Simple ITK multi atlas registration and segmentation: Methods and tutorials

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Expected cost (include direct and indirect/overhead costs) for the proposed work.

Total cost = \$99,995, Direct cost = \$62,497, Indirect cost = \$37,498

Short description or abstract of the proposed work

We propose to augment Simple ITK with an integrated framework for registration and segmentation of biomedical images. Three components will interact: (1) Scalable registration methods that employ point set representations of *both* fixed and moving images will, for suitable forms of data, allow accurate registration with reduced memory footprint; (2) Registration methods will feed data into classical prior-based image segmentation based on expectation-maximization algorithms; (3) Registration methods will also initialize multi-atlas methods, specifically the class of Joint Fusion multi-atlas segmentation methods. This contribution would extend the applicability of the current ITK version 4 analysis framework to include full image quantification pipelines that are appropriate for diverse application areas such as template-based brain mapping or quantitative high-resolution microscopy. We will provide Simple ITK tutorials, unit tests as well as the necessary JSON and other metadata needed for Simple ITK bindings.

Address of the Offering Institution.

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List of all named personnel/investigators in the proposal

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- James C. Gee, Ph.D., Department of Radiology, University of Pennsylvania.
- Paul A. Yushkevich, Ph.D., Department of Radiology, University of Pennsylvania.
- Nicholas J. Tustison, D.Sc., Department of Radiology and Medical Imaging, University of Virginia (consultant).

Technical Proposal

Purpose of the proposed work

Two fundamental segmentation approaches in medical imaging are:

- Multi-atlas segmentation and
- Bayesian segmentation with priors (anatomical or Markov Random Fields (MRF)).

Whereas the latter has a significant developmental history spanning 30+ years, the former has seen extreme interest in the medical imaging community recently due to the general success of crowdsourcing solutions to problems. Although other segmentation approaches are well-represented within the Insight Toolkit and SimpleITK (e.g., region growing and level sets), these popular segmentation approaches are glaringly absent. This proposal aims to remedy this deficiency.

In addition, we propose to provide two complementary items to the Insight Toolkit and SimpleITK:

- sparse registration and
- spatially adaptive patch-based denoising.

Since image registration is a crucial prerequisite for both prior-based segmentation approaches, the former serves to extend current ITK functionality to accommodate large images (e.g., microscopy) in mapping spatial priors. The latter will augment the current patch-based denoising ITK framework for efficient data cleaning—another crucial prerequisite for well-performing segmentation algorithms.

Multi-atlas segmentation/labeling

Expert anatomical labelings are critical to the interpretation and statistical analysis of biomedical images. However such expert labeling is both expensive and time consuming to obtain. For example, in the biomedical imaging domain, such annotations may exist at different scales from labeling cell types in histology to labeling microscopic structures in optical images all the way up to millimeter or centimeter scale neuroanatomy visible in MRI or CT. These digital annotations attached to biomedical images can take several hours to several weeks or more in order to create. Given these constraints, such annotations are often out of reach for many research g roups and institutions due to lack of local expertise and/or funding to hire such expertise. As an alternative, public data libraries of expert annotations, often exploited within a multi-atlas labeling context (see below), are becoming increasingly more commonplace. Therefore, it is of critical importance that such resources, both in terms of publicly available annotations and software, are distributed in a maximally beneficial way (e.g., ITK and SimpleITK for software distribution).

Multi-atlas labeling (MAL) is the current state-of-the-art for propagating expert labelings from a reference atlas library onto new instances of unlabeled data. The typical procedure for multiple atlas fusion involves three common steps regardless of the underlying method:

1. Normalization of the reference atlas grayscale images to the target image,
2. Transformation of the atlas segmentations to the target image, and

3. statistical prediction of the target segmentation.

In other words, image registration is used to align the atlas library (images + segmentations) to a common space. A statistical model is then used to combine the "guesses" from all the normalized atlas labels to provide a "best guess" estimate of the target labeling. Given a set of input data, factors which most heavily influence the quality of this optimal estimate are: 1) image registration accuracy and 2) the chosen statistical model. See, for example, the recent MICCAI 2012 Grand Challenge and Workshop on Multi-Atlas Labeling).[1]

The joint fusion (JF) algorithm of [1, 2] is one of the top performing MAL algorithms. JF is capable of predicting anatomical labels with accuracy that rivals expert anatomists [3]. It has proven its effectiveness in lung [4], cardiac data, the human brain [5], and in multiple modality canine MRI. Currently this technology is available through an ITK-style C++ implementation which can be found within Advanced Normalization Tools (ANTs).

