior ‘fiddling’ with the method. Filing a statistical plan works here as well.
Another way to increase rigor: pre-file your statistical analysis plans (Dekker)

Validation is a higher level of the scientific process than discovery...and it is easier!

1. Internal: good cross validation, including feature selection
2. Internal set-aside validation
3. External: same publication
4. External: separate publication/group

Validation is a higher level of the scientific process than discovery...and it is easier!

Better

Traditional statistical rule of thumb:
10 observations per predictor variable.


So for a modest—sized model (~5 or fewer variables), 50 ‘events’ is probably adequate.
Theoretically: if the model/hypothesis is not known, the bound on the error is not simple:

\[ R(h) \leq R_{\text{emp}}(h) + C(\mathcal{H},N,\delta) \]

\[ R(h) \leq R_{\text{emp}}(h) + \sqrt{\frac{8d_{\text{esc}}(\ln \frac{2m}{d_{\text{esc}}} + 1) + 8 \ln \frac{4}{\delta}}{m}} \]


If the model to be tested is known (Hoeffding’s inequality):

This is why validation with a fixed hypothesis is so much easier!

Epsilon is a given bound on the error
m is the size of the dataset
h is a given model/hypothesis

Radiomics: “Immunotherapy benefit for lung cancer patients is associated with tumor heterogeneity determined from computed tomography radiomic entropy feature”

Approach:
- measures of heterogeneity predict late (> 1 yr) immunotherapy response.
- 62 NSCLC patients treated with pembrolizumab.
- Four radiomic measures of heterogeneity were extracted from longitudinal CT scans, including entropy of values over small patches.
- High entropy implies neighboring voxels are relatively dissimilar in intensity.

Key result:
- High entropy at first treatment scan predicts durable response.
- The change in entropy from baseline is more important than baseline entropy.

H. Veeraraghavan\textsuperscript{1}, M. Hellmann\textsuperscript{2}, K. Ravi\textsuperscript{2}, J. Jiang\textsuperscript{1}, D. Halpern\textsuperscript{3}, A. Snyder\textsuperscript{2}, J. Deasy\textsuperscript{1}, MSKCC Depts. of \textsuperscript{1}Medical Physics, \textsuperscript{2}Medicine, and \textsuperscript{3}Radiology (in review)
Do we know the best machine learning tools for radiomics

- "No," but this is probably less of an effect compared to
  - variability between imaging systems/calibration practices/protocols
  - Data starvation
- Low dimensional modeling should always be tried
- If dataset is particularly rich, higher dimensional data analysis may be justified, with careful control of the risk of overfitting
Combined PET and CT radiomics features predict maximum FMISO uptake in head and neck cancer (Crispin-Ortuzar et al., Radiother. Oncol., 2018)

- FDG PET + contrast enhanced CT to predict maximum FMISO TBR
- 79 training, 42 hold-out validation
- LASSO + 10x10 CV
- Selected predictors:
  - P90 FDG SUV
  - Long run high grey level emphasis in low FDG subregion
- Validation AUC = 0.83 (Medical Physics, 2018) N=72
Prediction accuracy for IDC subtype was 81.4%
A key was augmenting the learning dataset with simulated data.

N=474, training
324, testing (NSCLC)
231, testing (H&N)
7 cohorts

Note the emphasis on reproducible features and dimensional reduction!
• 989 patients, 5 institutions
• treated with 3DCRT or IMRT to
• 70-86.4Gy@1.8-2.0Gy/fraction
**Training dataset**
- 243 samples
- 49 events
  - 740 50Ks (p < 0.001; Chi-square test)
- Validation dataset
  - 122 samples
  - 25 events

**Random Forest**

**Dataset for RB**
- Outcome: rectal bleeding
  - RTSG ≤ 1 (coded 0) vs RTSG ≥ 2 (coded 1)
- Data split: rectal bleeding
  - Training dataset
    - 243 samples
    - 49 events
    - 740 50Ks (p < 0.001; Chi-square test)
  - Validation dataset
    - 122 samples
    - 25 events
- 5-fold CV or bootstrapping with 100 iterations
- Additive model
  - Coded as the number of rare alleles
Results for RB using validation data

- Low risk: 2/40
- High risk: 13/42

“Deep learning enables fully automatic tumor segmentation and synthesis of MRI from CT images”

- Successfully segmented 1300 NSCLC tumors from three datasets irrespective of tumor size, location, and malignancy.
- Our method learns to synthesize MRI from CT images by training with highly limited number of MRI (n=9) with unrelated CT scans (n=300).
- Our method has auto-segmented largest number of lung tumors published.
- Awarded Best in Physics, AAPM 2018.

Slide courtesy: Harini Venkatakrishnan, Jue Jiang
The Computational Environment for Radiotherapy Research (CERR)

- Custom software extracts dose, volume, and structure data automatically
- [http://www.github.com/cerr/CERR](http://www.github.com/cerr/CERR)

Radiomics Image Quantifier (RIQ) Toolbox in CERR, Aditya Apte et al.

[www.github.com/cerr/CERR](http://www.github.com/cerr/CERR)

Different ways to compute Haralick entropy lead to different feature maps.
...it depends on the predictive modeling activity

- High dimensional modeling on binary data: > 75 events/ total N>200
- Low dimensional modeling on binary data: > 50 events/ total N>100
- Low dimensional modeling on continuous data: Total N>75
- Fixed hypothesis testing (H<3): > 25 events/ total N>50
- Independent model validation/testing: > 25 events/ total N>50

Source: PERSONAL OPINION BASED ON 15 yrs. MODELING EXPERIENCE (obviously a needed area of research!)