Temple University

Annual Progress Report: 2011 Formula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Formula Grant Overview

Temple University received $2,186,053 in formula funds for the grant award period January 1, 2012 through December 31, 2015. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Infrastructure: Construction of the Temple Clinical Research Institute – Academic medical centers have an obligation to pursue cutting-edge research that links the research bench with the clinical arena and facilitates the ability to bring cutting edge technologies to the community that the academic center serves. There is a particular need to improve the access of ethnic and racial minorities to clinical research protocols as these groups have historically been excluded from many clinical research studies. The purpose of the Temple Clinical Research Institute is to facilitate and enhance our ability to undertake cutting-edge clinical research both in our community and across the Commonwealth.

Duration of Project

1/1/2012 – 6/18/2014

Project Overview

The field of Clinical and Translational Medicine (Science) has become a major focus of the NIH and is critical for improving the health of our population. It encompasses four elements: T1or basic research, T2 or Clinical Research, T3 or Translation of Clinical Results to the Community and T4 or the combination of Bioethics and Health Policy. Temple University has recently developed a robust program in translational research with the creation of the new Center for Translational Medicine and has begun efforts to improve our ability to provide care for the under-served population we care for through the development of our new Center for Bioethics, Urban Health and Policy (CBUHP). A critical component of our focus on Translational Medicine is the creation of the Temple Clinical Research Institute (TCRI). The TCRI is being created with the recognition that: 1) all members of the clinical research team must have didactic training in clinical research; 2) academic medical centers have done a poor job of including members of urban communities in clinical research studies; 3) clinical research provides an opportunity for patients to have access to cutting-edge therapies especially in the fields of oncology and cardiovascular disease; and, 4) the various pieces of the clinical research enterprise

including education of study coordinators and trainees, bioinformatics support, information technology, pre- and post-award supervision of grants, compliance, institutional review board operations, and community outreach are most effectively undertaken when under the same roof. A major part of the creation of the TCRI will be the construction of a facility that will house all of the critical parts of the clinical research enterprise. The TCRI will serve as a training site for trainees and clinical research coordinators but will also include a sophisticated Information Technology component that will allow us to link clinical sites both within and outside of Temple University Hospital with the TCRI, with industry sponsors and with global clinical research organizations. The TCRI will also house the CBUHP so that the two organizations can share in their community outreach efforts and collaboratively address the areas of bioethics and health policy.

Principal Investigator

Arthur M. Feldman, MD, PhD
Executive Dean
Temple University School of Medicine
3500 N. Broad Street, Rm. 1150
Philadelphia, PA 19140

Other Participating Researchers

Joseph Cheung, MD, PhD; Thomas Force, MD – employed by Temple University School of Medicine

Expected Research Outcomes and Benefits

The project will entail renovations of 8,000 square feet of space in the Kresge Building on the Temple University School of Medicine campus. The TCRI will be located on a temporary basis in the Medical Office Building also located on the Temple University School of Medicine campus. However, the temporary space is inadequate in terms of size, does not provide the appropriate spaces or infrastructure support for IT capabilities, and has been designated for future remodeling and utilization as outpatient clinical space. The temporary space is also not adequate to bring all of the existing offices that oversee clinical research together – a group that is now found in four different buildings and on two separate campuses. The expected outcome of this project is that 8,000 square feet of space in Kresge will be remodeled in order to house a staff of 40 individuals who are part of the TCRI and 10 individuals who are part of the Center for Bioethics, Urban Health and Policy. No other metrics will be useful during the period of this funding. Metrics that will be used over time to assess the success of the TCRI will include: 1) the number of extramurally funded clinical research studies undertaken by the TCRI; 2) a significant increase in the number of patients from the North Philadelphia community who participate in clinical research projects; 3) an increase in the number of medical students, residents and clinical fellows and nurses who participate in educational offerings of the TCRI; 4) an increase in the number of NIH grants for clinical research; 5) an increase in the number of investigator-initiated clinical trials; and 6) a decrease in the time it takes for new technology and innovations to transition from clinical trials to everyday use by community practitioners.

Summary of Research Completed

During the third calendar quarter 2013 the design construction documents were issued for general contractor lump sum competitive bids. In the fourth quarter 2013, LaMarra Construction was awarded the construction contract and began on-site work in December 2013. Substantial completion of the base contract occurred in February 2014 and furniture/furnishings installed by May 30, 2014. Beneficial occupancy occurred in June 2014 with the relocation of the Clinical Trials offices followed by the newly created Department of Clinical Sciences which incorporates the Temple Clinical Research Institute. All occupants including faculty and staff from the Department of Clinical Sciences, Temple Clinical Research Institute (TCRI), and the Center for Bioethics, Urban Health & Policy, have now transitioned into this newly constructed/renovated shared space which includes approximately 8,000 sq. feet on the 2nd floor of Kresge Science Hall on the Temple University Health Sciences campus. Attached are photos of the completed space.

Entry from Main Elevator Lobby

Reception/Waiting Area

Main Conference Room with comprehensive audio/visual-teleconference technology

Open Plan Systems Workstations

Typical Office Corridor

Staff Break/Lunch Room

Research Project 2: Project Title and Purpose

The Development of Biofilm Inhibitors – This project will develop a library of synthetic analogs of the natural product cyclic diguanylate, which is involved in many processes in pathogenic bacteria. The compounds will be tested for biofilm inhibition and antibacterial properties. Ultimately this work has the potential to yield an entire new class of antibiotics.

Duration of Project

1/1/2012 – 12/31/2012

Summary of Research Completed

This project ended during a prior state fiscal year. For additional information, please refer to the Commonwealth Universal Research Enhancement C.U.R.E. Annual Reports on the Department's Tobacco Settlement/Act 77 web page at http://www.health.state.pa.us/cure.

Research Project 3: Project Title and Purpose

Effects of Obesity and Environment on Oocyte Quality and Inheritance – Recent studies in mice indicate that maternal obesity can lead to intrauterine growth restriction and subsequent obesity in progeny. Obesity can lead to disruptions in oocyte-follicle communication, and reduced egg quality that is later manifested as altered embryo phenotype. Maternal exposure to environmental "obesogens" can promote obesity in progeny. The goals of this project will be to

define the impact of maternal obesity and environmental obesogens on oocyte quality, define the mechanisms of these effects in the oocyte and early embryo, determine the ability to mitigate these effects via changes in maternal diet, and investigate the potential contributions of environmental obesogens to the obesity epidemic.

Anticipated Duration of Project

1/1/2012 – 12/31/2015

Project Overview

Obesity is a serious and escalating health concern. Available data indicate that maternal obesity can promote obesity among progeny. Our hypothesis is that maternal obesity compromises oocyte quality, leading to early embryonic stress, which in turn promotes obesity. Environmental toxins contribute to this process by promoting obesity in mothers and by altering embryonic gene expression. We will define the impact of maternal obesity and environmental obesogens on oocyte quality, define the mechanisms of these effects in the oocyte and early embryo, define the ability to mitigate these effects via changes in maternal diet, and investigate the potential contributions of environmental obesogens to the obesity epidemic. Aim 1 will take advantage of genetically modified mice (mutations affecting the polyamine metabolic flux pathways) with either obese or lean phenotypes to test the effect of maternal adiposity on reproductive performance and progeny adiposity, determine effects on oocyte and embryo gene expression, and determine whether embryos from obese mothers manifest stress response and mitochondrial activity alterations that contribute to later obesity. Aim 2 will test whether dietary supplementation to promote enhanced polyamine flux and alleviate maternal obesity can overcome the effects of maternal obesity in progeny. Aim 3 will use geographic information science to examine distributions of environmental obesogens and test for correlations with childhood obesity rate. Collectively, these studies will provide novel data on the transgenerational impact of maternal obesity, on the roles of environmental factors in childhood obesity, and on the potential for dietary interventions affecting polyamine metabolism to lessen the impact of maternal obesity.

