EXAMPLE

1

Social Facilitation of Little Blue Penguin Breeding Behavior:
Impacts on Female Mate Choice and Male-Male Competition

Abstract

I recently received a Fordham Faculty Fellowship to investigate the socially-facilitated breeding behavior of Little Blue Penguins (*Eudyptula minor*) in New Zealand. Through socially-facilitated behaviors, populations can increase reproductive success by better synchronizing breeding. I will conduct a series of playback experiments to explore the interrelationship between social facilitation and both female mate choice and male-male competition. I will be hosted by and collaborating with Dr. Joseph Waas of the University of Waikato in Hamilton, New Zealand. I am requesting a Fordham Faculty Research Grant (FRG) to complement the University of Waikato's contribution to my Faculty Fellowship research project—specifically, to travel to the field research site and hire a research assistant—as the Faculty Fellowship does not provide funding for these research costs. The University of Waikato will provide me with office space and access to all institutional facilities necessary. My lab has substantial video/audio equipment, and Dr. Waas' lab has an extensive array of audio/video gear, boats if necessary, excellent technical support, and a network of local expertise. Dr. Waas' extensive experience will facilitate the acquisition of necessary permits for this research.

With FRG support, I will arrive in New Zealand May 2011 and begin field work at penguin populations as soon as I arrive. New Zealand has more penguin species than any other country, and my collaborator, Dr. Waas, laid the foundation for much of our current understanding of penguin behavioral ecology, particularly vocalizations and their role in social facilitation. Potential field sites are convenient: Tiritiri Matangi Island is two hours from the University of Waikato and has research facilities and accommodations, and the City of Tauranga is only an hour away. My proposed research is compact enough to be completed by the end of the Fellowship period and the Fordham 2011 Fall Semester. I plan to submit two peer-reviewed articles for publication and an external grant proposal to the National Science Foundation the subsequent year.

Background

This project is a direct extension of my Ph.D. dissertation research, which focused on the vocalizations of Magellanic Penguins (*Spheniscus magellanicus*), particularly their role in individual recognition, female mate choice, and social facilitation of breeding activity, primarily through observation, call analysis, and playback experiments (Clark 2006). My research with Magellanic Penguins showed reduced sexual activity in less densely populated areas of the colony and that playing prerecorded vocalizations increased both calling rates and sexual activity (Clark & Boersma, in revision). Recently, I and my undergraduate students conducted playback experiments at the Bronx Zoo to determine whether we could use social facilitation techniques to increase the breeding success of the Zoo's populations of endangered Northern Bald Ibis (Clark et al., in prep.), as well as both American and Chilean Flamingos (Clark et al. in review). All three studies were successful in increasing breeding behaviors. I have conducted playbacks experiments of the type proposed here on nine bird species. My collaborator in New Zealand, Dr. Waas, has studied and published extensively on the behavioral ecology of both penguins and other avian species. Dr. Waas and I are the two leading researchers in the field of social facilitation of breeding behavior in penguins. Our hope is that this research project will lead to substantial future collaborative research.

More specifically, "social facilitation" is the increase in a behavior's intensity or frequency resulting when individuals of the same species perform the same behavior (Darling 1938). For example, in seabirds and other animals, vocalizations and sexual activity are often socially-facilitated: when one bird vocalizes, neighbors may vocalize in response (Gochfield 1980). In humans, yawning is sometimes considered a socially-facilitated behavior. Socially-facilitated behavior is an important component of nesting colonially (Waas et al. 2005). Benefits of social facilitation include increased foraging success, improved defense of nests and young, and reproductive synchrony (Clayton 1978).

Social facilitation via vocalizations has been documented in several penguin species (Waas 1988, 1995, 2000; Clark 2006). Major hypotheses for why calling in penguins might be socially-facilitated

include intra-sexual competition for mates and nest defense (Waas 1995). These two hypotheses are not mutually exclusive. Single males often produce display calls in the presence of potential mates, and consequently, neighboring males may perceive the display calls of other males as an indication that an available female is present. The neighbor's subsequent calls may then be an attempt both to attract the female to their nest and warn neighbors away (Waas 1995). Male calls also contain individually-specific vocal signatures that have the potential to code information on identity and male quality (Clark 2006). Females may use the information coded in these vocalizations during mate choice (Clark & Boersma, in revision).

I propose to test how social facilitation effects influence both male-male competition and female mate choice. In particular, I am interested in how the rate of male solo calling—given that calling is likely to be energetically expensive—may be accepted as an "honest signal": one that not only demonstrates superior strength to neighboring males, but also demonstrates the male's true condition to females.

Contribution

A surge of recent research by entomologists has escalated focus and attention on the study of social facilitation. The research I propose extends this recent research, and I will draw connections and overarching principles from social facilitation research on both vertebrates and invertebrates. In addition, the role of vocalizations in facilitating breeding behavior has substantial conservation relevance, particularly for recovery and reintroduction efforts for endangered species. Worldwide, nearly all penguin and many other colonial species are in serious decline. The basic applied research I propose will add significantly to our understanding of the role of vocalizations in facilitation of breeding behavior and how the use of acoustic enrichment and stimulation can help recover, maintain, and establish populations of declining, threatened, and endangered species.

