

Review on removing variability

Neuroimage processing pipeline

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Purpose of normalization and harmonization

- Impact of technical variability:
 - Brain volume changes
 - Regional cortical thickness
 - Voxel-based morphometry
 - SUVR quantification
- Total variability:
 - Biological variability (desired signal)
 - Technical variability (unwanted signal)

Break down variability (ANOVA point of view)

Class	Source of variability	Cause	Method to reduce variability
Biological	Within-subject	- Subject's anatomic/functional information (Signal)	-
Biological	Between-subject/scan (Cross-sectional effect & Longitudinal effect)	- Cohort's anatomic/functional difference (Signal) - subject's longitudinal drift (Signal)	Structure homogenization: - Intensity-preserved registration
Technical	Within-scanner and Between-subject/scan/voxel (Intensity unit effects)	- Subject positioning - Contrast (uniform, receiver-related non-uniform) - voxel-level Shot noise or Poisson noise (Residual)	Structure homogenization: - Alignment Intensity homogenization: - Intensity normalisation (Rescaling) - Intensity inhomogeneity correction (Bias field correction)
Technical	Between-scanner (Scanner effect)	- Contrast (uniform, tissue-related) - Resolution	Intensity homogenization (or Structure-preserved Harmonization): - Intensity normalisation (standardizing histogram scale, standardizing resolution)

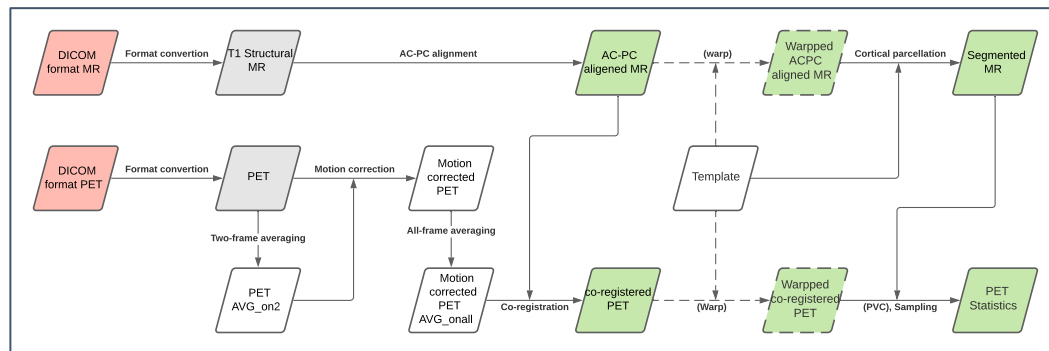
Solutions: Remove technical variability

- **Increment pipeline:** *explainable for every step*

- 1) Intensity inhomogeneity correction
 - Result no bias field
- 2) Alignment:
 - resulting same orientation
- 3) Registration:
 - resulting same structure
- 4) Harmonization:
 - resulting same histogram, intensity scale, resolution

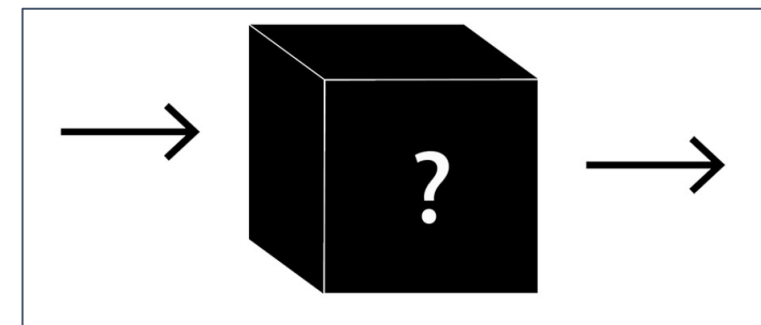
- **End-to-end model:** *black box, explainable when all LEGO are clearly defined*

- 1) Deep model (e.g., GAN)
 - resulting no bias field, same orientation,, structure, histogram, intensity scale, resolution at once



Our standard pipeline

V.S.



