

# Image-Based Informatics for Preclinical Biomedical Research

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**Abstract.** In 2006, the *New England Journal of Medicine* selected medical imaging as one of the eleven most important innovations of the past 1,000 years, primarily due to its ability to allow physicians and researchers to visualize the very nature of disease. As a result of the broad-based adoption of micro imaging technologies, preclinical researchers today are generating terabytes of image data from both anatomic and functional imaging modes. In this paper we describe our early research to apply content-based image retrieval to index and manage large image libraries generated in the study of amyloid disease in mice. Amyloidosis is associated with diseases such as Alzheimer's, type 2 diabetes, chronic inflammation and myeloma. In particular, we will focus on results to date in the area of small animal organ segmentation and description for CT, SPECT, and PET modes and present a small set of preliminary retrieval results for a specific disease state in kidney CT cross-sections.

## 1 Introduction

Imaging performs an extremely important role in the understanding of human disease through its preclinical application to small animal research. High-resolution, high-throughput, multi-modality imaging provides the capability to carry out non-destructive, longitudinal studies on large populations of animals that previously required animal sacrifice and painstaking dissection to accomplish. A result of this advancing capability is the generation of copious amounts of digital image and

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ancillary data. Most preclinical researchers today maintain this data in an ad-hoc manner, distributed across a number of computers, on different media types, and in different physical locations. For those who have dedicated picture archiving and communications systems (PACS) in their facilities, the largest data component in the system - the imagery - is only marginally indexed for retrieval using simple associated text fields. Over time this image data loses its informational power simply because it becomes irretrievable, limiting a researcher's ability to pursue research questions that leverage the historical image repository.

The Oak Ridge National Laboratory (ORNL), the University of Tennessee Graduate School of Medicine (UTGSM), and the University of Tennessee Department of Computer Science (UTCS) are working together to develop an informatics system for small animal imaging that will support UTGSM's research in the study of amyloid disease in mice. Amyloidosis is a protein aggregation disorder associated with a growing number of fatal and debilitating diseases, such as Alzheimer's disease, type 2 diabetes, chronic inflammatory disorders, and myeloma.

Our main focus area in this regard is to apply content-based image retrieval (CBIR) methods to describe and index the multiple modes of anatomic and functional imagery that are generated through these studies and to make that image data retrievable in future studies. CBIR refers to techniques used to index, retrieve, and manage images from large image repositories based on visual content. Visual content is derived from the structures, morphology, and textures intrinsic to the 2D and 3D multi-modal imagery used for small animal imaging today such as micro CT, PET, SPECT, and MRI.<sup>1</sup> There are many researchers today that are applying CBIR to the general problem of image retrieval [1] and to the biological or biomedical fields [2], but there is not yet a functional PACS that takes advantage of both the extrinsic and intrinsic characteristics of imagery - particularly anatomic and functional imagery - to facilitate "what-if" search scenarios through terabytes of image data to locate images related by morphology, visual phenotype expression, and disease pathologies in the preclinical research environment.

We have developed and fielded CBIR technology and data management systems for the semiconductor industry that address similar problems created by the growing proliferation of automated microscopy inspection in semiconductor manufacturing applications, i.e., the management and reuse of the large amounts of image data collected during semiconductor wafer inspection and review [3, 4]. We have adapted this technology to other fields including geographical information science [5] and retinal diagnostics.<sup>2</sup> In this paper we will describe our preliminary results to date in the area of small animal organ segmentation and description for CT, SPECT, and PET modalities and present a small set of preliminary retrieval results for a specific disease state in kidney cross-sections. Our goal is to present the utility of applying CBIR methods and technology to the informatics of preclinical, small animal research. In Section 2 we will review our previous research and motivation for the use of mouse models to research disease, in particular amyloidosis. In Section 3 we will review our

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<sup>1</sup> Computed Tomography (CT), Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), and Magnetic Resonance Imaging (MRI).