Aims:
Aim 1. Evaluate the transgenerational effects of lean and obese maternal phenotypes arising from genetically altered SSAT activity on oocyte quality, fertility, and reproductive performance.
Aim 2. Test whether maternal dietary supplementation with polyamines restores oocyte quality and fertility, and whether this avoids adverse effects of maternal obesity and environmental obesogen exposure on progeny.
Aim 3. Use Geographic Information Science methods to evaluate environmental obesogen burden across Pennsylvania and whether this burden correlates with rates of obesity, particularly amongst children.

Principal Investigator

Michele M. Masucci, PhD
Interim Vice Provost for Research and Business Development
Professor, Geography and Urban Studies
Temple University
1801 North Broad Street
Philadelphia, PA 19122

Other Participating Researchers

John Gaughan, PhD; Donald Gill, PhD; Madesh Muniswamy, PhD; Dianne Soprano, PhD; Yong Cheng; Oscar Perez-Leal; Salim Merali, PhD – employed by Temple University

Expected Research Outcomes and Benefits

Obesity in general, and childhood obesity in particular, are significant health problems. Our studies will enhance health by determining effects of maternal obesity on progeny, identifying environmental factors contributing to maternal obesity, and exploring novel ways to mitigate maternal obesity effects on progeny through the use of dietary supplementation to enhance polyamine metabolic flux. The mechanistic studies to be undertaken with the SSAT knockout and transgenic mouse lines will provide new, cutting-edge information about how maternal adiposity affects progeny adiposity. Dietary interventions using this mouse model will reveal whether a similar strategy might benefit humans. Follow-up studies will examine polyamine metabolic flux in obese women, with the eventual objective of testing for trans-generational effects in a human population, and pursuing clinical trials to evaluate efficacy of dietary supplementation. Additional studies addressing the susceptibility of these mice to environmental obesogens (gene-environment interaction), and maternal exposure effects on progeny, will also become feasible.

We will also develop a database of point source and system impacts of endocrine disrupting compounds known as "obesogens" in Pennsylvania to provide a geographic distribution context for the analysis of epidemiological data related to obesity across the state by different demographic groups, with a particular focus on children, race and ethnicity, socio-economic status and gender. This will test the correlation between the spatial variation of these toxins at the state, regional and local scale with the epidemiological observance of obesity rates, particularly childhood obesity.

The data obtained should provide a foundation for additional clinical/translational studies.

Summary of Research Completed

Aim 3: The scope of work related to Aim 3 for this project involves developing a geographic database that reflects origins of obesogens in the environment. This information will be used to conduct future studies of the relationship between loci of obesogens, pathways for individual exposure and contact with obesogens, and mechanisms for health consequences and concerns

due to proximity and exposure. During the past year's reporting period, a GIS database was developed for Pennsylvania and an analysis of the literature related to the problem was conducted.

The study activities to date have included developing a database, establishing models for examining the association of geographic patterns of obesogens occurrences, and determining the correlation between the spatial variations of toxins on regional and local scales.

In particular, the study activities have included developing a database of point source and system impacts of obesogens in Pennsylvania to provide a geographic distribution context for the analysis of epidemiological data related to obesity across the study area by different demographic groups. In addition, the activities have included establishing models for examining the association of geographic patterns of obesogens occurrences with health in order to conduct analysis related to distance, including determining significance of the relationship between the mean distance to the nearest toxicity point source, neighborhood socioeconomic characteristics, and rates of obesity. OLS regression analyses are performed at the scale of the entire Southeastern Pennsylvania five county region, and again at the scale of Philadelphia County alone. Furthermore, the activities have included determining the correlation between the spatial variation of toxins regional and local scale with the epidemiological observance of obesity rates. The spatial information will be examined at the most granulated level available by location, which can include census tract, zip code, municipality, and county level data.

The study also reviewed geographic models on pollutants related to exposures, including ones related to pollutant emission, transportation, and dispersion; impacts of airborne chemicals on health; the limits of survey design for examining exposures; and prior use of GIS and spatial analysis for such analysis.

Finally, the geographic data that will be used for this work was aggregated as a basis for analysis of the environment-obesity relationships. This has included compiling demographic variables and geographical boundaries for the Philadelphia region and for the state. For Philadelphia and the surrounding counties of Bucks, Montgomery, Delaware, and Chester, data were obtained from the Census Bureau American Community Survey and Census Bureau and Census Bureau Tiger Shapefiles, respectively. The data is aggregated at the 2010 census tract level, providing the most current estimates at an appropriate scale for the research project.

In order to develop the database of point source toxicity data, environmental data sets that were examined include: the EPA TRI Database, Tri-Chip (a searchable database derived from the Toxics Release Inventory of point sources for obesogens); and Tri.Net – an analytical tool developed by EPA to conduct preliminary spatial analyses to probe toxic release data prior to integrating it within a GIS. Zoning and Land Use data was acquired from the City of Philadelphia.

The demographic variables, aside from population density, were chosen as explanatory variables due to their representation of vulnerable populations in environmental justice analyses (Mohai and Saha 2006). It is hypothesized that all of these explanatory variables, with the exception of

median household income, will have positive signs in regression analyses, indicating a correlation with unequally high exposure to environmental hazards.

Demographic variables explored for the study include population density, race, age, employment status, commute time, education, US citizenship, housing status, home ownership, household income, public assistance income, poverty levels, and household type health care coverage.