Bayesian segmentation with anatomical and/or MRF priors

Early statistically-based segmentation work appropriated NASA satellite image processing software for classification of head tissues in 2-D MR images [6]. Following this work, many researchers adopted statistical methods for n-tissue anatomical brain segmentation. The Expectation-Maximization (EM) framework is natural [7] given the "missing data" aspect of this problem. The work described in [8] was one of the first to use EM for finding a locally optimal solution by iterating between bias field estimation and tissue segmentation. Core components of this type of work is the explicit modeling of the tissue intensity values as statistical distributions [9, 10] and the use of MRF modeling [11] for regularizing the classification results [12]. A more formalized integration of generic MRF spatial priors was employed in the work of [13], commonly referred to as FAST (FMRIB's Automated Segmentation Tool), which is in widespread use given its public availability and good performance. Recently, reseachers have begun to rely on spatial prior probability maps of anatomical structures of interest to encode domain knowledge [14, 15] by providing spatial prior probability maps and an initial segmentation. Although this particular segmentation framework has significant application in the neuroimaging domain, it has also applicable to other domains such as breast MRI [16, 17] and functional ventilation of the lung [18].

However, despite the numerous algorithms and other developments which have been proposed over the years, there are an extremely limited number of software implementations to perform these types of segmentations *including within the Insight Toolkit and SimpleITK*. This lack within the segmentation community inspired us to create our own Bayesian-based segmentation framework [19] (denoted as Atropos) which we made publicly available within our own ANTs repository. The modular nature of this particular implementation would fit within the parameters of the ITK library.

Sparse image registration

Big data concerns not only affect the number of data sets for processing but also concern the size of the data sets. For image registration, this can involve images which exceed the size and

[1] An interesting note about this competition was that it was meant to evaluate the team's statistical model for combining atlas labelings. Without standardizing the normalization approach by the organizers, the results were somewhat inconclusive although it should be mentioned that the majority of the top ten performing algorithms all used ITK-based ANTs registration.

memory requirement of a typical brain MRI. As developers of the ITK registration v4 framework, we are in a knowledgeable position to extend the existing classes to incorporating sparse image metrics and transforms which are capable of handling sparse information. As part of our previous ITK development efforts, we developed image- and point-based metrics. What we propose in this submission is a hybrid of the two where sparse point-sets are directly sampled from the image voxels along with voxel-specific intensity and gradient information which is then used to drive registration.

Patch-based Denoising

As part of the v4 round of ITK development, a patch-based denoising framework was contributed based on the work described in [20, 21]. Such work is critical for data 'cleaning' prior to subsequent processing such as segmentation or normalization. More recently, an alternative approach to denoising was proposed in [22] which we implemented and put in ANTs. This filter performs well with limited parameter choices to consider and is also relatively fast. We believe that this additional work would provide a much-needed complement to the existing denoising framework as well as the segmentation tools proposed. Similar to the other tools discussed, a denoising application would be easily integrated into SimpleITK and increase the functionality of the toolkit.

This proposal will bring JF to the ITK and SimpleITK user community. We will also document and promote the models with tutorial material that will illustrate the application of JF to template based segmentation of T1-weighted MRI of the brain. Furthermore, we will support the successful and efficient application of JF to both standard size and large datasets via novel improvements to the existing ITK segmentation and registration frameworks. For segmentation, we will add a complete implementation of (spatial) prior-based statistical segmentation via guassian mixture or non-parametric models. This framework will build upon existing ITK resource and will be extensible with other likelihood models. For registration, we will extend the current framework with more memory efficient image data representations. This approach will build upon existing sub-sampling frameworks within ITK version 4 registration to allow registration to be driven by a sparse image representation. This efficent data representation will allow adaptive registration strategies that can be customized for large datasets and will extend the reach of these methods.

- Joint label fusion is a multi-atlas segmentation method.
- It performed well in several recent competitions (SATA 2012, SATA 2013)
- We use it regularly in our studies to build template priors and to label cortical or deep structures in the brain.