To make these contributions, I will test how social facilitation impacts both male-male competition and female mate choice by undertaking a series of playback experiments. Initially, I will conduct several simple playback experiments to determine if females are more likely to be attracted to a

speaker producing high call rates than to speakers producing average and low call rates. I will then test

whether call rates influence the likelihood of male approach. Finally, I will alter call rate during playback,

i.e., treatments where call rate is increased during the sequence versus treatments where call rate is

decreased. I will use traditional playback equipment, including field speakers, digital recorders, and

digital music players.

Furthermore, the results of this research and its commensurate collaboration with Dr. Waas will

go beyond mere academic interest. Dr. Waas and I plan to build upon our efforts this summer to jointly

develop a lecture series and media program to increase public awareness of the underappreciated plight of

mainland Little Blue Penguins in New Zealand, most of which have disappeared because of habitat loss

and introduced mammalian predators. I also plan to use my background and experience in endangered

species law and policy to give several lectures/workshops for the Department of Conservation, University

of Waikato, and Auckland Law School outlining lessons learned from North American approaches to

endangered species protection and recovery.

Costs

As noted above, my New Zealand collaborator, Dr. Waas, has generously offered to provide me

with office space at the University of Waikato and all equipment necessary for this proposed research,

including boats, recording equipment, playback equipment, etc. The purpose of this FRG application is to

request the following:

Budget Item	Rationale/Role
B. Graduate Research Assistant (RA)	Stipend of $500.00 – representing approximately 20 hours/week for two weeks at $12.50/hour. The graduate student (who will already be in New Zealand) will help with experimental setup and implementation and will greatly increase the feasibility of portions of this proposed research.
D. Foreign Travel	Flight from New York to Auckland, New Zealand is required to access research project study sites.
D. Lodging & Expenses	Lodging is needed near the study sites, and funding will facilitate rental of housing during the first three months of the research period.

Conclusion

  A Fordham FRG will facilitate implementation of my Fordham Faculty Fellowship research. The goal of the Fellowship and this FRG request is to establish a new line of collaborative research that will be used as the foundation for an application for funding from the National Science Foundation. Because the Little Blue Penguin breeding season in New Zealand occurs during the northern summer, new opportunities for undergraduate and graduate student research will become available. My research on South American penguins proved problematic for continuing research, as those penguins breed during the austral summer, when I and my students are teaching and/or taking classes.

  I have worked directly with the Wildlife Conservation Society/Bronx Zoo to apply my background in social facilitation theory to improve the breeding success of several colonial bird species at the Zoo through acoustic stimulation. These acoustic stimulation projects were highly successful, leading to significant public press and invitations for assistance from other zoos and from managers of endangered populations of colonial birds to participate in additional research projects. Building an even better understanding of social facilitation and acoustic enrichment will not only provide advances in the academic field of behavioral ecology, but it will (1) provide a foundation for increasing the success of captive breeding and reintroduction programs for endangered species, and (2) contribute to the further expansion of Fordham's collaborative relationship with the Wildlife Conservation Society through the development and implementation of new behavioral techniques to benefit captive populations.

  I expect to produce two peer-reviewed publications based on this research by January 2012 and to submit a grant application to the National Science Foundation to expand on this research in July 2012. These publications and any successful grant applications will help further establish me as an expert in behavioral ecology and animal conservation. Finally, the research I propose builds on my past and present research, allows me to tighter integrate my conservation and ecology research goals, advances the fields of behavioral ecology and conservation, furthers my academic credentials, extends the reach of Fordham University's reputation, and provides the foundation for a long-term collaborative research program with potential benefits to both myself as well as Fordham's undergraduate and graduate students.

EXAMPLE

2

Alzheimer's Disease in the Workplace:

A Proposed Collaboration with the University of Haifa, Israel

Abstract

The proposed project will build on the work of my Spring, 2011, Fordham Faculty Fellowship, which is examining the impact of an aging workforce on employers. Specifically, I am conducting a survey on the impact of dementia on the workplace including the policies and practices of employers towards employees who are caregivers of persons with Alzheimer's disease or other forms of dementia; and employer responses to employees who may themselves have symptoms of Alzheimer's. The aging of the population has become a worldwide phenomenon, concomitantly; addressing Alzheimer's disease and its impact has become a global challenge (Alzheimer's International, 2010).

A Faculty Research Grant (FRG) would enable me to take advantage of an invitation to collaborate with researchers in Haifa, Israel, who have been studying workplace responses to caregivers of aging relatives (Katz,, Lowenstein, Prilutsky, & Halperin, (forthcoming). The collaboration would permit us to share our findings, develop policy and practice recommendations, and formulate plans for further research, including other international studies. Our work would be the first international and comparative examination of how employers are responding to specific issues associated with an older workforce. I will be working closely with Dr. Ariela Lowenstein, Head of the Center for Research and Study of Aging, Department of Gerontology, School of Social Welfare and Health Sciences, University of Haifa (see attached letter). We plan on presenting our research at the 2012 International Federation of Aging Conference as well as submitting articles to *The Gerontologist* and the *International Journal of Aging and Human Development*.

Background

The Alzheimer's Association estimates that 5.3 million Americans have Alzheimer's disease (AD) or another form of age-related dementia and that approximately 500,000 of these persons are below the Social Security retirement age (Alzheimer's Association, 2010). In 2009, more than 10 million family members and friends were caregivers for a person with one of these illnesses. Many have to quit work, reduce work hours, or take time off because of care giving, with a commensurate cost to US businesses of $61 billion per year, more than half of which is attributed to lost worker productivity. By the middle of the 21s Century, the number of people affected by Alzheimer's disease will increase 350 percent.