Black box

Structure homogenization - Intensity-preserved (MR-specific)

(Recap) MR-to-MR Image registration algorithm	Evolved to match the diffeomorphism assumption from small to large deformation
SPM8 Normalization (Ashburner et al, 2005)	Unified image registration and partitioning algorithm, which is mainly an EM algorithm between warping (bias field and deformations) and classification (Mixture of Gaussians parameter)
Original Shoot (Beg et al, 2005)	LDDMM + Geodesic Shoot that (unidirectionally) deforms an image with a velocity vector field with geodesic conservation of momentum.
SPM8 Dartel (Ashburner, 2007)	Stationary Velocity Field
SPM12 Shoot (Ashburner and Klöppel, 2010)	The efficient optimization scheme via Gauss–Newton optimization
ANTs SyN (Avants et al, 2008)	LDDMM framework with bidirectionally formulates the velocity field with constant arc length constraint
Template-generating algorithm	Natural extension from the pairwise to group registration
Original Shoot (Beg et al, 2006)	Naturally extends LDDMM + Geodesic Shoot from single velocity vector fields to average velocity vector fields
SPM12 Shoot (Ashburner and Friston, 2009)	EM algorithm, by alternating between estimating deformation parameters by multiple tissues with softmax and computing the template.
ANTs SyGN (Avants et al, 2010)	Naturally extends SyN from single image forces to average forces

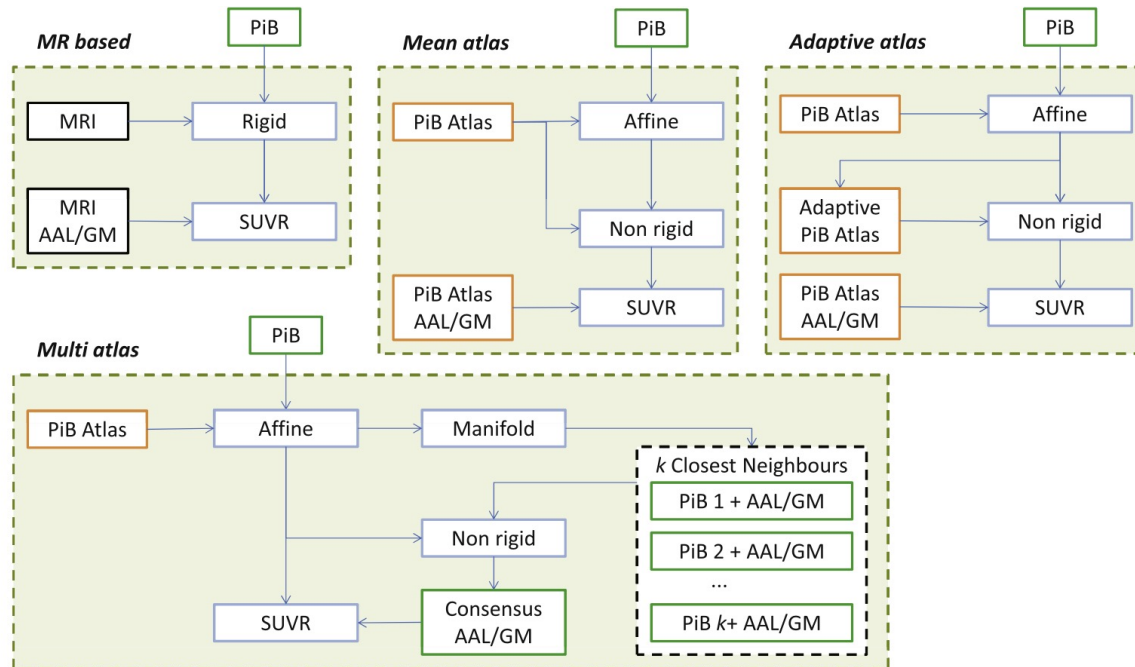
Structure homogenization - Intensity-preserved (PET-specific)