<sup>2</sup> R01 EY017065-01, Edward Chaum (PI); Automated Screening for Diabetic Retinopathy by Content.

progress to date on 2D and 3D segmentation of soft tissue organs in micro CT imaging along with some preliminary results for fusing anatomic CT and functional PET data. In Section 4 we will review our preliminary results related to the indexing of a small population of kidney cross-sections from CT and discuss architectural concepts for structuring the representation of image features in a small animal informatics environment.

## 2 Small Animal Imaging in the Study of Amyloidosis

The amyloidoses represent an ever growing number of insidious diseases characterized by the aggregation of normally innocuous, soluble protein or peptides into highly ordered fibrils that accumulate in tissues and vital organs leading to organ dysfunction and ultimately death [6, 7]. The history of basic and clinical amyloid research has been strongly dependent on imagery and visual peculiarity.

Recently, advances in medical imaging and tracer development have made possible the visualization of amyloid lesions in patients with systemic and cerebral disease and micro-imaging technologies have fueled preclinical research into the pathobiology of amyloid disease in mouse models and the development and evaluation of novel diagnostic and therapeutic agents. For example, UTGSM has developed a multi-disciplinary research program<sup>3</sup> that focuses on non-invasive microimaging of amyloid deposits in mice to better understand the pathogenesis of these fatal diseases and to provide tools (e.g., including both animal models and imaging methods) to examine the efficacy of novel therapeutic, anti-amyloid agents *in vivo* [8, 9].

More specifically, UTGSM, UTCS, and ORNL, working with Siemens Preclinical Solutions, have fabricated a hybrid SPECT/CT microimaging system (see Fig. 1, top) and used it, in addition to a dedicated microPET instrument (Fig. 1, bottom), to provide quantitative images of amyloid deposits in transgenic mice using, as a tracer, a highly specific radioiodinated amyloid-binding protein [8, 10].



**Fig. 1.** UTGSM/ORNL *in vivo* laboratory animal systems used for imaging systemic amyloidosis in mice. Siemens microCAT™ II + SPECT (top); microPET P4 system (bottom).

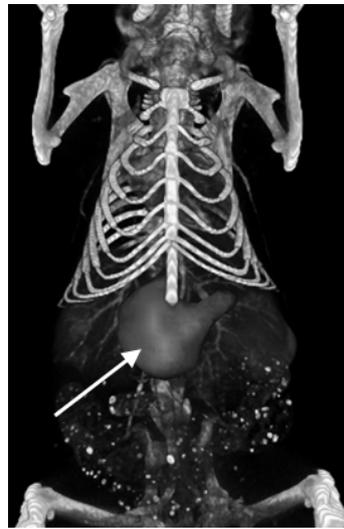
<sup>3</sup> RO1 EB000789, Jonathan Wall (PI); "SPECT/CT Imaging of Systemic AA-Amyloidosis in Mice."

We have developed extensive experience with high-fidelity reconstruction of both CT and SPECT images. We have thus developed a parallel-processing version of the Feldkamp algorithm for cone beam imaging [11, 12] in a distributed computing framework that facilitates the use of iterative reconstruction algorithms, e.g. [13, 14]. With respect to SPECT we have implemented an OSEM algorithm using a conic view based system model as described in [15]. These codes have all been integrated with the RVA<sup>TM</sup> software that runs on the Siemens microCAT<sup>TM</sup> family of machines from which the SPECT/CT image data shown in this paper have been obtained. MicroPET/CT co-registered images (e.g. Fig. 2) were generated using data from a P4 microPET imaging system (Siemens Preclinical Solutions) and contrast-enhanced CT data from the microCAT II. Imaging protocols have now been developed that allow us to generate high-resolution SPECT and PET images of amyloid deposits in the viscera of mice, that are readily co-registered with anatomic CT, to provide highly detailed easily interpreted visualizations, as shown in Fig. 2 [16].