The United States is not alone in dealing with economic, social, and personal costs of this devastating illness. The International Federation of Aging has made Alzheimer's disease one of the themes for its 2012 Conference. Moreover, Alzheimer's Disease International (2010) has presented a charter to the World Health Organization (WHO) to encourage it to make dementia a global health priority and to improve policy and services for those impacted by the disease.

I have been doing research about the social impact of Alzheimer's disease for over twenty years (see references}. I have worked as a consultant for the Alzheimer's Association evaluating their care management (Cox and Albisu, 2001) and national respite program (Cox, 1997, Cox & Vierdieck, 1998) and I continue to be a grant reviewer for the Association. I contributed the section on Alzheimer's and Social Work for the 2008 Encyclopedia of Social Work and am the editor of Dementia and Social Work Practice: Theories and Interventions (Springer, 2007). In 2009, the Eastern Australia Dementia Study and Training Center invited me as a guest lecturer to present a series of workshops and lectures on AD to researchers and professionals in Queensland, Australia. The invitation to work with the team in Haifa would

enable me to expand my current research on AD and dementia in the specific area of the workplace and to study it from a cross-national perspective.

Contribution

The proposed project will advance scholarship in the areas of sociology and social issues associated with the workplace. As the workforce continues to age, it is critical to develop new policies relevant to the needs of these changing employees. Flexible work schedules, job sharing, and part time work are among the options that employers may need to consider. In addition, specific training in counseling and referrals and making appropriate accommodations and transitions for employees with the illness may also be required. By helping to define the current status of the workplace with regards to these challenges, the findings from this study should assist in identifying the areas where further research, guidance, policies, and interventions are needed.

During the first week of January, the Human Resource Association of New York sent to its more than 2000 members, via Survey Monkey, a survey that I have developed regarding the experiences of human resource personnel with AD and dementia among their workers (see attached letter and survey). Within the next few weeks, the survey will be expanded to include human resource associations in other areas of the country. This is the first study to explore the impact of the illness in the workplace. Whereas the researchers in Israel have much data on employed caregivers, they have not studied the specific impact of AD or dementia. Thus our studies are complementary and will provide an important foundation for further research on policies and practices.

During the time in Israel, we will be comparing our data to determine similarities and differences in responses and any specific patterns in the results. As an example, we will be

looking to see if there are variations related to size of company, type of employer, or employer training and their policies and responses to employees. We will also be looking at the data for interactions between variables such as size and type of workplace and the characteristics of the managers and their relationships to employer responses.

Multivariate analysis using techniques such as logistic and linear regression will be utilized to examine the input of several independent variables on outcomes such as employer responses. By doing this with each of our independent data sets, we will be able to determine if similar factors have the same relevance in the two countries. This is necessary for generalizing the findings and making recommendations for further research. We will also pursue the possibility of creating one pooled data set that we can use for further analysis.

Another area that we will be exploring is the extent to which government legislation may impact workplace policy. Israel provides government assistance for caregivers in terms of respite and home help and it will be interesting to see how this may relate to individual employer policies. Such findings may be particularly relevant to policy development and initiatives in the United States and other countries.

The specific objectives of the analyses will be to:

1) Determine what factors relate to specific employer policies and practice with regards to caregivers and employees that may have symptoms of dementia.

2) Determine what factors relate to employer willingness to adapt specific policies for these populations.

3) Determine similarities and differences between New York and Israel with regards to employee policies and responses.

4) Identify specific areas in which employers may require further training, consultation or information

5) Explore the impact of government policy on employer responses and practices.

6) Develop recommendations that may be adapted by employers to help improve their responses and accommodations to caregivers and to employees who may suffer from the disease.

7) Develop a survey instrument that builds on our findings that may be used in other cross national studies of how employers are responding to Alzheimer's disease among caregivers and employees.

Cost

I am requesting $3510 for this project. The full amount of the award will be used toward airfare ($1350 RT approx from Washington DC to Tel Aviv), local transport and per diem (within US State Department guidelines) during my 18-day stay in Haifa. I am estimating these costs at $120 per day as The University of Haifa is giving me a reduced rate for accommodation in student housing ($50.00 per day) as well as providing me with an office, administrative assistance, and technological support.

Conclusion

If awarded, an FRG would enable me to capitalize on an invitation to collaborate with researchers in Haifa, Israel in the first international and comparative examination of how employers are responding to issues of an aging workplace. With the opportunity to directly interact with the researchers and share our data, we will be in a position to develop new insights into the factors associated with developing responsive policies. As well as the development of presentations and papers, the collaboration will enhance the global ties of Fordham University and its Graduate School of Social in a project that has potential significance for all countries working to meet the challenges of an aging workforce.