  The key difference between joint label fusion and other label fusion methods is that it explicitly considers correlations among atlases, i.e., the dependence matrix, into voting weight assignment to reduce bias in the atlas set.

FIXME stuff about sparse representation

Simple ITK Integration: This proposal may appear ambitious given the modest budget. However, our proposal builds upon existing work within ANTs to make these goals achievable. Primarily, we will port the near-ITK quality existing code into the ITK ecosystem for review by other developers via the Gerrit code review system. We are strongly familiar with this system as the team members, particularly lead developer Nicholas Tustison, regularly contribute to ITK. Thus, the effort, here, will follow a natural progression:

- Augment existing ANTs classes that implement prior-based and JF segmentation with ITK-style tests;
- Pass these for review to Gerrit;
- Implement code refactoring/documentation requested by ITK core;
- Implement appropriate wrapping, documentation and metadata for Simple ITK.

Beyond these first steps, we will also (most importatly, perhaps) implement step-by-step tutorial material based on the Simple ITK platform. We feel this is best illustrated with examples of this tutorial material which follows here.

As mentioned previously, much of the functionality that we are proposing already exists in an ITK-style format within ANTs. Specifically, the following ITK-style filters exist within the current ANTs repository:

- MAP-MRF segmentation ITK-style classes (details found in [19]):
  - `AtroposSegmentationImageFilter`
  - `ListSampleFunction` (parent class—sample probability estimation)
    - `GaussianListSampleFunction`
    - `HistogramParzenWindowsListSampleFunction`
    - `JointHistogramParzenWindowsListSampleFunction`
    - `JointHistogramParzenShapeAndOrientationListSampleFunction`
    - `LogEuclideanGaussianListSampleFunction`
    - `ManifoldParzenWindowsListSampleFunction`
    - `PartialVolumeGaussianListSampleFunction`
  - `ListSampleToListSampleFilter` (parent class—outlier filtering)
    - `BoxPlotQuantileListSampleFilter`
    - `GrubbsRosnerListSampleFilter`
    - `PassThroughListSampleFilter`
- Multivariate multi-atlas fusion (details found in [1, 2]):
  - `WeightedVotingFusionImageFilter`
- Sparse registration
  - `ImageIntensityAndGradientToPointSetFilter`
  - `MeanSquaresPointSetToPointSetIntensityMetricv4`
- Patch-based denoising (details found in [22]):
  - `AdaptiveNonLocalMeansDenoisingImageFilter`

Although these filters are tested frequently within the ANTs framework, certain improvements/modifications would be required before direct integration into the ITK library such as the inclusion of ITK-specific testing protocols.

FIXME Nick can you add a section in appropriate location regarding sparse transformation models (and say what we already have for sparse metric possibilities - i think we need to skip the ICDM stuff — too complex)

Simple ITK tutorial material for JF-augmented brain mapping

We will employ freely available *real neuroimaging data* on which to base the tutorial material and to promote reproducibility and transparency. We will employ the Pediatric Template of Brain Perfusion (PTBP) at figshare which includes free multiple modality MRI data with demographics and psychometrics. The data is accompanied by an organized csv file with full data available at figshare. We will use a lightly processed version of the data to make examples quick enough for "on the fly" tutorial material.

We will use the sample PTBP subjects to:

- *Tutorial 1:* Build a template based on deformable registration done in Simple ITK
- *Tutorial 2:* Construct template priors with Joint Fusion and based on freely available labeled data
- *Tutorial 3:* Normalize and segment the population data based on spatial prior-based gaussian mixture modeling.

FIXME say some stuff about scripting and experience with ANTs MNI and ANTs USC and MICCAI and ITK tutorials ...

This will all be put together to create a reproducible analysis for a subset of the PTBP. This material will be invaluable for better introducing the neuroscience and larger biomedical image analysis community to this broadly applicable and powerful quantification technology. **FIXME** repeat technology again ...

Relationship and benefits of the project to the SimpleITK/ITK effort

Registration and segmentation are complementary tools that have often existed along independent software development paths. Registration teams rarely intersected with segmentation teams. Joint Fusion and related methods, however, serve as an integrative meta-algorithm which uses components of both classic registration and classic segmentation to improve upon the results obtained by either independently. Making these bleeding edge algorithms available to the ITK and Simple-ITK community will break down barriers between "code aware" and "code naive" user bases further allowing the computational scientist to communicate effectively with biological and medical scientists.

