Error Assessment in Serial Morphometry: Application to Multiple Sclerosis

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Outline

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Background

- The measurement of brain atrophy has become an established method of estimating MS disease severity and progression.
- The atrophy is quantified by MRI morphometric measurements such as brain parenchymal fraction (*BPF*).
- Atrophy is a slow process and thus requires high level of measurement precision/sensitivity.

Background

- The reliability of *BPF* and other morphometric measurements is frequently measured with scan-rescan experiments.
- In scan-rescan experiments two MRI's of the patient are obtained within a short interval (e.g., 30 minutes).
- Between the two imaging sessions patients may be asked to exit and re-enter the scanner area
- In the absence of true biological/structural change, any differences in the measurements from the two scans is attributed as measurement precision.

Sources of error

Principal sources of error are:

1. Patient re-positioning error
2. Instrument variability (e.g., magnet and/or receiver coil)
3. Algorithm specific errors (e.g., stochastic algorithms or nonlinear algorithm transfer function)

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Problem Statement

Questions:

- Is scan-rescan error a reliable indicator of real-life error?
- Can we analyze reliability of the scan-rescan error ?
- For a given image segmentation algorithm, how much change in BPF indicates “real change” ?
- Various techniques exist for error assessment: which one has greatest practical utility ?

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Datasets Used

- 20 MS patients
- 5 MRI per patient (baseline MRI plus 4 weekly MRIs each) .
- Axial dual-echo PDw/T2w protocol on a 1.5T
- Acquisition parameters
  - TE 30/80 ms, TR = 3000 ms
  - resolution: 0.93-by-0.93-by-3 mm
- None of the patients had received any form of therapy or steroids.

Image analysis

- Template-driven segmentation algorithm (TDS) used for image segmentation
- Segmentated classes: White matter (*WM*), Gray matter (*GM*), Cerebro-spinal fluid (*CSF*).
- Brain Parenchymal Fraction (BPF) was computed as:

$$BPF = \frac{WM + GM}{WM + GM + CSF} = 1 - \frac{CSF}{ICC}$$

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Error assessment techniques

We compare the following three methods to analyze measurement error:

1. Standard error of measurement
2. Voxel-wise classification consistency
3. Intra-class correlation coefficient: a measure of agreement

Standard error of measurement (*SEM*)

$$SEM = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\sigma_i^2}, \text{ where } \sigma_i = \sqrt{\frac{1}{M-1}\sum_{j=1}^{M}(x_{i,j}-\mu_i)^2}$$

M : no. of observers, N : no. of subjects

$x_{i,j}$: measurement made by observer j for subject i

Given the *SEM*, the threshold value (δ), that represents 95% of change beyond chance is:

$$\delta = \sqrt{2} * 1.96 * SEM$$

δ is the threshold's which signify "real change" (with 95% certainty).

Voxel-wise classification consistency

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Voxel-wise classification consistency

Intra-class correlation coefficient

$$ICCoeff = \frac{\text{variability in the BPF measurements of patients}}{\text{Total variability (from all sources)}}$$

$$ICCoeff = \frac{MS_R - MS_E}{MS_R + (k-1)MS_E + \frac{k}{n} \cdot (MS_C - MS_E)}$$

n denotes the number of images, MS_R is the mean square error between images, MS_E is the residual mean square error, MS_C is the mean square error between observers.

Table: Interpretation of ICCoeff

ICCoeff value	Strength of Agreement
ICCoeff < 0.4	Indicates poor reproducibility
$0.4 <$ ICCoeff < 0.75	Indicates fair to good reproducibility
ICCoeff > 0.75	Indicates excellent reproducibility

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Pair-wise comparisons of MR scans

Table: *SEM* and δ values for *BPF*, *WM* and *GM* for each of the four pair-wise comparisons. bMR denotes the baseline MRI.

		Pair of time-points compared			
		bMR & week 1	bMR & week 2	bMR & week 3	bMR & week 4
BPF	*SEM*	0.0040	0.0048	0.0057	0.0055
	δ	0.0111	0.0134	0.0157	0.0154
WM	*SEM*	0.0046	0.0050	0.0053	0.0054
	δ	0.0128	0.0138	0.0146	0.0149
GM	*SEM*	0.0045	0.0055	0.0042	0.0044
	δ	0.0126	0.0151	0.0116	0.0122

Note for scan-rescan experiment: $SEM = 0.0020$, $\delta = 0.0056$

Comparison across multiple MR scans

Table: *SEM* and δ values for *BPF*, *WM* and *GM* variables obtained by comparing the measurements of these variables from multiple MR scans.