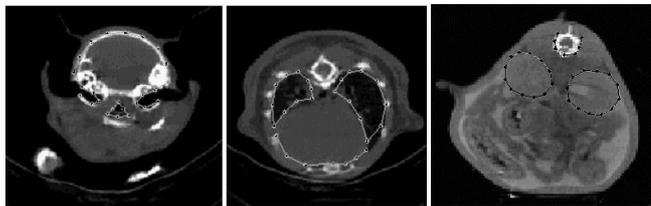
### 3 Image Analysis Segmentation and Registration

Quantitative analysis of small animal imagery requires the segmentation of anatomic structures of interest. The results of such segmentation – the shape and volume of a specific organ, for example – can serve as important features for query and retrieval from a CBIR system. In our earlier work in 2D biomedical image segmentation, we applied probabilistic shape and analysis models

(PSAM) to the segmentation of soft-boundary anatomic structures [17]. The PSAM method uses an *a priori* model based on a set of landmark points selected by the user during a training step. The PSAM method has been shown for effective for anatomic structures



**Fig. 2.** MicroPET/CT visualization of AA amyloid deposits (arrow) in a mouse using <sup>124</sup>I-SAP. Visualization generated by UTGSM.



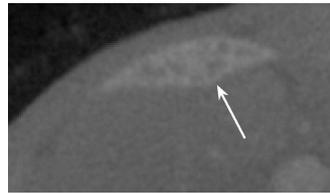
**Fig. 3.** Examples of segmentations achieved on various anatomic structures using the PSAM method. Cranium (left), heart and lungs (middle), and kidneys (right).

that are relatively uniform across populations such as the kidney or skeletal components (see Fig. 3), but for other organs with greater morphological variability, we have taken an alternative approach.

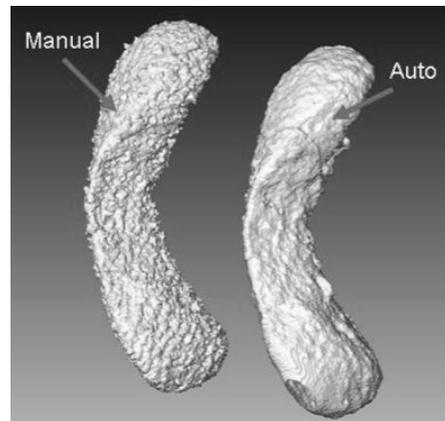
We have recently developed relevant 3D image segmentation methods [18] in support of quantifying amyloid deposits in a transgenic mouse model of AA-amyloidosis [19] via anatomic and functional imaging. To date, we have focused on identifying the spleen surface using contrast-enhanced CT data with the aim of applying that surface to co-registered SPECT or PET data to quantify the amount of amyloid tracer inside the spleen. Content defined by 3D visual information is a growing topic of research today as a result of the increasing availability of volumetric imaging modalities.

Segmentation of the mouse spleen (and other organs) in CT imagery can be difficult because of poor contrast, even with the use of contrast-enhancing agents. An example CT slice showing a spleen region can be seen in Fig. 4; this data was acquired using 350 $\mu$ l of Fenestra vascular contrast (VC) agent (Advanced Research Technologies/ Alerion Biomedical Inc., Quebec, Canada). The blood pool of the spleen is relatively bright, while the darker interior regions represent the lymphoid follicles. We previously [18] adapted a 2D level sets segmentation method [20] for semi-automatic 3D spleen segmentation. We extended the 2D algorithm to 3D via slice-by-slice processing and also improved performance by introducing statistical and proximity (relative to the previous slice) weighting terms. An example result from this approach can be seen in Fig. 5, where the spleen labeled “Auto” was segmented with our approach and the spleen labeled “Manual” was segmented via manual slice-by-slice thresholding, which is often the method of choice in the pre-clinical setting.