PET-to-PET Image registration algorithm	
Free-From Deformation (Rueckert et al, 1999)	Optimize the Normalized Mutual Information (NMI) to generate the deformation field with cubic B-splines and a control-point spacing.
Template-generating algorithm	<i>(more detail on slide 8, 9)</i>
MR-base template	Standard pipeline (<i>The automatic parcellation and quantification of PiB PET images without any structural information is a complex problem</i>)
mean template (Edison et al. 2013)	All PET images were non-linearly spatially normalised to a PIB PET template
Adaptive template (Fripp et al, 2008)	Generate the subject-specific atlas by optimizing the weight between PiB + and - via maximizing the NMI between the adaptive atlas and the target.
Multi template (Bourgeat et al., 2012)	Reduce the training set to a 2D sample space with manifold embedding, then find the K nearest neighbors of a PET image to compute the consensus parcellations and masks, therefore the subject-specific atlas.
Deep learning approach (e.g., Kang et al. 2018)	Typical GAN style transfer

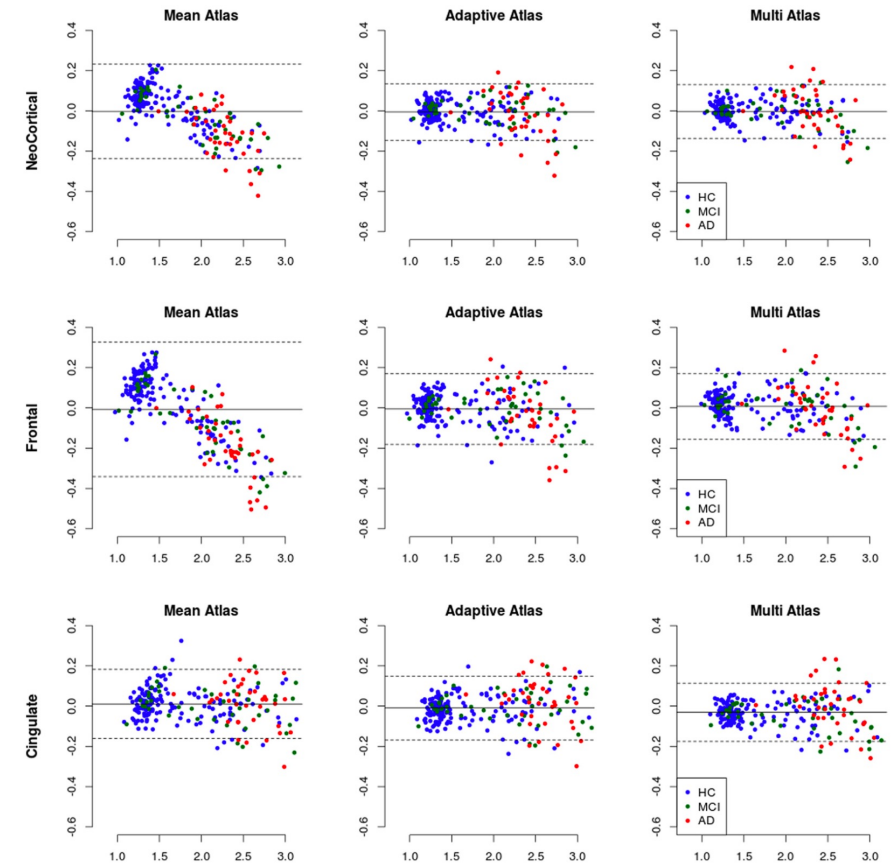
PET adaptive template

Comparison of MR-less PiB SUVR quantification methods (Bourgeat et al. 2015)

- In general, adaptive template seems to be a better choice by considering the trade-off between implementation difficulty and performance.



The flowchart of the four SUVR quantification methods

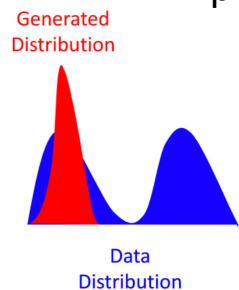


The Bland-Altman plots of three less-MR SUVR quantification methods (by columns) compared to the MR-based quantification as the reference.