		No. of MRIs compared			
		2	3	4	5
BPF	*SEM*	0.0040	0.0045	0.0047	0.0048
	δ	0.0111	0.0125	0.0130	0.0133
WM	*SEM*	0.0046	0.0048	0.0046	0.0047
	δ	0.0128	0.0133	0.0127	0.0130
GM	*SEM*	0.0045	0.0049	0.0043	0.0042
	δ	0.0126	0.0135	0.0120	0.0115

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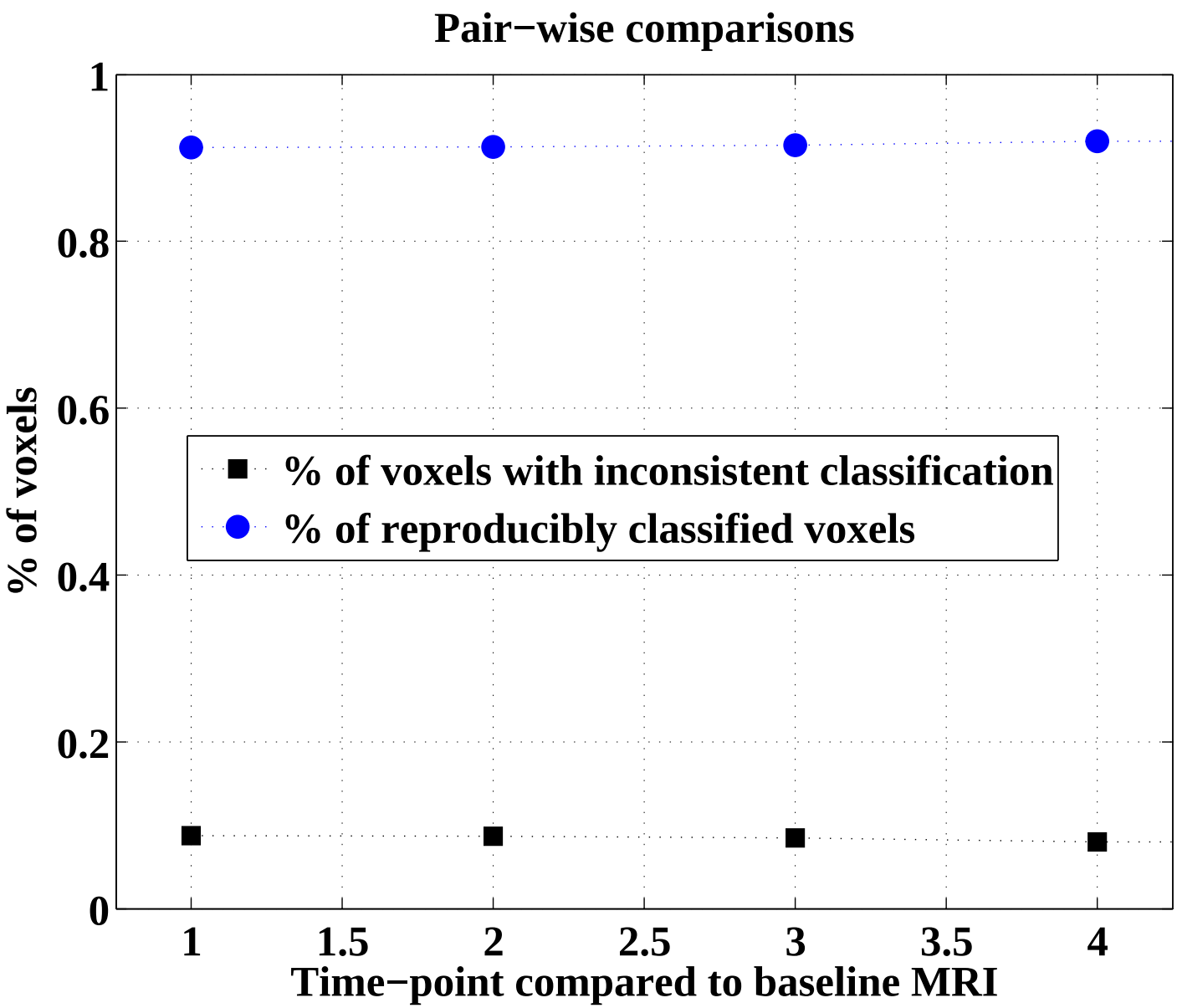
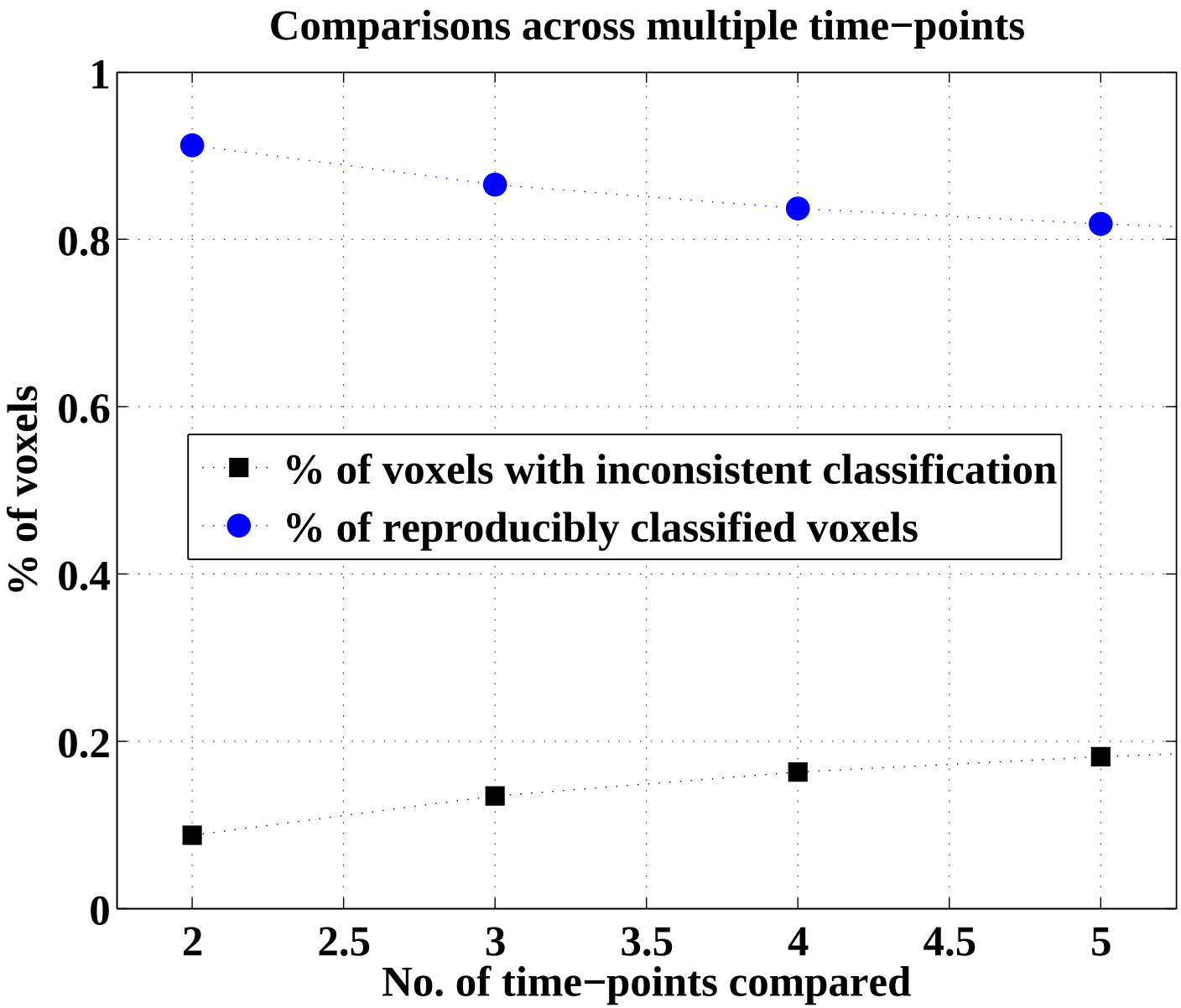

