QUANTITATIVE EVALUATION OF BIOPHYSICAL MODELS OF THE DIFFUSION WITH IN VIVO DATA BY ASSESSMENT OF THE GENERALIZATION ERROR

Benoit Scherrer[1], Maxime Taquet[1], Mustafa Sahin[1], Sanjay P. Prabhu[1], and Simon K. Warfield[1]

[1] Boston Children's Hospital, 300 Longwood Avenue, Boston, MA, 02115, USA

PURPOSE.

- Biophysical models: describe the MR signal formation with a model whose parameters reflect the underlying biophysical mechanisms
- Of crucial interest to characterize and compare tissue properties
  - In disease: in vivo biomarkers for diagnosis, prognosis, tailored intervention and evaluation of success of therapy
  - To study normal brain development
- How to <u>quantitatively</u> evaluate various generative models? An open question

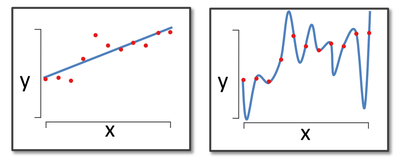
- Common approach

Fitting error + Penalization term

Quality of fit — To avoid overfitting

(With noise, a more complex model will always fit the data better)

e.g.
- Bayesian Information Criterion (BIC)
- Aikake Information Criterion (AIC)
  Asymptotically optimal (Unlike BIC)

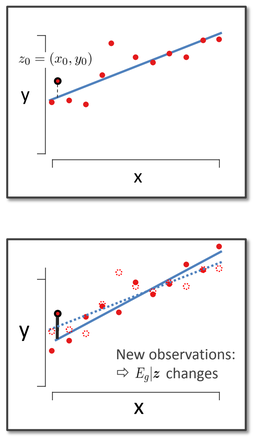


HYPOTHESIS: A BIOPHYSICAL MODEL THAT WELL CAPTURES THE UNDERLYING BIOPHYSICAL MECHANISMS OUGHT TO ACCURATELY PREDICT THE SIGNAL FOR NEW GRADIENT DIRECTIONS AND STRENGTHS.

ASSESSMENT OF THE GENERALIZATION ERROR.

$$\boldsymbol{z} = \{z_1, ..., z_n\}, z_i = (x_i, y_i)$$

x_i Input b-values, gradient directions → Biophysical Model $r_{\boldsymbol{z}}(x)$ → Output DW signal attenuation y_i



Generalization error conditional on the observed data:
Error made for a new hypothetical data point z_0

$$E_g|\boldsymbol{z} = E_{z_0 \sim F}\left[|y_0 - r_{\boldsymbol{z}}(x_0)|^2 \middle| \boldsymbol{z}\right]$$

$$E_g| \cdots = E_{\bullet \sim F}\left[|-|^2 \middle| \cdots \right]$$

Unconditional generalization error

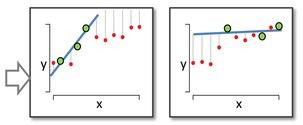
To take into account variability of the observed data points

$$E_g = E_{\cdots \sim F}\left\{E_g| \cdots\right\} = E_{\cdots \sim F}\left\{E_{\bullet \sim F}\left[|-|^2 \middle| \cdots \right]\right\}$$

$$E_g = E_{z_i \overset{\text{iid}}{\sim} F}\left\{E_g|\boldsymbol{z}\right\} = E_{z_i \overset{\text{iid}}{\sim} F}\left\{E_{z_0 \sim F}\left[|y_0 - r_{\boldsymbol{z}}(x_0)|^2 \middle| \boldsymbol{z}\right]\right\},$$

But *F* is unknown

Estimation of the generalization error
- Leave-one-out: low bias but high variance
- K-fold cross validation: lower variance but higher bias
- Better approach:



632 Bootstrap estimation of the generalization error

Efron, B., Estimating the Error Rate of a Prediction Rule : Improvement on Cross-Validation, Journal of the American Statistical Association, 1983. 78(382): p. 316-331.