EXAMPLE

3

**Evaluating the Effectiveness of Subsidized Training Programs
for Low Income Women in New Delhi, India: A Randomized Experiment**

Abstract

If awarded, a Fordham Faculty Research Grant would provide critical funding to complement start-up money received from Australia's Monash University by my co-researcher Professor Pushkar Maitra in support of our research collaboration in New Delhi, India with the NGO Pratham (http://www.pratham.org).   The objective of this collaboration is to conduct a randomized filed experiment to estimate the causal effect of a specific, well-designed vocational training program on employment opportunities and earning potential among 18 to 39 year old women residing in selected slum communities of New Delhi, India. The timeline for our collaboration will be as follows:

Completed	Selection of slums, conducting pre-baseline survey to assess potential need for/benefits of such training programs (the pre-baseline questionnaire is appended)
March-April 2010	Prepare and pre-test questionnaires to be used for the baseline survey and all subsequent follow-ups
May-June 2010	Invite applicants for participation, conduct randomization and baseline survey of all participants
June-August 2010	Provide vocational training to all participants in the treatment group
December 2010	Conduct three-month follow-up survey of all participants to measure the impact of the training program
February-April 2011	Conduct six-month follow-up survey of all participants, treatment and control groups

The results of this experiment will result in at least two research papers that will be:

(i)   presented at the 2011 Econometric Society meetings and the 2011 North East Universities Development Conference

(ii)   submitted to refereed international journals like the Journal of Development Economics, Journal of Human Resources, and/or Journal of Labour Economics;

(iii) of immense practical value to the development efforts of Pratham, government of India, and its peers in India.

(iv) In addition to the two papers already mentioned, this project will also result in 2 or more research papers in which we will be collaborating with Professor Utteeyo Dasgupta (Assistant Professor of economics at Franklin and Marshall College) and Professor Lata Gangadharan (Professor of economics at Monash University) to run games in the field to measure behavioral outcomes such as confidence, trust, tastes and preferences, household decision making etc. Both these collaborators have experience in running lab experiments and we are extending some of these laboratory tests to our field in New Delhi, India. We are currently in the process of working out how to extend the lab games into the field with the help of Professors Dasgupta and Gangadharan. Additional funding for these games will come from Franklin and Marshall College and or Monash University.

Background

I specialize in the field of development economics and have and continue to work with large-scale micro-level household survey data to examine programs and policies that foster economic development at the individual and household level. My own research and others in the field have found that there is a strong positive association between early childhood development and future well being hence greater emphasis on improving children's welfare outcomes [Mani (2008), Mani et. al (2009), Strauss and Thomas (2008)]. Among children's programs, conditional cash transfer programs have had significant impact on improving children's health and educational outcomes in developing countries (see Parker et. al (2008) for a recent review). In the long run, such interventions are seen as major instruments for combating poverty in developing countries.

While it is generally accepted that such programs are suitable for young children, there is insufficient evidence on programs and policies that can improve earning and living conditions

among young adults in developing countries, where low levels of education combined with lack of skilled training constrain earnings among the poor. The opportunity cost of obtaining formal education is very high for individuals already of working age; for this reason vocational training may be a more suitable support to provide in order to improve this group's standard of living. Furthermore, if a vocational training program were demonstrated to achieve these results, it would also have a commensurate impact on long-term economic development due to the demonstrated association between increased income and improvements in the health and education of the next generation. [Mani (2008), Mani, et. al (2009)].

Although there is a vast literature that assesses the impact of vocational training programs on earnings and employment opportunities using data from developed countries (see Heckman, LaLonde and Smith, 1999 for a review), to apply these findings to developing country economies may be inappropriate. First, much of this literature focuses on simple "on the job training" programs (Ashenfelter, 1978) as opposed to comprehensive skill building programs geared to enable entry into the general market for higher end labor. Second, much of this literature also uses non-experimental data, and therefore cannot estimate the causal effect of training on employment related outcomes due to selection bias (Lalonde, 1986; Ashenfelter and Card, 1985). This is because participation in training programs is often voluntary, making it difficult to disentangle the impact of training from other factors such as innate ability or preferences that have a direct affect on the outcome variable.

Unfortunately, there is only limited literature that evaluates the impact of vocational training programs on employment and earnings, and almost none that evaluates these programs in developing countries (Attanasio, Kugler and Meghir, 2009 and Card et al., 2007 are two exceptions).

Contribution

The proposed research collaboration will contribute to closing this gap by assessing the impact of a vocational training program using randomized field experiment methods on the

income and employment among 18 to 39 year old women residing in a set of slums in New Delhi, India. The vocational training will be a stitching/tailoring program designed in part and implemented in whole by our partner NGO Pratham. Pratham is the largest NGO in India and has successfully initiated and implemented various educational programs among children all over India and has an ongoing vocational skills program in agriculture and banking in Maharashtra, India. In our initiative we have chosen stitching/tailoring based on the results obtained from a pre-baseline survey I created and collected with the help of Pratham, in which more than 52% of respondents showed interest in developing vocational skills in this arena (see Q15 of the appended questionnaire).

Women interested in participating in the program will be required to submit an application form to the agents of Pratham. Only 1 applicant from each household will be eligible for training. The applications that fulfill the age eligibility criteria will be set aside and a list of all potential eligible participants will be drawn: the "master list". We will then randomly assign individuals from this master list into two groups: the "treatment" group and the "control" group. The treatment group will receive no cost vocational training, while the control group will not receive training for the duration of the experiment (although training will be offered to all participants' post the conclusion of the experiment). Randomization will occur at the individual level within each of the three selected slum communities of New Delhi. Our research protocol will be submitted for approval to the IRB of Monash University and Fordham University.

Professor Pushkar Maitra (please see his complete resume at the following web address http://www-personal.buseco.monash.edu.au/~maitra/cv.pdf) from Monash University has over 12 years of research experience in the field of development economics. His theoretical and empirical contributions in the field make him a suitable partner in this project. His research experience combined with my research initiatives and ideas will help us publish interesting papers through this project.