Pair−wise comparisons
% of voxels
1
0.8
0.6
0.4
0.2
0
% of voxels with inconsistent classification
% of reproducibly classified voxels
1
1.5
2
2.5
3
3.5
4
Time−point compared to baseline MRI


Comparisons across multiple time−points
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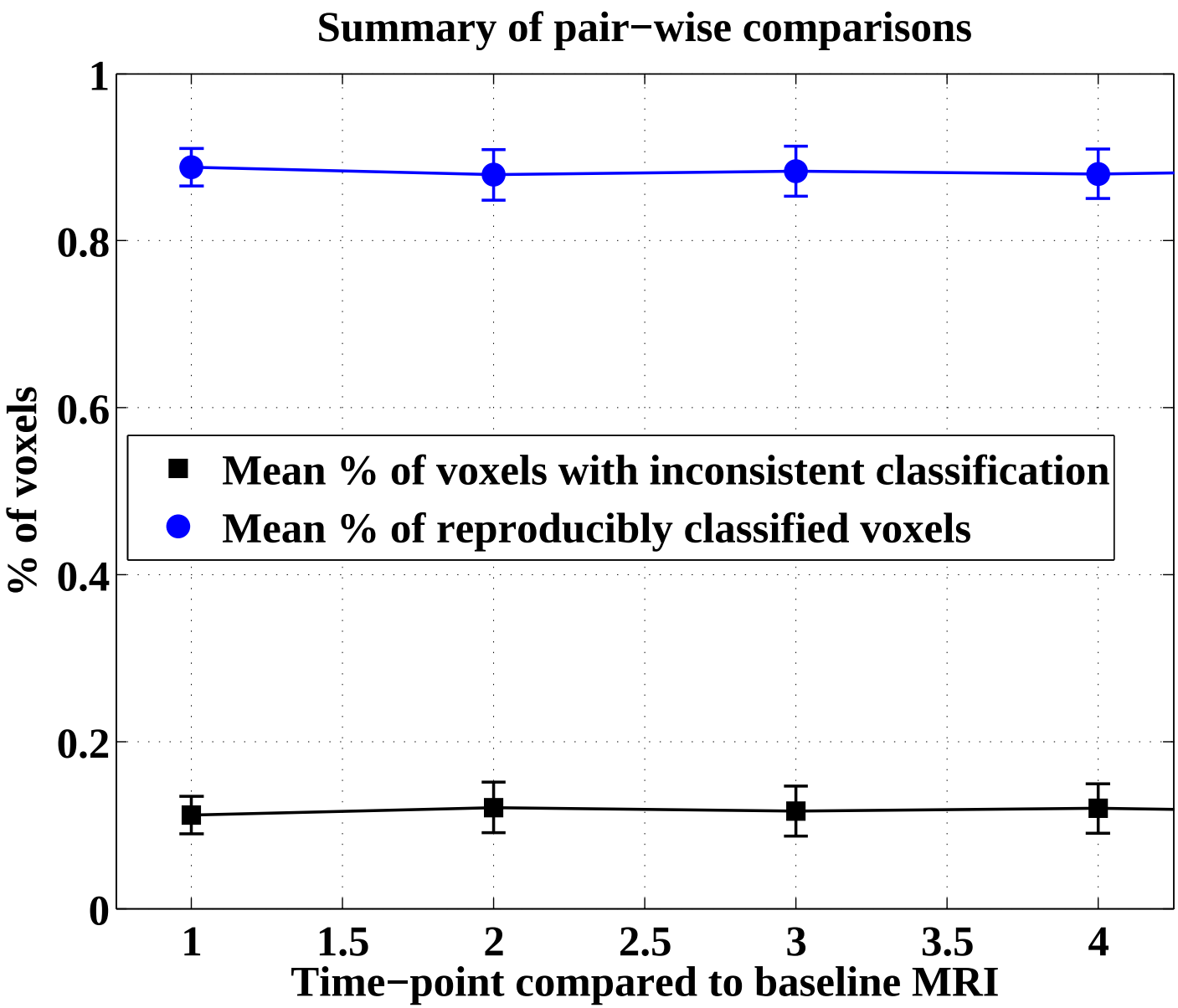
3.5
4
4.5
5