We have very recently developed a fully 3D (i.e., not slice-by-slice) level set method for segmentation of both the spleen and its interior follicular architecture [21]. In addition to adapting our statistical and proximity weighting terms to the 3D case, we also implemented a modification to the level set energy functional that significantly improved follicle segmentation. An example

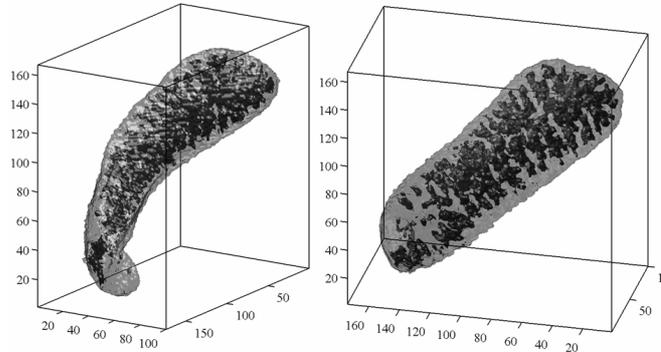


**Fig. 4.** Example CT slice showing mouse spleen (arrow) after injection of a venous contrast agent. Bright interior regions represent the blood pool and the darker regions represent follicles.



**Fig. 5.** Example spleen segmentation result (“Auto”) using our 3D slice-by-slice approach. The “Manual” spleen was acquired using slice-by-slice, manually-adjusted thresholding.

result from this algorithm is shown in Fig. 6, where the spleen is rendered transparently and the follicles are opaque. Segmentation of the follicles is important for two reasons. First, we are interested in quantifying the volume occupied by the “blood pool” red pulp as this is decreased as

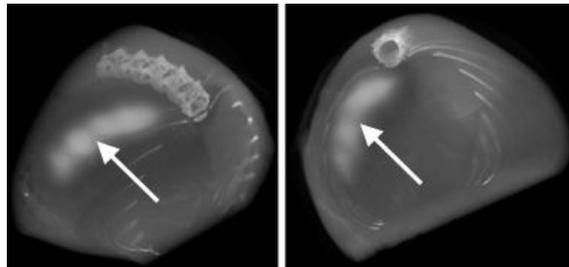


**Fig. 6.** Result from our recently developed fully 3D spleen (transparent) and follicle (opaque) segmentation technique

as amyloid deposits accumulate in the spleens of mice with systemic AA amyloidosis. Secondly, variations in the follicular architecture may indicate changes in the extent of the amyloid disease and that of other lymphoproliferative disorders that involve the spleen, such as lymphoma. Quantifying the follicle structure and storing in the CBIR system will allow us to detect changes – statistically across populations and/or in single-subject longitudinal studies – that indicate important biological changes. Thus, indexing the volumetric data by its image content becomes extremely relevant to the study of amyloid disease.

We have also used the results from anatomic (CT) image analysis to quantify functional (PET) data. For example, we have recently applied the spleen and follicle boundaries from segmentation to co-registered PET data to quantify the amount of amyloid-specific tracer in the blood pool and follicular regions of an effected spleen. We aligned the CT and PET data sets using fiducial markers visible in both CT and PET modalities. Rigid transformation parameters were calculated via

constrained gradient descent, though more sophisticated approaches certainly exist if needed [22, 23]. Two viewpoints of volume-rendered, co-registered PET and CT



**Fig. 7.** Volume renderings (two viewpoints) of co-registered CT and PET data. The bright PET region (arrow) corresponds to induced amyloid deposits in the spleen. The spleen boundary is applied to the PET data to quantify the amyloid-bound radiotracer in the blood pool and follicular regions.

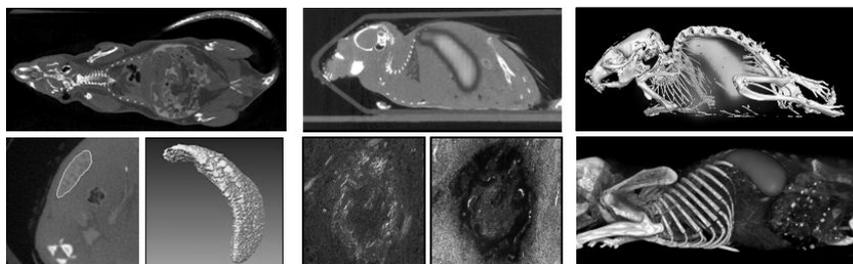
data can be seen in Fig. 7, where the bright PET region (arrow) corresponds to amyloid burden in the spleen.