Together, we will assess the direct impact vocational training had on participants' employment and earnings. We will also assess the impact of some of this training on measures of

household bargaining and transfers. We are likely to find that our treatment group will have higher probability of employment and earnings compared to our control group. Our treatment group, due to participation in the program is also likely to exhibit behavioral changes in tastes and preferences, confidence levels and motivation. These will be captured through laboratory games designed to be played in the field.

Cost

I am requesting Fordham-funding for data collection at baseline and during the follow-up period (funding for research assistants, photocopying and the provision of vocational training is covered by a research grant from Monash University). A total of three surveys remain to be conducted: the baseline household/socioeconomic survey of all applicants to the program and the two aforementioned follow-up surveys to estimate the effects of the program three and six months post its conclusion. The surveys will be conducted by Pratham, and both the treatment and the control group will be surveyed in order to ascertain the true effects of the program, controlling for receiving the training and initial conditions. We expect around 300 applicants to the program who will be randomly allocated to the treatment and the control group. The per unit cost of collecting, cleaning and providing summary report is Rs 170 ($4) per individual *3 rounds*300 participants = $3600.

Conclusion

This proposed project is an innovative initiative where we will be using a randomized field experiment methods to assess the impact of a vocational training program on the income and employment of 18 to 39 year old women residing in a set of slums in New Delhi, India. Our findings will be published in reputed journals in the field of Economics and will provide insights to local NGOs and government of India who invest in such initiatives.

EXAMPLE

4

Title: Phototoxicity of drugs and nanoparticles in the human eye

Abstract

If awarded, a Faculty Research Grant would enable me to capitalize on a peer-reviewed invitation to conduct research this summer in collaboration with my two post-doctoral fellows (Albert Wielgus, Ph.D. and Baozhong Zhao, Ph.D) at the National Institutes of Environmental Health Sciences (NIEHS), a North Carolina located unit of the National Institute of Health (NIH). Fordham's support is critical for five reasons:

(i) I do not have laboratory space at Fordham, and this type of collaboration is essential if I am to access the multimillion dollar photophysical equipment and human ocular tissues my research requires;

(ii) Due to the untimely death of the PI (Colin Chignell, July 2008) at the NIEHS' Photobiology laboratory, I have become the scientific head of this laboratory, requiring my presence as current titular PI for the successful completion of the projects that are the subject of this proposal;

(iii) Due to Federal budget cuts, in 2010 the NIEHS will not be able to cover my costs of travel and stay at their facility as in past years, and I will also have to cover some of my cost of supplies;

(iv) The NIEHS has, however, donated HPLC [High Pressure Liquid Chromatogram] equipment with fluorescence detectors (valued at $20,000) to Fordham's Department of

Natural Sciences through my initiative, the cost for packing and shipping of which would also be covered under this grant;

(v) In addition to the two scholarly articles I intend to produce from this summer's research for submission [Toxicology and Applied Pharmacology, Photochemistry Phtobiology]the NIEHS also anticipates making external grants available in my area of "nanosafety' for 2011-12, for which my work at their facility this summer will place me in an advantageous position.

Background

Everyone over the age of 65 is susceptible to developing cataracts and macular degeneration. In the next 30 years over 24 % of the population of the United States will be over the age of 65 and are therefore at risk for these blinding disorders. Although sight may be restored by an operation to remove cataracts, there is currently no effective treatment for retinal or macular degeneration. My ongoing research is to identify environmental risk factors that lead to these age-related blinding diseases and examine ways to prevent such damage. In addition to environmental hazards, there are dyes, drugs, over the counter medications and nanoparticles that can dramatically enhance phototoxic reactions in the human eye leading to early development (i.e., at 40 years old) of cataracts and macular or retinal degeneration.

The NIEHS facility at which I have been conducting this research for the past 12 years is a multidisciplinary lab that allows me access to multimillion dollar laser and photochemical equipment. During the summer of 2008 and my Spring 2009 Faculty Fellowship I developed at NIEHS an *in vitro* system using human lens epithelial cells to define phototoxic properties of nanoparticles with potential to damage the human lens.

(Phototoxicity and cytotoxicity of fullerol in human lens epithelial cells. Roberts JE, Wielgus AR, Boyes WK, Andley U, Chignell CF. Toxicology and Applied Pharmacology 2008 Apr 1;228(1):49-58.

In previous years at NIEHS, I have proven that ocular exposure to UVA and UVB (lens) or Visible blue light (430 nm) (retina) alone or in the presence of drugs or herbs (St. John's Wort) increases the human risk for developing cataracts and retinal degeneraton **(Wielgus AR, Chignell CF, Miller DS, Van Houten B, Meyer J, Hu DN, Roberts JE. Phototoxicity in Human Retinal Epithelial Cells Promoted by Hypericin, a Component of St. John's Wort. Photochem Photobiol.** (**2007) 83(3):706-13)**

Summer 2010 I will investigate how nanoparticles (fullerols), used for drug delivery to the eye, may cause very early retinal degeneration. I am also examining the potential for fluoroquinolone (i.e. cipro) antibiotics to cause early damage to the human lens. The final purpose of my research is to remove, modify or quench these toxic agents in order to prevent the formation of early or late onset cataracts and macular degeneration. These *in vitro* experiments are currently in progress and are expected to be completed by September 2010.