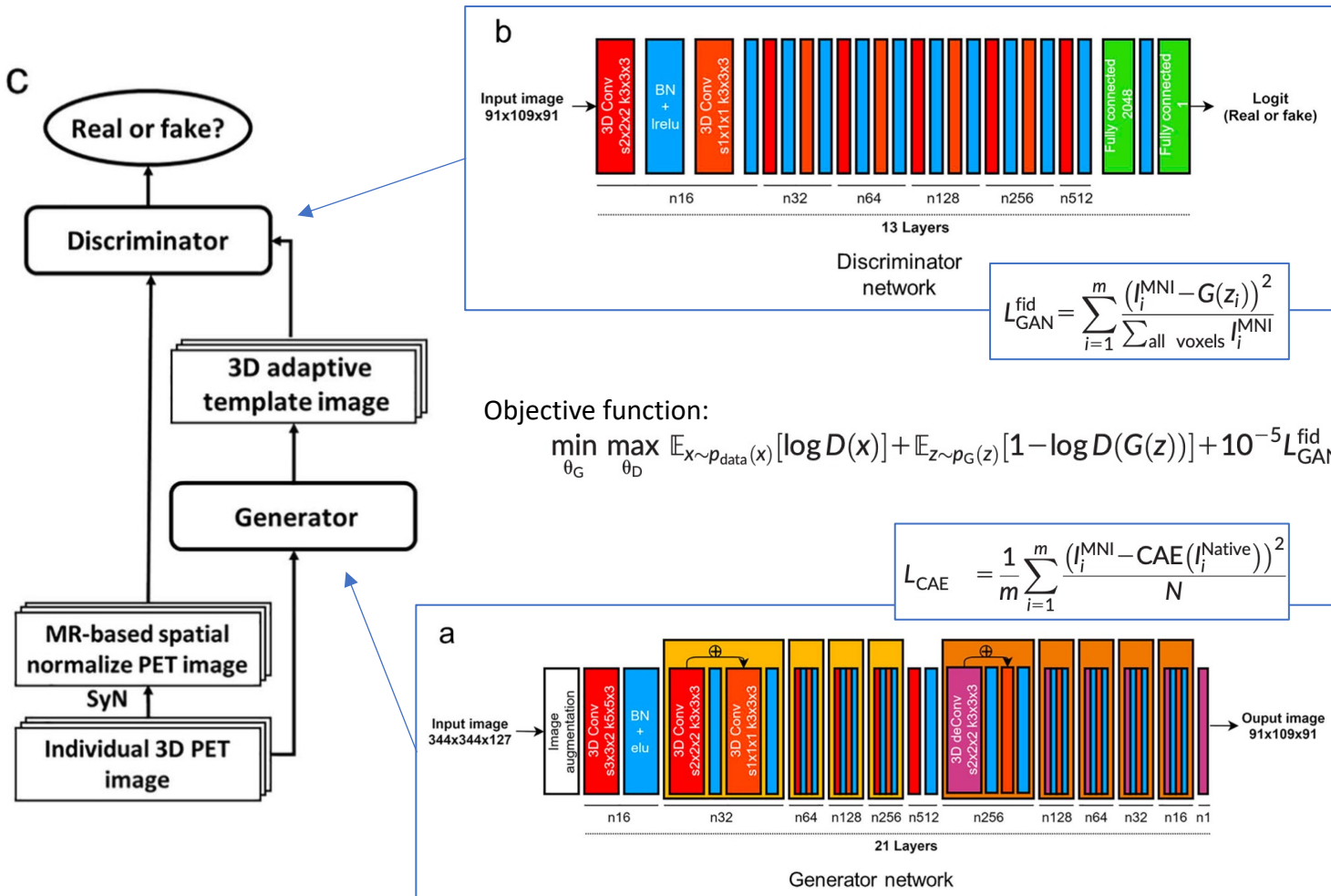
PET adaptive template

Adaptive template generation for amyloid PET using a deep learning approach (Kang et al. 2018)

- An application of GAN style transfer for PET spatial normalization;
- A **black-box** that spatially normalizes original PET to normalized PET image;
- may violate the diffeomorphism (differentiable manifold with differentiable inverse) and symmetry mapping;
- Many potential improvements.
 - Mode (manifold in geometry) collapse problem : need regularize on diversity