Methods

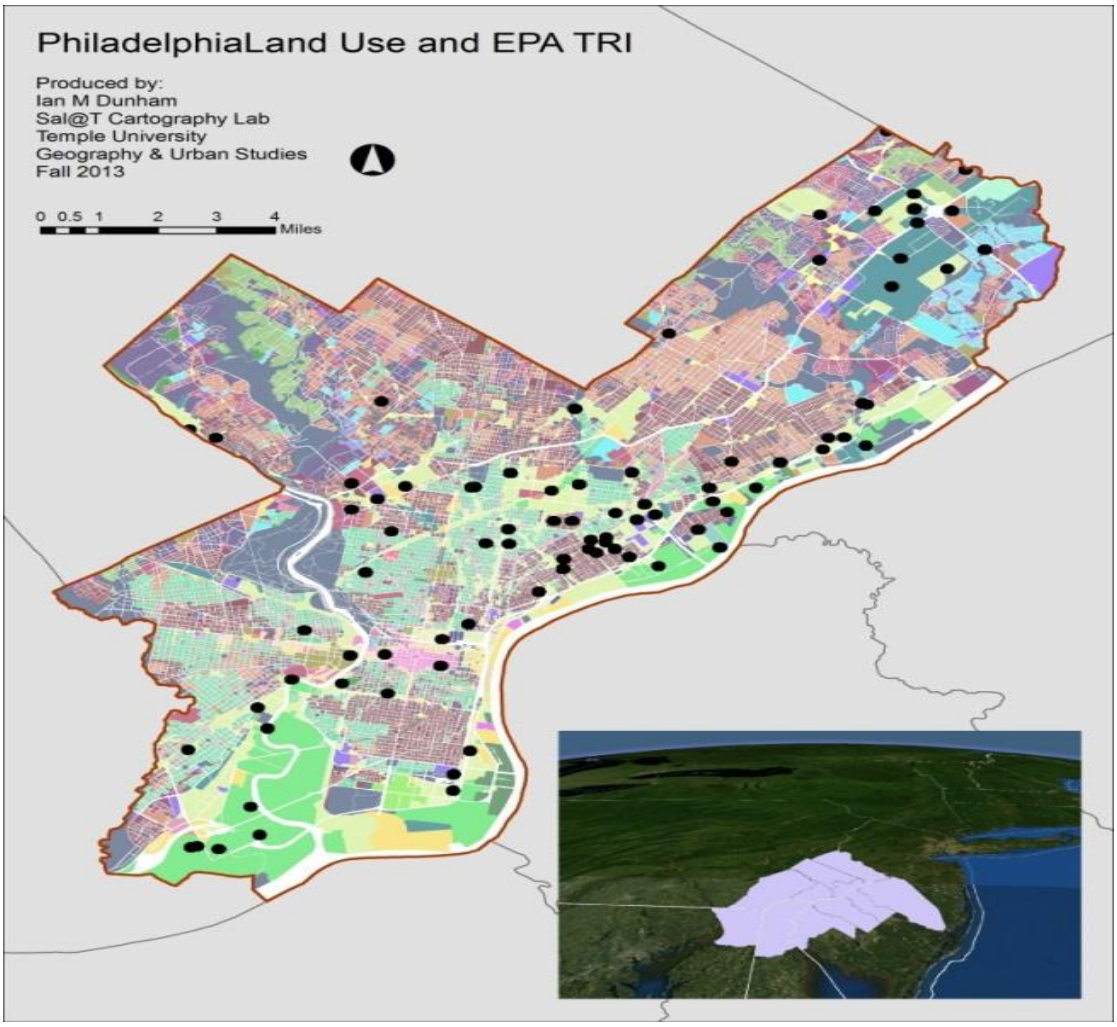
Euclidian distance between each census tract in the study area and the nearest toxicity point source was determined by creating a raster shapefile of Southeastern Pennsylvania census tracts with 10 m cell resolution and then calculating a measure of mean distance for all individual raster cells in each census tract using zonal statistics. Results were checked for multicollinearity, outliers, influential observations, and regression assumptions. Mean distance to nearest toxicity point source was log transformed in order to approach a normal distribution for the model residuals. Distance to the nearest location is an appropriate measure for this analysis. Rather than using presence or absence, the distance measure takes into account proximity to facilities located outside of the boundaries of the census tract (Downey 2003; Kearney and Kiros 2009). This distance measure provides a continuous dependent variable suitable for ordinary least squares (OLS) regression analysis.

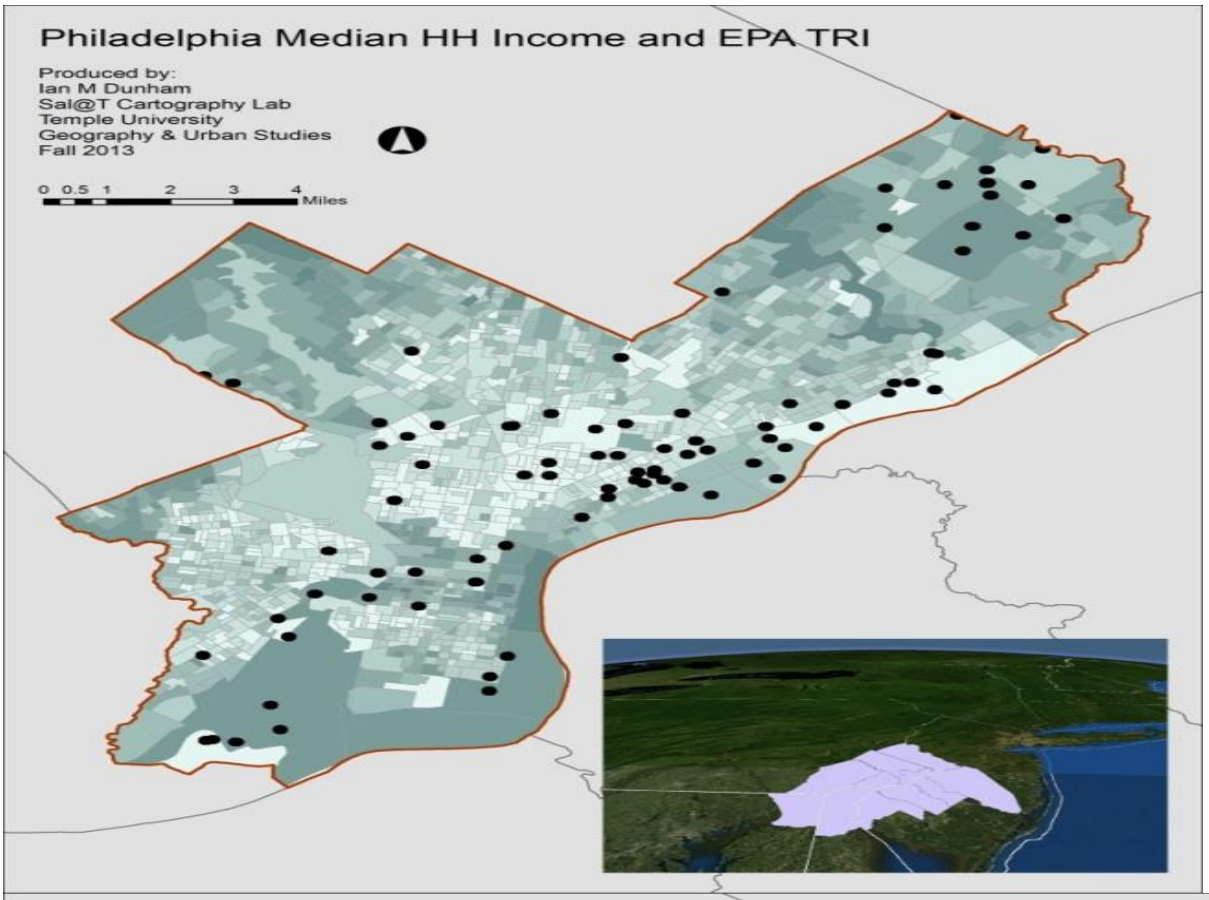
Independence of observations and error terms, one of the standard regression assumptions, has rightly become a major concern when examining spatial data similar to that used in this study. The issue is expressed concisely in Tobler's first law of geography, where the closer things are to each other; the more related they are (Chakraborty, 2011). This may lead to spatial clustering that violates the assumptions of independent observation and error terms, and incorrect interpretations of model outcomes. For this reason, tests were performed to detect spatial autocorrelation using the queen contiguity based method for defining the spatial weights matrix. While others have recommend using a distance-based approach to constructing spatial weights matrices (Landry and Chakraborty 2009; Chakraborty, 2011), the distance used should be based upon a theoretical understanding of the process at hand (Chakraborty, 2011). Unfortunately, because of unknown threat levels of the toxins we examine, as well as different dispersals means and ways to model dispersal, there is not an existing standard distance measure for how far away from a pollution point source presents a threat to human health and well-being. The Moran's I statistic is the standard measure of spatial clustering in an area. After obtaining results demonstrating a statistically significant positive spatial autocorrelation for all four models, spatial regression models that consider this violation of regression assumptions were considered. There are generally two options for incorporating spatial autocorrelation into regression equations, the spatial error and spatial lag models (Landry and Chakraborty, 2009; Chakraborty 2011; Radatz and Mennis 2013). The spatial error model associates the autocorrelation with the error term, while the spatial lag model associates it with the dependent variable. While the choice between these two types of spatial regression models should be determined by the theorization of the spatial process being investigated, instead most empirical analyses base this decision upon the Lagrange Multiplier statistic (Chakraborty 2011). As this statistic was higher for the spatial lag for all four OLS regression models, this was the type of spatial regression model used here.