Advantages that the proposed work derives from SimpleITK/ITK

We are excited about the opportunity to port our current JF and Atropos segmentation frameworks into the core of ITK. Our prior experience has shown that the quality and lifespan of such algorithms is greatly improved when they are merged within the ITK ecosystem. The deep testing, consistent use of valgrind to find memory defects and cross-platform CMake-based ctests are all integral to the further improvement of the C++ backbone of these methods.

How the proposed work differs from or relates to existing work in ITK and its related software

There is a substantial level-set framework within ITK. There also exists a relatively under utilized statistical framework that allows methods such as k-means clustering followed by Markov random field regularization to be implemented. However, both of these frameworks lack the ability to implement truly Bayesian statistical models that incorporate spatial probability maps and maximize the posterior probability of a segmentation map explicitly. Consider the equation implemented by Atropos. **FIXME.**

Personnel and resources to be committed to the proposed work

The personnel that will implement this plan has extensive background working on C++. Furthermore, the team has many decades of experience contributing specifically to ITK. Dr. Avants made his first commit to ITK on Tue Apr 9 19:09:13 2002. His most recent commit included a bug fix on Nov 29 11:22:12 2012. Despite his personal contributions to code, Dr. Avants has contributed perhaps the most through his leadership of the ITKv4 development team. Specifically, his team implemented a full refactoring of the ITK registration framework. A few contributions of this framework include thread safety, the ability to implement composite transformations, multi-channel registration, extensibility and addition of cutting edge diffeomorphic transformation models as well as image similarity metrics for both intensity and point set features. In addition, an early version of GPU-based registration was implemented with OpenCL. Dr. Gee was part of the original ITK development core and was also involved in the ITKv4 registration refactoring, as PI. He also obtained several A2D2 grants in collaboration with Drs. Avants and Tustison. Dr. Yushkevich began developing with ITK in 2003 as part of the first round of translationally focused awards which began the eminently popular ITK-SNAP interactive segmentation software. Dr. Yushkevich is a key contributor to the application of ITK core tools to neuroscience goals through his maintenance and continued development of the elegant and easily accessible ITK-SNAP user interface, which uses ITK underneath. Dr. Tustison has been involved in various aspects of ITK development since he arrived at PICSL in 2004. He was initially charged with fulfillment of the requirements of a 2004-2005 A2D2 grant. Specifically, he designed and coded a set of classes to handle graph data types and an implementation of the popular "graph cuts" segmentation algorithm [23]. Other widely-used contributions include generic scattered data approximation using B-splines [24], N4 bias correction [25], an RGB faux-colormapping framework [26], and point set registration [27].

Dr. Avants and Dr. Tustison also promote ITK through their software Advanced Normalization Tools (ANTs, originating at sourceforge.net on 2008-06-26 and now residing at http://stnava.github.io/ANTs/). ANTs is a systematic framework for quantitative biological image analysis based on the Insight ToolKit. ANTs was first created to rapidly disseminate our latest research to the community of scientists who depend on imaging analytics and to allow them to study different organ systems, species or modalities with the same sound foundation. While originally focused on diffeomorphic image registration, ANTs now incorporates novel and cutting-edge methods for segmentation, feature extraction and, more recently, complete statistical pipelines via ANTsR http://stnava.github.io/ANTsR/. In 2014, there were nearly 2,000 citations to ANTs and the software is cloned, downloaded or otherwise accessed over 100-200 times per week, on average at github. The sourceforge site hosts a similar number of visits and downloads. ANTsR is accessed on average 50 times per week—a substantial number for a new software. There are also over 500 discussion topics on the ANTs sourceforge community site, nearly 100 topics on the github site and over 50 help-focused emails to the personal addresses of developers. Generally, response time to requests for help is within a few hours with rare occasions taking up to a day or two. All of this effort magnifies the impact of ITK.

For institutional resources committed to this work, please see the business portion of the proposal.

Budget for the work.

We request a total of $100,000**FIXME** which includes both direct and indirect costs.