Mode collapse problem



Generative Adversarial Network (GAN) framework

Intensity homogenization - Structure-preserved (Harmonization)

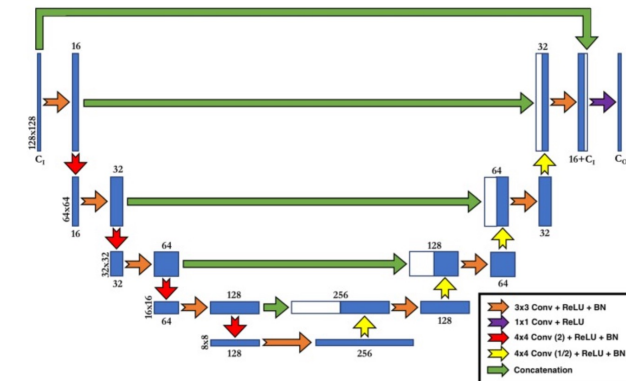
Histogram matching	
white stripe (Shinohara et al 2014)	tissue-specific histogram normalization
Regression	Assuming same structure and resolution, mainly focus on intensity normalization
location (mean) and scale (variance) adjustment	Voxel-wise regression that models the terms for additive and multiplicative scanner effects of scanner i for voxel g .
ComBat (Johnson et al, 2007), modified ComBat (Da-ano et al, 2020)	Developed upon the location/scale adjustment, with empirical Bayes estimation that assumes the parametric forms for prior distributions on the scanner effect parameters to be Normal and Inverse Gamma distribution
Hybrid framework	
RAVEL (Fortin et al, 2016)	identify patterns of variation in the control voxels across subjects (regression), and then assess the degree to which this variation explains the brain-wide intensity distributions (truncated singular value decomposition)
Deep learning	Assuming same structure, suitable on intensity normalization and potential for super-resolution reconstruction
DeepHarmony (Dewey et al, 2019)	deep fully-convolutional neural network based on the U-Net architecture for contrast harmonization
MISPEL (Torbati et al, 2021)	Two-step training: (1) learn the structural information (embeddings) by training both encoder and decoder (2) Intensity normalization with fixed structural information by training only the decoder .

Intensity homogenization – Method comparison

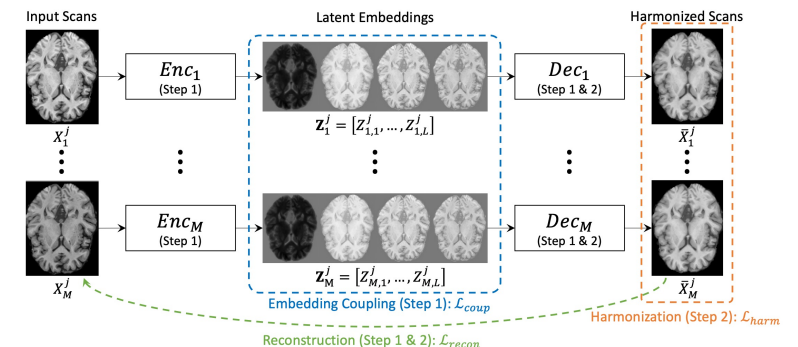
- Both DeepHarmony and MISPEL are black boxes, but MISPEL is more **explainable**.
- Location and scale adjustment model (e.g., ComBat)
 - models the voxel-intensity as mean and scanner effects as residual,
 - then standardize scans by removing scanner-specific residual
- One-step, single U-net (i.e., DeepHarmony)
 - Taking account of **spatial dependency** into normalization, but not necessarily fix the structure
 - Feature extraction via convolution, then reconstruction via deconvolution.
- Two-step, multiple U-net (i.e., MISPEL)
 - share same philosophy as location and scale adjustment model that explicitly **models the scanner effect**, and with considering **spatial dependency** of voxel
 - fixes the mean voxel-intensity for each scanner (structural info) then modify on variance (scanner effect) at voxel level