Summary of pair−wise comparisons
% of voxels
Time−point compared to baseline MRI
Mean % of voxels with inconsistent classification
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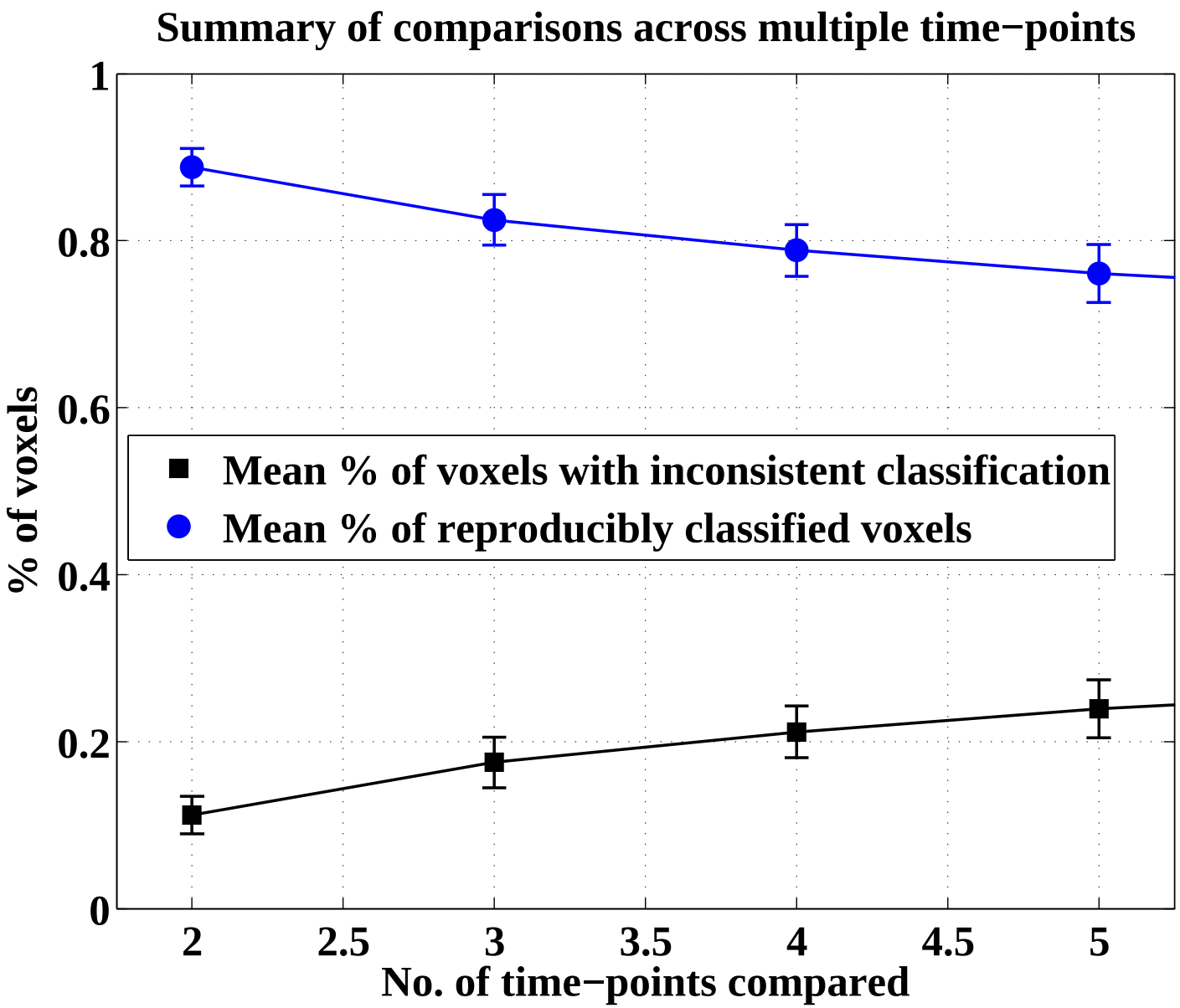
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Results

Table: *ICCoeff* for *BPF*, *WM* and *GM*, for each of the four pair-wise comparisons. bMR denotes the baseline MRI.

	Pair of time-points compared			
	bMR & week 1	bMR & week 2	bMR & week 3	bMR & week 4
BPF	0.9929	0.9898	0.9851	0.9860
WM	0.9933	0.9926	0.9916	0.9912
GM	0.9373	0.9195	0.9501	0.9448

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Scan-rescan experiments under-estimate measurement error:

- Measurement error in scan-rescan
- Previous work from our group (Wei, 2004) has shown that
  - $SEM = 0.0020$, $\delta = 0.0056$ (Scan-rescan)
  - $SEM = 0.0040$, $\delta = 0.0111$ (two MRI taken a week apart)
  - the *SEM* from weekly measurements is 2 times greater than that from scan-rescan .
- Utility of SEM
  - By comparing various methods to quantify measurement variability we find that the *SEM* demonstrates highest practical utility.
  - SEM is simple to compute and allows one to compute threshold's which signify real biological change (with 95% certainty).

Discussion

Table: *ICCoeff* for *BPF* for each of the four pair-wise comparisons. bMR denotes the baseline MRI.

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- In our example, the scan-rescan *ICCoeff* was 0.998,
- Recall, an *ICCcoeff* > 0.75 denotes excellent agreement.
- Using only the *ICCcoeff* implies that there is no difference in the measurement error computed from a scan-rescan setting versus that quantified from weekly MRI.
- We have two methods which produce very contrasting results.

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Future work

- Obtain or collect a weekly MRI data-set of healthy individuals
- Test the performance of multiple algorithms
- Limitations: Loss of spatial information.

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