Dr. Avants (5%) will manage the conduct of the project and oversee the project's successful completion of milestones and deliverables including testing, software development and construction of tutorial material.

Dr. Yushkevich (2%) is a co-inventor of the original Joint Label Fusion algorithm [**???**]. Dr. Yushkevich will contribute to testing and validating the ITK and SimpleITK implementations of JF.

Dr. Gee (2%) has been involved in the Insight ToolKit since its inception and will contribute his substantial registration expertise and project management skills to the team.

Dr. Tustison (consultant) will be the lead software developer for this project. Dr. Tustison is among the top contributors to the Insight ToolKit as judged by the number of lines of code from each author that have survived and are still intact in the current revision of the Insight ToolKit. He is the 11th overall contributor according to this metric as of September 1, 2015. **FIXME** Explain why we went consulting route given your critical role

1. Wang, H., Suh, J. W., Das, S. R., Pluta, J., Craige, C., and Yushkevich, P. A. "**Multi-Atlas Segmentation with Joint Label Fusion**" *IEEE Trans Pattern Anal Mach Intell* (2012): doi:10.1109/TPAMI.2012.143

2. Wang, H. and Yushkevich, P. A. "**Multi-Atlas Segmentation with Joint Label Fusion and Corrective Learning-an Open Source Implementation**" *Front Neuroinform* 7, (2013): 27. doi:10.3389/fninf.2013.00027

3. Yushkevich, P. A., Wang, H., Pluta, J., Das, S. R., Craige, C., Avants, B. B., Weiner, M. W., and Mueller, S. "**Nearly Automatic Segmentation of Hippocampal Subfields in in Vivo Focal T2-Weighted MRI**" *Neuroimage* 53, no. 4 (2010): 1208–24. doi:10.1016/j.neuroimage.2010.06.040

4. Tustison, N. J., Qing, K., Wang, C., Altes, T. A., and Mugler, J. P., 3rd. "**Atlas-Based Estimation of Lung and Lobar Anatomy in Proton MRI**" *Magn Reson Med* (Accepted):

5. Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., Kandel, B. M., Strien, N. van, Stone, J. R., Gee, J. C., and Avants, B. B. "**Large-Scale Evaluation of ANTs and FreeSurfer Cortical Thickness Measurements**" *Neuroimage* 99, (2014): 166–79. doi:10.1016/j.neuroimage.2014.05.044

6. Vannier, M. W., Butterfield, R. L., Jordan, D., Murphy, W. A., Levitt, R. G., and Gado, M. "**Multispectral Analysis of Magnetic Resonance Images**" *Radiology* 154, no. 1 (1985): 221–4. doi:10.1148/radiology.154.1.3964938

7. Dempster, A., Laird, N., and Rubin, D. "**Maximum Likelihood Estimation from Incomplete Data Using the EM Algorithms**" *Journal of the Royal Statistical Society* 39, (1977): 1–38.

8. Wells, W. M., Grimson, W. L., Kikinis, R., and Jolesz, F. A. "**Adaptive Segmentation of MRI Data**" *IEEE Trans Med Imaging* 15, no. 4 (1996): 429–42. doi:10.1109/42.511747

9. Cline, H. E., Lorensen, W. E., Kikinis, R., and Jolesz, F. "**Three-Dimensional Segmentation of MR Images of the Head Using Probability and Connectivity**" *J Comput Assist Tomogr* 14, no. 6 (): 1037–45.

10. Kikinis, R., Shenton, M. E., Gerig, G., Martin, J., Anderson, M., Metcalf, D., Guttmann, C. R., McCarley, R. W., Lorensen, W., and Cline, H. "**Routine Quantitative Analysis of Brain and Cerebrospinal Fluid Spaces with MR Imaging**" *J Magn Reson Imaging* 2, no. 6 (): 619–29.

11. Geman, S. and Geman, D. "**Stochastic Relaxation, Gibbs Distributions, and the Bayesian Restoration of Images**" *IEEE Trans Pattern Anal Mach Intell* 6, no. 6 (1984): 721–41.