$$Y_{ijg} = \alpha_g + X\beta_g + \gamma_{ig} + \delta_{ig}\epsilon_{ijg},$$

Location and scale adjustment model



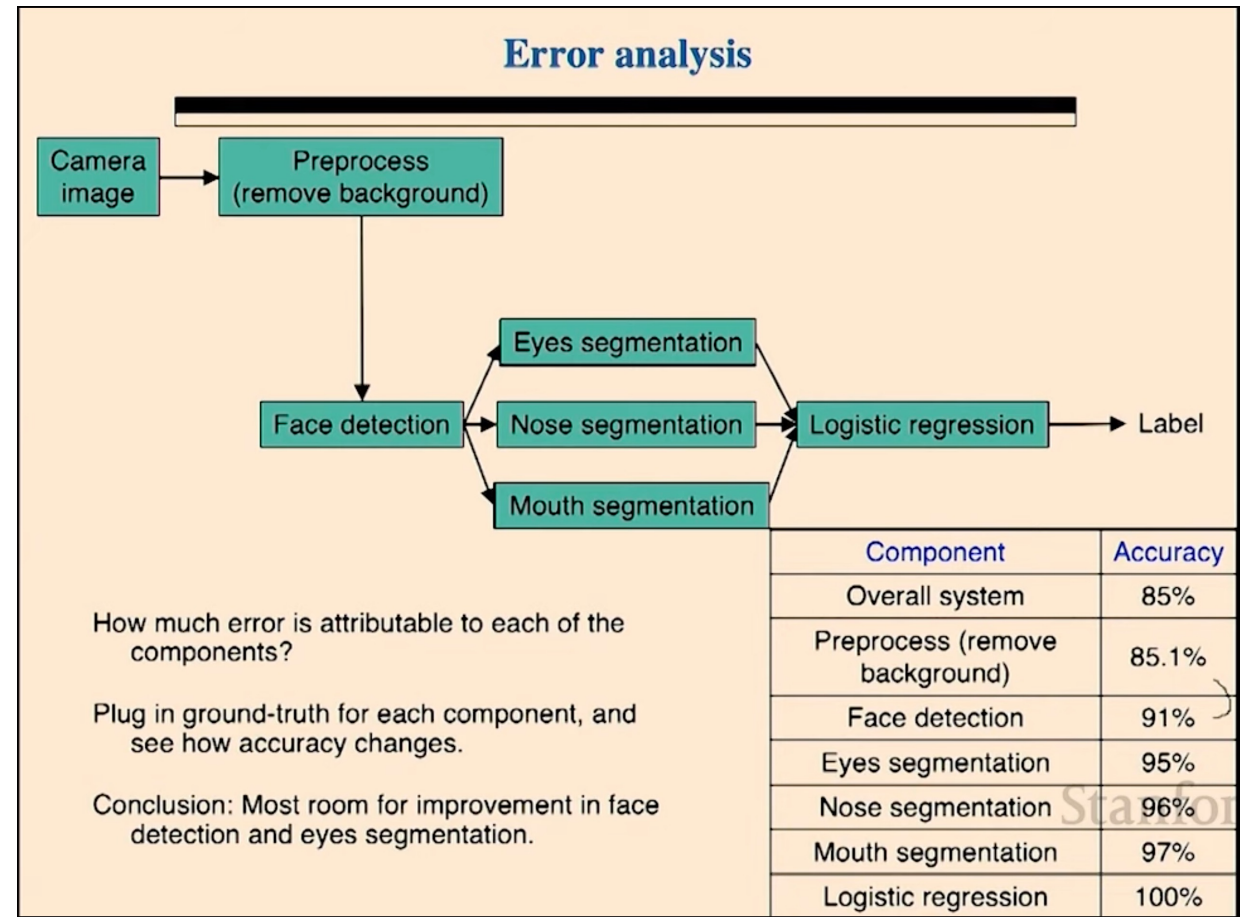
DeepHarmony training schema: a single U-net



MISPEL training schema: one U-Net assigned for each Scanner

Final thought - Diagnosis for big system

- Error analysis
 - Understand functionality of sub-elements and entire pipeline
 - Pin-point the element that gives most improvement
 - Might help to find consensus for the pipeline standard.



Source: Debugging ML Models and Error Analysis, Stanford CS229, Autumn 2018 : Machine Learning