Results

In Southeastern Pennsylvania visually, the majority of point source toxicity locations are spatially clustered in Philadelphia County, although each of the other counties in the Southeastern Pennsylvania region also contain facilities, as shown in the attached maps.

Aims 1 and 2 – No additional work completed during this reporting period.




Philadelphia Median HH Income and EPA TRI
Produced by:
Ian M Dunham
Sal@T Cartography Lab
Temple University
Geography & Urban Studies
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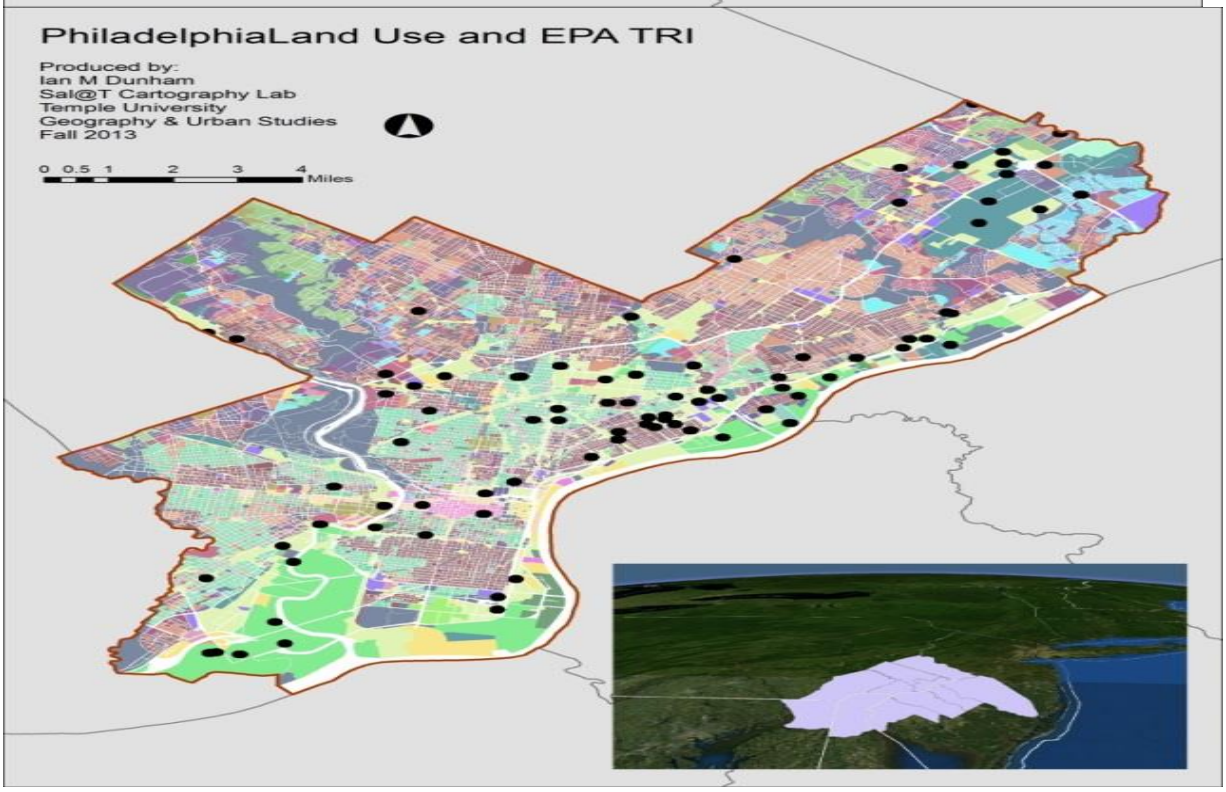
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Temple University
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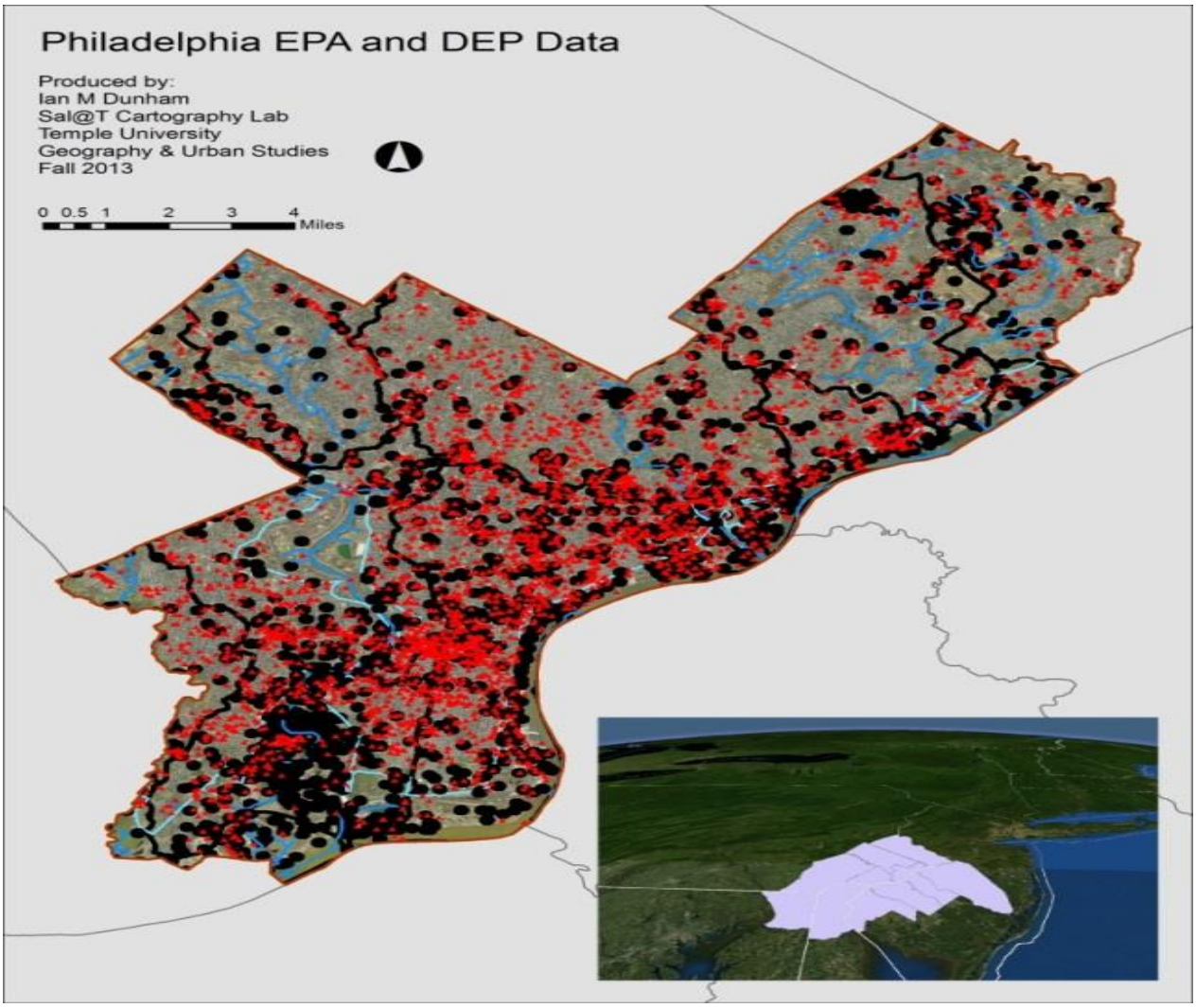
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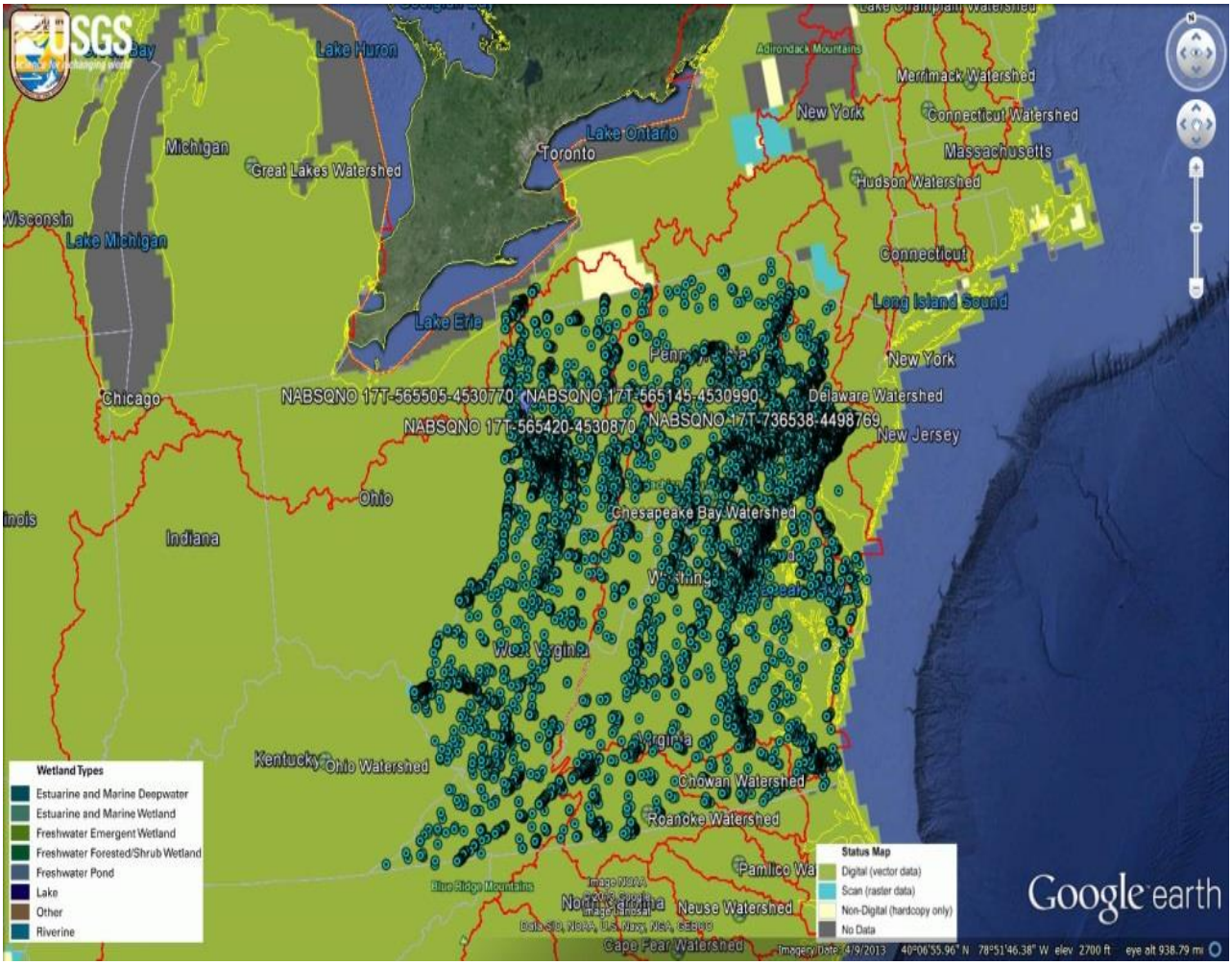