#### 4 Preliminary Results and Architecture Concepts for CBIR

Both the context and the content of image data represent an inherent source of information and learning that is only marginally accessed today in the biomedical clinical and preclinical environments [24, 25]. While researchers continue to discuss how this may be achieved, practical progress has not kept pace with the production of imagery [26-28]. *Image context* is represented by extrinsic properties such as the time and date of data acquisition, subject data regarding animal strain and parentage, study data such as the type of SPECT tracer or CT contrast agent used along with the route of administration, and perhaps textual information regarding other unique conditions under which the data were collected. For our purposes, we will refer to this extrinsic image data as metadata.

*Image content* is represented by the intrinsic properties of the image itself such as texture and regional structure [29], i.e., attributes that the human eye keys on to comprehend an image. Image content is extensive yet most data management systems today rely solely on extrinsic properties of the data to catalogue it for future use. Commercial relational database products and PACS reduce the ad-hoc nature of the cataloguing procedure by leveraging extrinsic image properties, but to effectively access the entire historical repository requires an ability to simultaneously engage both the extrinsic and intrinsic properties in a manner that is reasonably transparent to the user.

Fig. 8 shows examples of the wide variety of descriptive imagery that is generated at UTGSM and ORNL in support of our small animal research. Extracting, indexing, and managing the informational content of this data is of paramount importance.



**Fig. 8.** Examples of the wide variety of descriptive imagery that is collected in support of small animal studies. This data was generated by UTGSM and ORNL to support amyloid research and includes (left) contrast-enhanced CT and both planar and volume segmentation of the spleen, (center) registered CT and SPECT data plus autoradiographs of splenic amyloid deposits imaged with  $^{125}\text{I}$ -SAP, and (right) visualizations of amyloid burden generated from co-registered SPECT/CT (upper) and PET/CT data (lower).

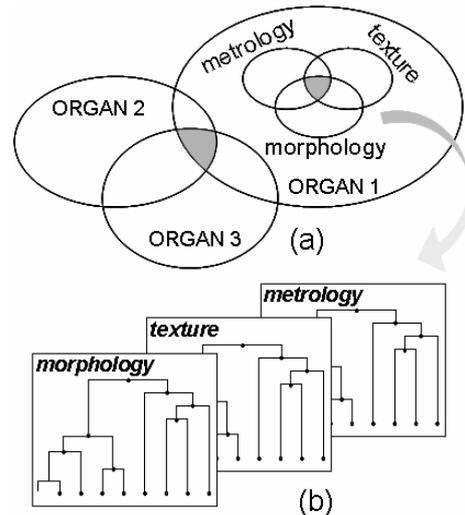
Our CBIR technology is a library of C++ objects that create, manipulate, and access database tables as well as measure unique numerical descriptions of image content. Two main procedures of indexing and retrieval are carried out. The indexing process consists of measuring features from images, then using the features to build

tree structures that describe the image population. The indexing procedure begins by reading an image and extracting the image features from multiple regions of interest. For this research, these regions are generated using the 2D and 3D segmentation methods described earlier. As images are added to the table, indexing trees are generated. We use a modified approximate nearest-neighbor (ANN) algorithm to build and maintain the indexing trees [30]. In practice, multiple trees are generated, each representing a group of attributes associated with the image population, e.g., shape attributes and texture attributes, as shown in Fig. 9.

In retrieving, features are extracted from a query image and each indexing tree is searched to find the closest examples based on an L-norm distance metric. The final retrieval is a function of the intersection of these sets. A user can easily enable or disable these various attribute sets while performing queries, therefore making the system flexible and useful to a large population of end-users, each with differing search goals.