Contribution

Cataracts and age-related macular degeneration (AMD) are the most common causes of visual impairment in the elderly. Although there is a genetic component to these blinding disorders, clinical and epidemiology studies have confirmed that environmental hazards (sunlight, phototoxic drugs and herbal medications) are major risk factors in initiating cataracts and AMD. All of these environmental hazards induce the formation of free radicals and reactive oxygen species (ROS) in the eye. The aged eye has limited protection against

free radicals and ROS, thus environmental hazards can put older people at severe risk of serious ocular damage. I have modeled this synergistic effect between environmental hazards and age by studying the interaction of sunlight with endogenous photoactive substances (xanthurenic acid, lipofuscin, A2E) whose production increases dramatically with age.

I have previously defined the damage to human ocular tissues induced by the endogenous agents. I am now defining the ocular damage induced by exogenous agents using *in vitro* and photophysical techniques. The ultimate goal is to develop appropriate strategies to ameliorate or prevent age related, environmental, drug and nanoparticle induced cataracts and macular or retinal degeneration.

Specifically, before attempting to define the effect of photoprocesses on biological systems, it is essential to get precise information about wavelength, photochemical yields/reaction rates, and biological targets. Mechanisms may be further defined through examination of the effects on the target molecules in live cells. This knowledge will facilitate risk assessment in humans and promote development of more sensitive ways to measure and screen for damage in individuals and in populations. Furthermore, once the mechanisms of damage are known, phototoxic agents can be modified to inhibit detrimental processes or to improve the efficacy of beneficial reactions.

Consequently, my research involves a multidisciplinary approach:

1) *in vitro*:

i. Models for Cataract formation Human Lens Epithelial Cells:

An *in vitro* model system (using human lens epithelial cells from human eyes) has been set up to determine potential phototoxicity of fluoroquinolone antibiotics and demonstrate specific damage end points (oxidative DNA damage, lipid peroxidation , apoptosis/necrosis, membrane damage, mitochondrial damage).

ii. Models for Macular Degeneration Human Retinal Pigment Epithelial Cells:

An *in vitro* model system (using retinal pigment epithelial cells from human eyes) has been set up to determine the potential phototoxicity of nanoparticles used for drug delivery) and demonstrate specific damage end points (oxidative DNA damage, lipid peroxidation , apoptosis/necrosis, membrane damage, mitochondrial damage).

iii. Models for Prevention of Damage to Ocular Cells

The effect of non-toxic quenchers known to cross blood lenticular and retinal barrier in humans. (i.e. lutein, N-acetyl cysteine) will be studied for their potentioal to block photodamage end points from the above in vitro experiments. These quenchers of phototoxic damage have been shown to be available to the human eye with supplementation.

2) Chemical and Photophysical Techniques

Time resolved photophysical techniques will be used to define the precise free radicals and reactive oxygen species formed by fluoroquinolones and nanoparticles. This will define the mechanism of phototoxicity for each agent. Dynamic Light Scattering will also be used to further define the chemical and physical properties of nanoparticles.

Cost

As stipulated in the abstract at the outset of this proposal, the costs for which I am requesting funding are paramount to my being able to travel to, supply my effective use of, and retrieve from the NIEHS in North Carolina the laboratory equipment necessary to the proposed research, some of which will now reside in the Fordham's Department of Natural Sciences due to my long-term collaboration with this facility.

Conclusion

Cataracts and age-related macular degeneration (AMD) are the most common causes of visual impairment in the elderly. In the next 30 years over 24 % of the population of the United States will be over the age of 65 and are therefore at risk for these blinding disorders. As stated at the outset of this proposal, not only will a Fordham Faculty Research Grant prove pivotal in supporting my longstanding line of research during a critical juncture in its funding, bring needed resources to the University, and provide a platform for future external support, it will prevent interruption of work that is already proving integral to our fight to preserve the sight of millions of Americans.

EXAMPLE

5

Faculty Research Grant Narrative:

A Variational Approach to Vesicle Membrane Modeling

Abstract : This project is a mathematical study of vesicle membrane fusion and lipid membrane mechanics. The cell membranes of almost all living organisms, as well as the membranes that surround a cell's nucleus and many other sub-cellular structures, are comprised of two thin layers of lipid molecules–the bilipid layer or lipid membrane. Vesicles are small sacs that life uses to store and transport substances in and out of the cell. A critical component of the vesicle's transport function is the ability of the lipid layer to fuse with other lipid layers. However, the mechanism underlying vesicle membrane fusion is not well understood, despite how commonly it occurs in nature and how reproducible it is to great precision in experiment. Moreover, the membrane fusion mechanism is not directly observable as it happens at extremely small length and time scales. Hence, vesicle membrane fusion remains one the most basic open problems in biophysics. This project proposes to simulate and study the origins of fusion by casting vesicles in a sophisticated mathematical model based on simple physical principles. Constructing the model and performing detailed numerical simulations will give spatial and temporal information not accessible by experiment. The project goals are: establish long term collaborations with biologists; obtain funding from the NSF and NIH; and make contributions to understanding the fundamental physics of lipid membranes.

This project is running in collaboration with Robert Eisenberg, PhD and Fredric Cohen, PhD of Rush University Medical Center in Chicago. Initiated earlier this year, the investigator and collaborators have to date agreed on a preliminary model. The model, a complicated system of partial differential equations, is solved numerically. Preparations are being made to run large scale simulations in October in the Laboratory Computing Resource Center at Argonne National Lab. Preliminary results from these simulations will be reported in a paper to be submitted to *Physical Review E* by December 2010. A more physically sophisticated model will be introduced and simulated in the early Spring for presentation at the Biophysical Society meeting in March.