Wetland Types	
Estuarine and Marine Deepwater	Freshwater Pond
Estuarine and Marine Wetland	Lake
Freshwater Emergent Wetland	Other
Freshwater Forested/Shrub Wetland	Riverine

Research Project 4: Project Title and Purpose

Breast Lesion Characterization Using Tactile Imaging System for Patient-Centric Healthcare – The long-term goal of this research is to develop an easy-to-use premalignant tumor identification system for breast tumors. This will be available in primary care physicians' offices near the patients' homes. The purpose of this project is to develop a tactile image platform for in vivo breast lesion characterization using a tactile imaging system, which is a critical step towards our long-term goal. The literature shows that malignant breast tumors are stiffer than benign tumors. If a system can detect the size, mobility, and elasticity of the tumor, this information can be used to decide whether further medical help should be sought. We propose to develop a tactile imaging system that characterizes the lesion through its mechanical properties.

Anticipated Duration of Project

1/1/2012 – 12/31/2015

Project Overview

Even though 67% of the US women are screened for breast cancer, over 40,000 deaths occurred in 2008. The breast cancer incidence rate did not change much since 1990s. These facts suggest that hospital-centric paradigm might have reached a saturation point. In order to significantly increase the cancer detection rate, we need a paradigm shift from hospital-centric to patient-centric detection, where women will have much easier access to breast tumor detecting device near their homes such as primary care physicians' offices. This will enable more women, especially women in remote regions, developing countries, and younger women to detect breast cancer early. The broad research objective is to develop a device that will characterize breast lesions.

We hypothesize that a tactile imaging system that provides mechanical properties of a lesion will effectively characterize them. We believe that a tactile imaging system is able to distinguish between malignant tumors from healthy nodules with high probability. We have identified the following three specific aims.

Specific Aim 1. Tactile Imaging System Development. Emulating a human finger, we will design, build, and test a tactile imaging platform that can detect the size, mobility, and elasticity of breast lesions.

Specific Aim 2. Calibration and Intelligent Classification Algorithms. We propose to use custom made phantoms and real patient data to calibrate the system. Based on artificial intelligence, we will develop effective classification algorithms that can discern cancerous tumors from healthy nodules.

Specific Aim 3. System Test and Data Security. We will perform a small scale clinical test and assessment of the system. A critical part of the patient-centric cancer detection platform is data security. We will develop secure communication and access control schemes to protect patient data.

Principal Investigator

Chang-Hee Won, PhD
Associate Professor
College of Engineering
Temple University
1947 N. 12th Street
Philadelphia, PA 19122

Other Participating Researchers

Xiaojiang Du, PhD; Brian P. Butz, PhD – employed by Temple University
Dina F. Caroline, MD, PhD; Kathleen J. Reilly, MD – employed by Temple University Hospital

Expected Research Outcomes and Benefits

The expected outcome of the specific aim 1 of the project is a tactile imaging system that can identify elasticity, mobility, and size of a breast lesion. The outcome of aim 2 is a calibration method and intelligent classification algorithms. The outcomes of aim 3 are the performance analysis of the tactile imaging system and secure data communication/access schemes. Successful completion of this project will open a new chapter in early malignant tumor characterization. This will significantly increase the early breast cancer detection rate. Tactile imaging system has the potential to detect other forms of cancers, such as skin cancer, because tissue elasticity is an important discerning parameter. Furthermore, tactile imaging platform can be augmented with hyperspectral and thermal imaging techniques to provide more accurate cancer detection.

The benefits of tactile imaging system are good performance (in terms of sensitivity and specificity), harmless and noninvasive (no radiation), simple to use (operated by a nurse or the primary physician), and convenient (near patient's home such as in primary care physician's office). This system allows women in remote regions and developing countries to identify malignant lesions early. Tactile imaging system will discern malignant and benign lesions through the mechanical properties.