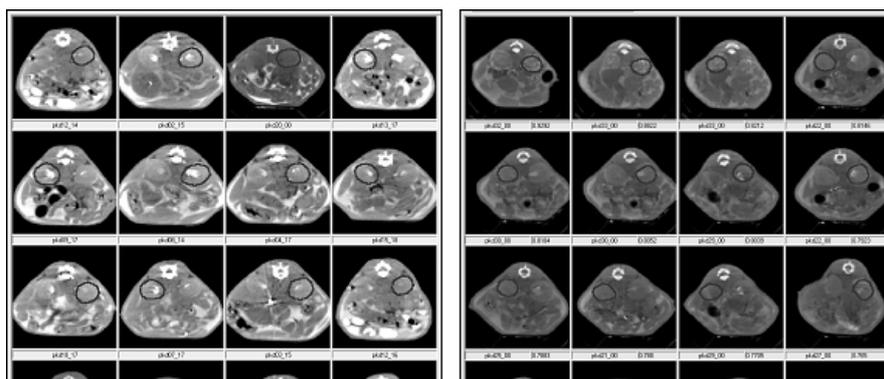
To demonstrate the initial application of our CBIR technology to this research, we have built a small CT cross-section databases for testing with existing feature constructs. The database contains 239 images from the microCT system of normal kidneys and polycystic kidney disease (PKD) cross sections. Each kidney image in the database is indexed individually such that one mouse is represented twice, once for each kidney. The kidney mask (i.e., segmentation) was automatically generated using the 2D PSAM algorithm of Gleason in [17]. The left image in Fig. 10 shows a random population of images from the database. The right image shows the result of querying with the left kidney of Mouse #32, which has PKD. Note that the first query result in the list contains Mouse #32's right kidney. The second and third results show Mouse # 33's right and left kidney respectively. Mouse #33 also has PKD. There were no other PKD mice in the database.

For this example the image texture attributes in the segmented kidney regions plays an important role in differentiating PKD from normal mice, although a total of 111 features representing intensity, texture, and shape were applied. Even though this was a simple example on a relatively small data set, it represents the inherent



**Fig. 9.** Example feature indexing architecture. In (a) users select the descriptors of interest for each queried organ. The retrievals for each organ type (if multiple are selected) are returned in a list based on the Boolean intersection of the sets. In (b) the ANN indexing trees are represented that are accessed for each selected subgroup within an organ.

investigative power that could be achieved by a fully developed informatics system that leverages visual content to perform queries on historical data populations. The incorporation of other study data (i.e., metadata) into the query process will extend this capability further and facilitate rapid investigations through hundreds of thousands of images while providing for the effective reuse of large historical repositories.



**Fig. 10.** Example database of normal and PKD kidneys generated using the micro CT imaging at ORNL. The left image shows a random retrieval of kidney image cross-sections. The right image shows a query with Mouse #32's left PKD kidney.

## 5 Conclusions

Micro imaging has become a predominant means for generating high-resolution, high-throughput, multi-modality small animal data. A result of this advancing capability is the generation of copious amounts of digital image and ancillary data that must be indexed and managed to retain its usefulness in the preclinical study of genetics and disease. We have presented results of our preliminary research to segment and describe anatomic and functional structures, primarily soft organ tissue, collected from CT, SPECT, and PET imaging modalities. We have also shown an example of image indexing and retrieval on a small CT database of mice exhibiting polycystic kidney disease, demonstrating an ability to locate similar diseased mice in a population using kidney morphology and texture. The goal of this research is to develop a small animal information system that will improve the ability of preclinical researchers to make important biomedical discoveries by drastically increasing the achievable scope and size of their studies, therefore accelerating the translation of the preclinical investigation of disease to the clinical environment. More importantly, through the effective analysis and indexing of image content, the data system will provide researchers with unprecedented access to information in the imagery, which comprises the largest data component of the system.

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