Two grant applications will result from this work. The first will be to the NSF's Applied Mathematics Division in November 2010 and the other to the NIH in the fall of 2011. The investigator's continual application to these national grants will greatly be aided by the support of a "1st Year at Fordham" Faculty Research

Grant (FRG). The FRG will also permit the investigator to increase his scholarship and visibility in the applied and interdisciplinary mathematics community. Funds would be used to cover travel expenses to the collaborators' university, bring the investigator's collaborators to Fordham for face to face planning and discussion, employ Summer Undergraduate Research Assistants and acquiring a workstation for undergraduate researchers to implement large scale numerical experiments.

The remainder of this narrative is divided into background on the investigator and the mathematical field within which this project is framed and expected contributions of the project. The mathematical methodology is then described, followed by an outline of project expenses and a conclusion.

Background: The mathematical formulation of problems involving fluids and structures–such as the formulation the investigator is proposing to lend to the study of lipid membranes and vesicle fusion–has a long history. Beginning with Van der Waals theory of phase transitions and Landau's description of magnetism, this history includes the DeGennes' and Erikson-Leslie's theory of liquid crystals before progressing to today's popular approaches of using mathematical field theories and numerical methods to describe the processes of multi-physics condensed matter. Studies of liquid crystals [14], polymer electrolytes [16], super condictivity [5], charged gels [18], blood clotting [9] and blood flow [10] are a few examples. The range of physics addressed in this field is equal to the analytical and numerical techniques used. Building upon the investigator's dissertation and prior published work (see bibliography and CV), a guiding principle of the investigator's work is formulating comprehensive theories capable of guiding mathematicians in multi-physics problems, [22, 23]. It is from this foundation that the investigator forged collaborations with Drs. Eisenberg and Cohen, whose respective roles as Chairman and Director of Rush University Medical Centers Division of Molecular Biophysics and Physiology places their collective left foot firmly in physics while the other falls in the field of biology, where there is an even greater need for the comprehensive approach mathematics provides for understanding otherwise irreducibly complex systems.

Contribution : Biological membranes rearrange themselves in many biological processes. Fusion is a phenomenon specific to lipid bilayers, enabling transport of waste and engulfing of molecules by cells. It is the means by which a virus infects a cell and by which a sperm fertilizes and egg. Fusion occurs thousands of times in a single synaptic transmission, the firing of a nerve cell, [3]. A fusion pore, typically nanometers[1] in diameter, forms in a few nanoseconds. Well below the wavelength of light in size and too fast to be captured by today's fast digital microscope cameras (which image at just below milliseconds), the full fusion dynamic cannot be observed directly, [11]. Although it is one of the fundamental mechanisms of all living organisms, the detailed pathway by which two bilipid layers connect is unknown ([4]) and the energy required to

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[1]nano is the SI prefix for 10^{-9}.

undergo those pathways presently proposed is prohibitive, [13]. Moreover, traditional membrane mechanics in use by biophysicists today is a conservative, equilibrium theory and so cannot, a priori, describe the time course and the evolution of a true system. It is precisely because of this apparently irreducible complex system at the nexus of biology and physics that mathematics–and precisely this proposal–is poised to make a critical contribution to our understanding, not only of vesicle membrane fusion, but how to pursue an interdisciplinary agenda. Therefore, this project's use of well established mathematical tools will have a four-fold impact.

First, the mathematical approach will enable investigators to predict dynamics of fusion by positing consistent physical energies and initial data. Therefore, in stark contrast to traditional approaches in biophysics where information is taken from static or a priori configurations (e.g. spheres), [1, 12], the mathematical model will calculate the cascade of bilipid layer energy, forces and configurations as consequence of the field theory and be able to quantify physical parameters from more well established experimental models, [1]. See figure 1. Because the calculations yield values of all key variables over time, movies that precisely illustrate the time evolution of the membrane configuration can be generated. This allows one to appreciate changes over time, without having to refer to the physics or equations that underlie the fusion processes. Second, by thus facilitating the comparison of simulation with experiment, this study will challenge researchers' current hesitation to use detailed partial differential equations to model biological phenomena simply because of their (biological) complexity. If successful, the investigator's study will demonstrate that such complexity yields to concise and elegant mathematical descriptions which are therefore essential for research in biology. Third–a related impact–the success of this study will provide further evidence that the future of science will be dictated by interdisciplinary work. This project–along with the investigator's other research involvements–require expertise in chemistry, biology, engineering, mathematics and numerical methodology. Fusion is an example of merely one problem where the constant and close relationship between researchers in these areas is essential to making real progress. For this reason the investigator is fortunate to already have relationships with Rush University Medical Center and will also seek to work with biologists local to Fordham University and at the Einstein Medical School. Working in the context of these collaborations will also prove formative for future generations of scholars as the study engages undergraduate and graduate researchers to conduct numerical experiments. Finally, many mathematical tools are used in the formulation of fusion. These include geometry, partial differential equations, functional analysis and numerical methods. Writing a mathematical formulation of fusion leads to several interesting mathematical questions related to stability [2], well-posedness and the plethora of the connections between geometry and differential equations, [6, 19, 24].