12. Held, K., Rota Kops, E., Krause, B. J., Wells, W. M., 3rd, Kikinis, R., and Müller-Gärtner, H. W. "**Markov Random Field Segmentation of Brain MR Images**" *IEEE Trans Med Imaging* 16, no. 6 (1997): 878–86. doi:10.1109/42.650883

13. Zhang, Y., Brady, M., and Smith, S. "**Segmentation of Brain MR Images Through a Hidden Markov Random Field Model and the Expectation-Maximization Algorithm**" *IEEE Trans Med Imaging* 20, no. 1 (2001): 45–57. doi:10.1109/42.906424

14. Van Leemput, K., Maes, F., Vandermeulen, D., and Suetens, P. "**Automated Model-Based Tissue Classification of MR Images of the Brain**" *IEEE Trans Med Imaging* 18, no. 10 (1999): 897–908. doi:10.1109/42.811270

15. Ashburner, J. and Friston, K. J. "**Unified Segmentation**" *Neuroimage* 26, no. 3 (2005): 839–51. doi:10.1016/j.neuroimage.2005.02.018

16. Gubern-Mérida, A., Kallenberg, M., Mann, R. M., Martí, R., and Karssemeijer, N. "**Breast Segmentation and Density Estimation in Breast MRI: a Fully Automatic Framework**" *IEEE J Biomed Health Inform* 19, no. 1 (2015): 349–57. doi:10.1109/JBHI.2014.2311163

17. Ribes, S., Didierlaurent, D., Decoster, N., Gonneau, E., Risser, L., Feillel, V., and Caselles, O. "**Automatic Segmentation of Breast MR Images Through a Markov Random Field Statistical Model**" *IEEE Trans Med Imaging* 33, no. 10 (2014): 1986–96. doi:10.1109/TMI.2014.2329019

18. Tustison, N. J., Avants, B. B., Flors, L., Altes, T. A., Lange, E. E. de, Mugler, J. P., 3rd, and Gee, J. C. "**Ventilation-Based Segmentation of the Lungs Using Hyperpolarized (3)He MRI**" *J Magn Reson Imaging* 34, no. 4 (2011): 831–41. doi:10.1002/jmri.22738

19. Avants, B. B., Tustison, N. J., Wu, J., Cook, P. A., and Gee, J. C. "**An Open Source Multivariate Framework for n-Tissue Segmentation with Evaluation on Public Data**" *Neuroinformatics* 9, no. 4 (2011): 381–400. doi:10.1007/s12021-011-9109-y

20. Awate, S. P. and Whitaker, R. T. "**Unsupervised, Information-Theoretic, Adaptive Image Filtering for Image Restoration**" *IEEE Trans Pattern Anal Mach Intell* 28, no. 3 (2006): 364–76. doi:10.1109/TPAMI.2006.64

21. Buades, A., Coll, B., and Morel, J.-M. "**Nonlocal Image and Movie Denoising**" *International Journal of Computer Vision* 76, no. 2 (2008): 123–139.

22. Manjón, J. V., Coupé, P., Martí-Bonmatí, L., Collins, D. L., and Robles, M. "**Adaptive Non-Local Means Denoising of MR Images with Spatially Varying Noise Levels**" *J Magn Reson Imaging* 31, no. 1 (2010): 192–203. doi:10.1002/jmri.22003

23. Tustison, N. J. "**Graph Cuts, Caveat Utilitor, and Euler's Bridges of Konigsberg**" *The Insight Journal* (2008): Available at http://hdl.handle.net/1926/1503

24. Tustison, N. J. and Gee, J. C. "**N-d C^k B-Spline Scattered Data Approximation**" *The Insight Journal* (2005): Available at http://hdl.handle.net/1926/140

25. Tustison, N. J. and Gee, J. C. "**N4ITK: Nick's N3 ITK Implementation for MRI Bias Field Correction**" *The Insight Journal* (2009): Available at http://hdl.handle.net/10380/3053

26. Tustison, N. J., Zhang, H., Yushkevich, P., and Gee, J. C. "**Meeting Andy Warhol Somewhere over the Rainbow: RGB Colormapping and ITK**" *The Insight Journal* (2008): Available at http://hdl.handle.net/1926/1452

27. Tustison, N. J., Awate, S. P., and Gee, J. C. "**A Novel Information-Theoretic Point-Set Measure Based on the Jensen-Havrda-Charvat-Tsallis Divergence**" *The Insight Journal* (2008): Available at http://hdl.handle.net/1926/1497