Summary of Research Completed

The developed TIS hardware is shown in Fig. 1. We developed a new algorithm to estimate the size and elasticity of the embedded inclusions. This is used to estimate the tumor size and elasticity. The phantoms are developed to test the system. Then we developed a classification algorithm.

Inclusion Size Estimation
The shape of the inclusions is assumed to be spherical. Fig. 2 shows the geometry of the silicone probe in contact with an inclusion or tissue under applied normal force, F. We developed a 3D interpolation model to estimate the size of tumors using TIS. In TIS application, the method correlates dependency among applied normal force, F, number of pixels on the compression-induced image, N_p, and the true diameter of the imaged inclusion, D. We developed 3D interpolation surfaces for a range of depth layers from the experimental data. The depths were assumed to be known and were not calculated in experiments prior to the size calculations. The combination of applied force, F, and number of pixels, N_p, in tactile image will be unique for a given tumor size and its depth. Thus, in order to find the size of the tumor, we have to specify its depth and the applied force during experiment, as well as to calculate the corresponding number of pixels on the tactile image.

Inclusion Stiffness Estimation

Elasticity describes ability of a tissue to recover its shape after the applied stress was removed. Human skin and soft tissues are perfect examples of elastic tissue recovery. Also, biological tissues have time dependent elasticity properties. We eliminated this dependency by applying the force with the constant small rate (2 N/s) during all experiments. For our calculation, we assumed the linear elastic behavior of the material. In this work, we developed an algorithm for the relative stiffness estimation. We used the changes in the indentation volume of the PDMS probe in order to capture the deformation of the tissue from compression.

The stiffness calculation procedure is as follows. First, we calculate the number of pixels, N_p, for each segmented compression-induced image. Second, we calculate the sum of intensities, *I*, for each image. Next, we calculate the indentation diameter for each image. In order to proceed with the indentation size calculation, we introduce a parameter called size scale factor, *SSF*. This parameter accounts on the relation between the area of contact and the applied to TIS force. The size scale factor is defined as follows,

$$SSF = \frac{A}{N_p}\ , \tag{2}$$

where *A* is the area of contact in mm^2, and N_p is the number of pixel in the captured TIS image. With the change of the applied force, the area of contact also changes, hence the number of pixel in TIS image. To predict a scale factor from force, area of contact, and number of pixel mapping, a polynomial regression model was used. If *F* is the force, applied perpendicularly to the surface of the probe, and *SSF* is the scale factor, obtained from the area of contact and number of pixel for that force *F*, the linear regression model is expressed as

$$SSF = p_1 F + p_2\,. \tag{3}$$

In order to calculate the indentation diameter for each TIS image *k*, we assume the area on the compression image to be circular.

$$d(k) = 2 \cdot \sqrt{\frac{SSF(k) \cdot N_p(k)}{\pi}}\ , \tag{4}$$

where integer *k* is a number of the corresponding compression-induced image.
Stress equation (5) will have the form

$$\sigma(k) = \frac{F(k) - F_{ref}}{A_{contact}}\ . \tag{5}$$

The reference values were chosen for each calculation out of the available data, and were assumed as the offset value. Next, we calculate the strain in vertical *z*-direction, ε_z, for each tactile image as follows,

$$\varepsilon_z(k) = \frac{I(k) - I_{ref}}{I_{ref}}\ , \tag{6}$$

where *I(k)* stands for the sum of intensities on the *k-th* tactile image, and I_{ref} is the sum of intensities on the image corresponding to the F_{ref}. Then, we calculated the stiffness, *E*, for sequential pairs of the acquired images.

$$E(k) = \frac{\sigma(k)}{\varepsilon_z(k)} \ . \tag{7}$$

Tumor Classification

Tumor classification was done using three well known clustering techniques: K-Nearest Neighbor (KNN), Support Vector Machines (SVMs), and Naïve Bayes (NB). The classification techniques were implemented in Matlab environment. K-Nearest Neighbor (KNN) is a non-parametric classification technique that may be used with arbitrary distributions and with no assumption on the forms of the underlying densities of the data. The approach of the method is to estimate density from the given data points. The number of neighbors, *k*, is one of the inputs to this classification method.

Support Vector Machines (SVMs) are a two-class classifier, which suits our application of breast cancer diagnostic well. SVMs classifier finds optimal decision surface for linearly separable data. If data is not linearly separable, SVMs map it into higher dimensions, where it will be linearly separable. Some of classification problems do not have a simple hyperplane to separate their data. As a solution for that, the SVMs algorithm relies on kernel methods. Commonly used kernels are polynomials and radial basis function, which are Gaussian functions. Overall, SVMs classifier searches for the optimal solution for particular data set, without it been trapped in the local minima.

Naïve Bayes (NB) uses the Bayes theorem as a parametric technique. It assumes independence of the data set features. This well-known method searches for the most likely class in the given data set. The assumption of the NB classifier is independence of features within a class. The method works in two steps: training and prediction. In the training step, it calculates the parameters of the assumed probability distribution for the training data. At the prediction step posterior probability is calculated for each new data point. Class assignments are made based on the largest posterior probability.

Breast Tissue Phantom

To test TIS algorithm, we developed a custom experimental silicone breast tissue phantom and soft inclusions. Tumor mimicking inclusions were of two different types: polyacrylonitrile (acrylic) spheres of different sizes, or fabricated polydimetyl siloxane spheres of varying stiffness. As a result, we implemented depth, size, and stiffness characteristics of tumors in our phantom. The phantom's schematics are shown in Fig. 3. Breast is composed of multiple layers and tissues. Our PVC phantom was fabricated to mimic breast tissues. It has skin, depth, intermediate, and base layers. The base layer (~125 kPa) mimics deep muscle and fibrous tissue. The intermediate layer (~10 kPa) imitates fatty tissue. Thin skin layer (~80 kPa) is a protection layer for phantom during compression experiments. Different layers were obtained by using premixed plastisol material or custom mixtures of regular liquid plastic, super soft liquid plastic, and softener components. Table I presents the phantom description in detail. The elastic moduli

of fabricated tissues and spherical phantoms were measured using Instron 4442, Instron Inc., in multiple compression experiments. The preload for all samples was 0.2 N. Crosshead speed was 300 mm/min. Spherical inclusions were not embedded in the tissue phantom permanently. To address the experimental objectives for the size and stiffness estimation, the inclusions were of two types. The first type was acrylic spheres of different sizes and constant stiffness. Those were used for the size algorithm development and its validation. The second type of tumors was made as PDMS spheres of different stiffness and constant size. Those were used for development and validation of the elasticity properties calculation algorithm. Table II describes properties and composition of the inclusions. Fig. 4 illustrates the components of the PVC tissue phantom and shows six soft PDMS spherical inclusions.