Counteract negative bias of fitting error with positive bias of the bootstrap estimate

$$\hat{E}_g^{632} = \underbrace{0.368\,\hat{E}_g^{\text{fit}}}_{\text{Bias<0}} + \underbrace{0.632\,\hat{E}_g^{\text{BS}}}_{\text{Bias>0}}$$

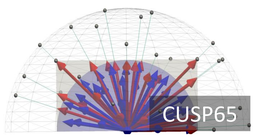
Bias≈0

Was shown to have low bias and low variance [Efron1983]

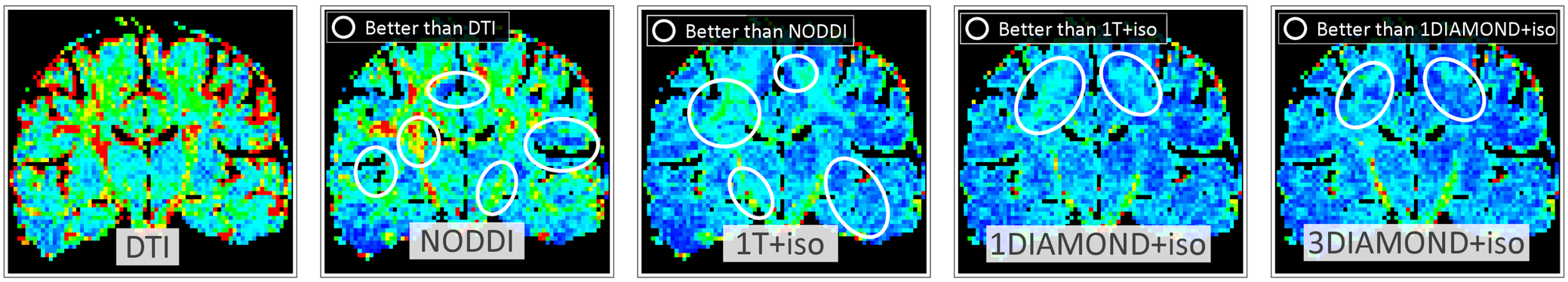
$$\hat{E}_g^{\text{fit}} = \frac{1}{n}\sum_{i=1}^{n} |y_i - r_{\boldsymbol{z}}(x_i)|^2 \qquad \hat{E}_g^{\text{BS}} = \frac{1}{n}\sum_{i=1}^{n}\left[\sum_{b=1}^{B}\delta(N_i^b)\left|y_i - r_{\boldsymbol{z}^*_{(-i)}}(x_i)\right|^2 \Big/ \sum_{b=1}^{B}\delta(N_i^b)\right]$$

N_i^b: Number of times sample *i* is used in the training set of the b[th] bootstrap replicate

RESULTS



- We evaluated five biophysical model of the diffusion
- CUSP65 acquisition - FOV=240mm, matrix-size=128x128, 68 slices, resolution=1.8x1.8x2mm3, TE=78ms, TR=10.1s, ~12min acquisition time
  Provides a large number of different b-values between 1000s/mm² and 3000s/mm² with low TE and high SNR.
- Generalization error estimated with B=300 bootstrap iterations



	Mean Generalization Error
1T	57.72
NODDI	41.20
1T+iso	28.93
1DIAMOND+iso	26.54
3DIAMOND+iso	26.37

NODDI: Zhang H, Schneider T, Wheeler-Kingshott CA, Alexander DC, NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain, Neuroimage, 61(4), 1000-16, 2012 DIAMOND: Scherrer B., Schwartzman A., Taquet M., Prabhu S.P., Sahin M., Akhondi-Asl A., Warfield S.K., Characterizing the DIstribution of Anisotropic MicrO-structural eNvironments with Diffusion-weighted imaging (DIAMOND)., Proc. of the 16th Int Conf Med Image Comput Comput Assist Interv (MICCAI)(8151), Nagoya, Japan, 2013, 518-526

Fig.a - DTI is the worst predictor of the diffusion signal

Fig.b - NODDI provides a lower generalization error in regions of crossing and close to the cortex because models the fascicle dispersion in each voxel and accounts for freely diffusing water.

Fig.c - 1T+iso better predicts the signal than NODDI. This is likely because a number of parameters are fixed in NODDI (fixed parallel diffusivity, no radial diffusivity)

Fig.d - Accounting for the heterogeneity of each compartment (DIAMOND) slightly improves the generalization error in regions of crossings.

Fig.e - Accounting for each fascicle in each voxel and accounting for the compartment heterogeneity leads to the smallest generalization error

CONCLUSION

- Novel framework to achieve quantitative evaluation of biophysical models of the diffusion with in-vivo data.
- Characterizes how well each model predicts unseen data
- Identify the model that best captures the underlying biophysical mechanisms for the data at hand