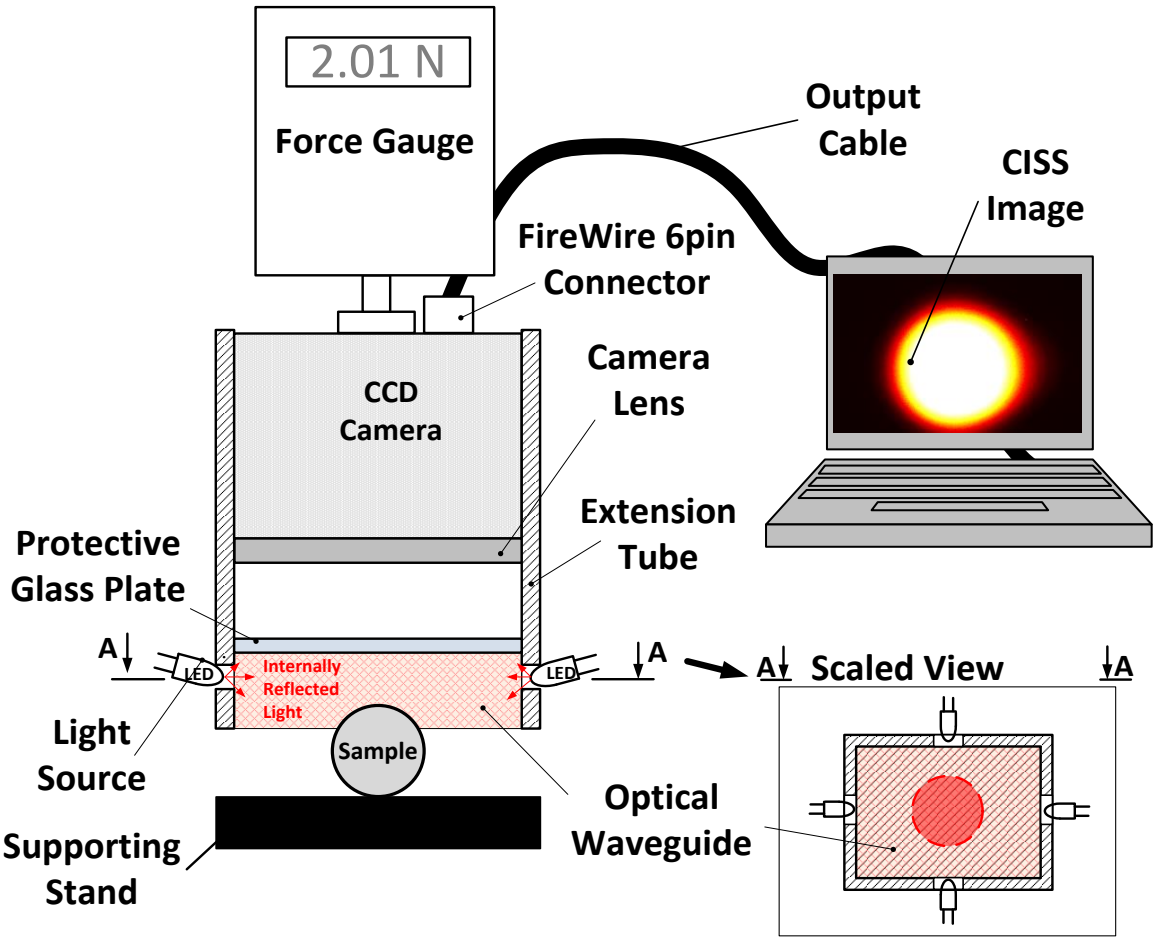

Figure 1: TIS Hardware Design

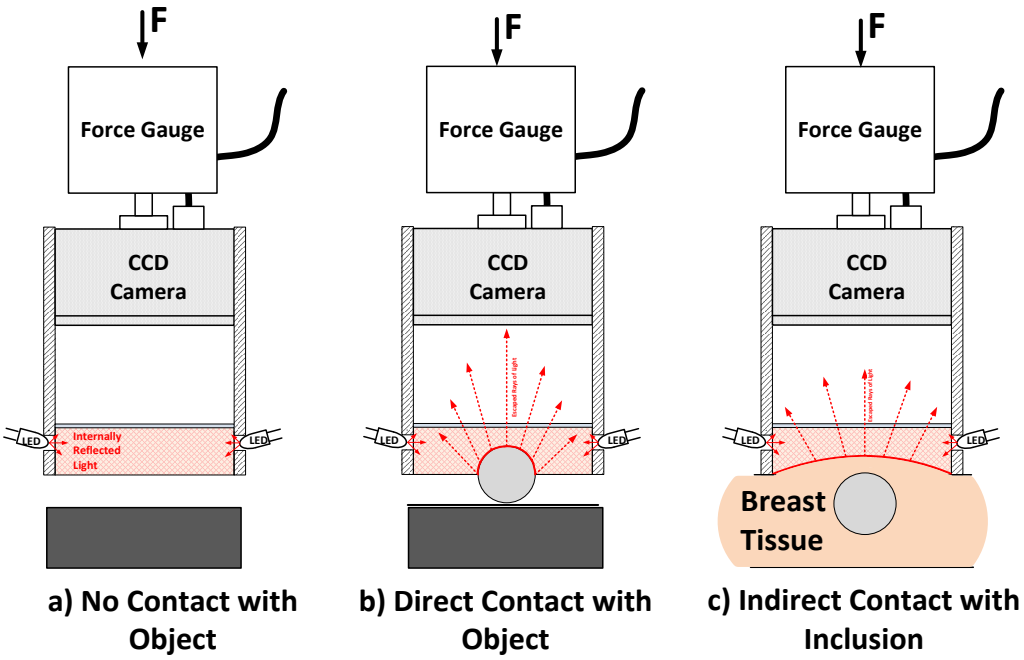

Figure 2: Conceptual Diagram of TIS Sensing Principle

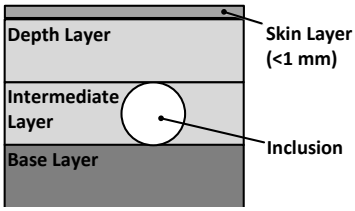

Figure 3. Schematics of the silicone tissue phantom with an inclusion.

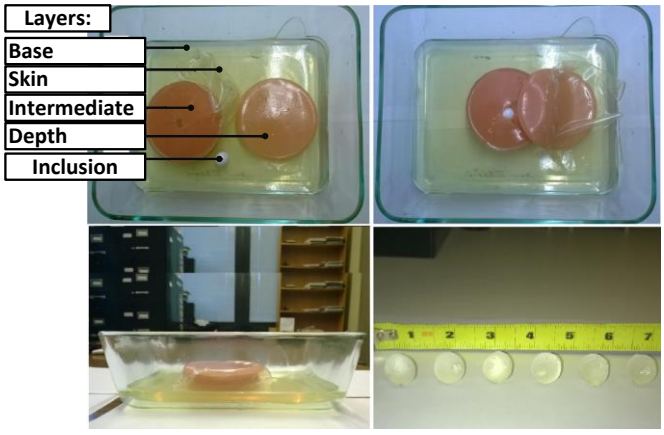

Figure 4. Images of PVC tissue phantom and soft spherical inclusions.

TABLE I

COMPOSITION AND PROPERTIES OF THE PVC TISSUE PHANTOM LAYERS

Layer	Color	Composition	Height, mm	Young's Modulus, k Pa
Base	Transparent	Regular Liquid Plastic	15	124
Depth	Fair Skin	Regular Liquid Plastic : Softener = 1:1	2, 4, 6, 8, 10	7
Intermediate	Fair Skin	Regular Liquid Plastic : Softener = 1:1	10, 16	7
Skin	Transparent	Super Soft Liquid Plastic	<1	78

TABLE II

COMPOSITION AND PROPERTIES OF THE SPHERICAL TUMORS

Material	Used in Development of	Size, mm	Fabrication Ratio (Base : Curing) agent	Young's Modulus (stiffness), kPa
Polyacrylonitrile (Acrylic)	Size Algorithm	8.02, 8.80, 9.85, 11.85, 13.78, 15.47	N/A	200,000 ~ 390,000
Polydimethyl siloxane (PDMS)	Elasticity Algorithm	16.00	1:2, 1:3, 1:4, 1:5, 1:7.5, 1:10, 1:20	18, 134, 192, 236, 308, 355, 466

Research Project 5: Project Title and Purpose

Neurodevelopmental Markers of Intermittent Explosive Disorder: From Neurotransmitters to Neighborhoods – The proposed study will evaluate neurodevelopmental and contextual processes linked to Intermittent Explosive Disorder (IED). This will be done by comparing 30 youth with IED and 30 youth without IED aged 12-14 at baseline, 6 month and 1 year follow-up on a comprehensive battery of self-report, behavioral, neurofunctional and biological measures. This will be the first comprehensive examination of neurodevelopmental and contextual factors associated with IED among at-risk adolescents. Study data would be used for a large scale (R01) multi-site extension of the proposed study and a (R34) treatment study to address biological, cognitive-affective, and contextual problems identified during this developmental period.

Anticipated Duration of Project

3/1/2013 – 12/31/2015

Project Overview

The proposed study will evaluate neurodevelopmental and contextual processes linked to Intermittent Explosive Disorder (IED). Sixty youth (30 with IED and 30 without IED) aged 12-14 will complete a comprehensive baseline neurodevelopmental battery using multiple levels of analysis. The battery will include self- and parent-report measures indexing IED symptoms and comorbid psychopathology, executive functioning, emotion regulation, and contextual variables (e.g., exposure to aggression, childhood trauma, family and neighborhood environment). In addition, youth will complete behavioral measures of emotion regulation and executive functioning. Neighborhood-level data (e.g., violence, poverty levels, service accessibility) will be obtained to index contextual influences. Participants then will complete a neuroimaging session that includes an emotion regulation task, impulsivity task, and behavioral aggression task developed by the Principal Investigators (PIs). Serotonin (5-HT) functioning will be assessed non-invasively using the loudness dependence of auditory evoked potentials (LDAEP). Finally, blood will be collected for genetic analysis. Youth will receive the same neurodevelopmental battery and IED assessment (without neuroimaging) at 6-month and (including neuroimaging) at 1- year follow-up. This study will constitute the first comprehensive examination of neurodevelopmental and contextual factors associated with IED ever conducted and the first among at-risk, young adolescents. The broad research objective is to increase our understanding of neurodevelopmental and contextual processes associated with affective aggression. Our specific aims are as follows: 1. Identify neurodevelopmental and contextual variables associated with concurrent IED: We hypothesize that youth with IED will differ in levels of biological (e.g., increased amygdala activity and LDEAP), cognitive-affective (e.g., poorer emotion regulation), and contextual (e.g., higher familial conflict) domains from youth without IED, and 2. Identify neurodevelopmental and contextual variables that predict IED diagnostic status: We hypothesize that the aforementioned deficits will predict IED diagnostic status at 6-month and 1- year follow-up.

Principal Investigator

Deborah Drabick, PhD
Associate Professor of Psychology
Temple University
Weiss Hall, 1701 N 13th Street
Philadelphia, PA 19122

Other Participating Researchers

Michael McCloskey, PhD; Melissa Gilbert, PhD – employed by Temple University
Feroze Mohamed, PhD; Diedre Reynolds, MD – employed by Temple University Hospital

Expected Research Outcomes and Benefits

Recurrent, impulsive aggressive behavior poses significant concerns and costs for our society from the viewpoints of the individual who engages in these behaviors and the people and property that these behaviors target. Recurrent, problematic, impulsive aggressive behavior may

be present in up to 7% of the general population and recent, severe incidents of youth violence highlight the impact of this aggression on society. Thus, there is an obvious need and obligation to treat youth with problems with aggression, particularly during early adolescence when the neurodevelopmental processes underpinning IED may be more amenable to intervention. *The proposed study would represent a seminal investigation into the neurodevelopmental trajectory of the primary disorder of affective aggression, IED*. Findings from the study will have immediate and long-term benefits to the research community, Temple University, and society. This study would introduce a translational, biologically, developmentally, and contextually informed approach to the study of IED. Data from this study would also pave the way for larger investigations into the etiology and treatment of IED (i.e., NIH RO1 grants on the prevention of IED among at–risk adolescents, and the development of neuro-developmentally informed treatments for IED), with the long-term result of reducing the sequelae to patients and society associated with IED. In addition, with the combined expertise of their research team and other expert researchers at Temple University, this research would help to position Temple University as an *international leader* on IED and related aggressive disorders across the lifespan.

Summary of Research Completed

No subjects have been recruited during this period. Recruitment was delayed primarily due to the IRB amendment and revision of the fMRI tasks. The IRB amendment took several months for completion and approval. Additionally, the FMRI tasks were modified 4 times to ensure optimal compatibility for our age group. After just having piloted our final subject for the fMRI tasks we are now beginning recruitment. Although no subjects have been recruited and thus no data have been generated during this reporting period, we anticipate enrolling subjects in the next 6-9 months. We have completed the following tasks to date:

Recruitment and Training of Project Personnel
A research assistant has been hired to assist with project management (i.e., updating the protocol, modifying self and parent report measures and interviews, development of assessment protocol, piloting of protocol, development of advertising materials, facilitating training sessions and overseeing participant visits). Graduate-student-level interviewers have been trained in the administration of self and parent report measures, interviews, buccal swab, and the Paced Auditory Serial Addition Task.

Piloting and Troubleshooting of fMRI Tasks
Initial fMRI pilot scan was run after tasks had been revised and completed by NIH collaborators. Scan time was reduced by reducing the Justice Paradigm to three instead of four trials and by removing all inanimate objects from the Looming Task. After running the initial pilot scan, the initial 5 repetition time (TR) and remaining fixed TR of 2000ms was removed from all tasks to cut down scan time further and to allow for consistency in timing of the tasks.

All fMRI tasks were programmed for both the scanner response box and keyboard for troubleshooting outside of the scanner. Shortened versions of the tasks were created as practice versions for subjects prior to the scan visit.

The Justice Paradigm keyboard response version has been modified for keys 2-5 to correspond to

index – pinky finger for the scanner response box.

Our fMRI technician, research assistant, PIs, and our collaborators who work at NIH have run tasks again to troubleshoot for additional timing issues and to compare tasks timing prior to next trial run. Further piloting will be completed by the end of July 2014 to facilitate recruitment in August 2014.

Development and Finalization of Self and Parent Report Measures and Behavioral Tasks
Our list of study measures has expanded immensely. A literature search was completed to assist in the development of protocol measures. This included the addition of 11 new measures (including neighborhood cohesion, aggression, self-harm, suicidal ideation, and other psychopathology measures), as well as identification of community-based indices and assessment procedures for indexing these factors. An updated IRB protocol was developed and submitted with these new and revised tasks and responses to IRB requests have been submitted. Changes to the protocol and IRB requirements delayed participant recruitment as well.

Once the measures were located and reviewed, they were added to our surveying instrument and were piloted by graduate level interviews and research assistant. All measures have been modified for our participant age group, including editing of instructions and potential responses so that the measures are all developmentally appropriate. All questionnaires and interviews have been finalized for the commencement of study recruitment.

Detailed procedural manuals have been created for the administration of the visits including separate instructions for administering all self and parent report measures, behavioral tasks, and fMRI tasks. These protocols have been piloted and reviewed and also are ready for study initiation.
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Additional Study Preparation Tasks
Additional tasks have been completed to prepare for recruitment. These tasks have included setting up the space where visits will be held, updating and installing of all tasks onto our computers, finalizing recruitment materials (brochures, flyers, ads), researching potential resources to aid in recruitment (community centers and public libraries), setting up a petty cash account for subject payment and purchasing necessary office supplies such as receipt books for subject payment, envelopes, binders and stamps for participant communication between visits, and a freezer to store Oragene kits for DNA testing.