Methodology : The primary impact of this project is gaining an enhanced understanding of vesicle membrane fusion. We begin by positing a membrane energy, denoted by E, which is defined in terms of a continuum variable $u(x,t)$ encoding the location of the membrane. The definition of $E[u]$ must be relatively simple, yet detailed enough to capture the physical energies relevant to the system. Typically $E[u]$ is a functional defined over a space of functions with certain differentiablity. We use a functional motivated by the theory of phase transitions, [19], whose efficacy was demonstrated in [6, 8];

$$E[u] = \int \frac{\epsilon}{2} \left(\Delta u - \frac{1}{\epsilon^2} f(u) - \frac{c}{\epsilon} g(u) \right)^2 \, dx + \frac{M}{2s} \left(\int \frac{\epsilon}{2} |\nabla u|^2 + \frac{1}{\epsilon} F(u) \, dx - s \right)^2 + \frac{N}{2v} \left(\int u + u_0 \, dx - v \right)^2.$$

The energy includes the surface tension, incompressibility and curvature effects of the classical Helfrich model. The representation is, however, more flexible and can readily account for multicomponent systems, inhomogeneities, and changes in topology. By solving the gradient descent equation

$$u_t = -E'[u], \quad u(0) = u_0, \tag{1}$$

one may explore the space of stable, equilibrium configurations of the vesicle. Here $E'[u]$ is the Euler-Lagrange derivative of $E[u]$. Equation (1) alone is not sufficient to describe the dynamics of real physical systems, especially when fluid motion is involved (indeed vesicles typically are in an aqueous medium.) For our purposes it is sufficient to solve the Navier-Stokes equations

$$\begin{cases} v_t + v \cdot \nabla v + \nabla p = \lambda \Delta v + f, \\ \nabla \cdot v = 0, \end{cases} \tag{2}$$

for the velocity $v(x,t)$ of the fluid (in fact, it is sufficient to solve the simpler and well-posed Stokes system as the flow at the micron length scale is typically of low Reynolds number.) The vesicle moves with the fluid and imparts the force $f(x,t)$ in (2) on the fluid. Writing down the form of f from physical considerations alone is typically difficult. However, using a variatonal formalism from the calculus of variations, one defines $f(x,t) = -E'[u]\nabla u(x,t)$. In total, the system enjoys the following property; the total energy

$$\frac{1}{2}\|v\|_{\mathbf{L}^2}^2 + E[u] \tag{3}$$

is nonincreasing. In mathematics, this property–that the energy is nonincreasing–is called an energy law and is the basis of the mathematical existence theory for (2). Profound to experimentalists is the following fact; the exchange of energies, fluid and vesicle motion and forces are outputs from these equations.

These equations are carefully discretized, using finite differences, and the discrete equations are solved numerically. This step involves a Newton's method and solving a system of linear equations with 100,000 and plus unknowns. On a standard workstation, this takes a minimum of four hours. The results from the simulation are stored and then interpreted. The entire process of modeling biological systems in this way is time consuming and fraught with technical complexities. Solving a large system of linear equations,

especially the Stokes system, requires a great deal of sophisticated numerical linear algebra. Moreover, care must be taken in choosing the spatial discretization–so that the system is even solvable–and the temporal discretization so that the energy law (3) is preserved (and that the numerical method is stable). Numerical schemes, designed specifically for this field theory, are implemented. However, the advantage of modeling a biological system in this way is that, because the configuration of the system is known at all points in space and time, the results contain information not accessible by experiment. It is for this reason that this variational approach to vesicle membrane modeling holds such promise for solving one of the most basic open problems in biophysics: vesicle membrane fusion.

Cost : Because of the time consuming, technical complexities of the mathematical modeling at the core of this inherently interdisciplinary–and consequently cross-country collaborative–project, the investigator seeks expenses to: (i) facilitate face to face meeting with his co-researchers at facilities that can accommodate both their simulation and experimental methods; (ii) employ one to two Summer Undergraduate Researchers Assistants at Fordham in preparing and conducting simulations; (iii) presentation at the Biophysical Society meeting in March 2011, which will be necessary to obtain peer feedback in preparation for future NIH funding applications; (iv) purchase one workstation devoted to remotely running resource intensive, parallelized, multiday simulations. It will be necessary for implementing the numerical routines by undergraduate researchers, who otherwise do not have access to such computing resources.

Conclusion : The proposed project builds upon the investigator's training in applied mathematics – particularly fluid mechanics, complex fluids and numerical simulation–and a platform of publications on the mathematical framework for modeling vesicles using the classical Helfrich energies, the Willmore energy and Euler number, [6, 7] as well numerical methodologies for solving complex fluid problems involving interfaces and electrostatic effects, [20, 21, 22]. The mathematics this project will employ is largely based on these works, and as such it is a natural extension of his work to bring this expertise into collaboration with researchers in diverse disciplines. These collaborators steer the investigators work to design more detailed mathematical models which are directly relevant to the types of questions biologists are interested.

By cementing relationships already initiated with biophysicists at a premier research institution, the proposed paradigm of interdisciplinary scientific inquiry with mathematics at its core will enable the investigator as a junior scholar to establish a track record in conjunction with the support of senior experimentalists to increase funding opportunities for the investigator and Fordham. These goals are critical to attracting distinguished researchers and funding to Fordham, increasing the research profile of the University, promoting the investigator's grantmanship and engaging the next generation of researchers and education at the undergraduate and graduate level.
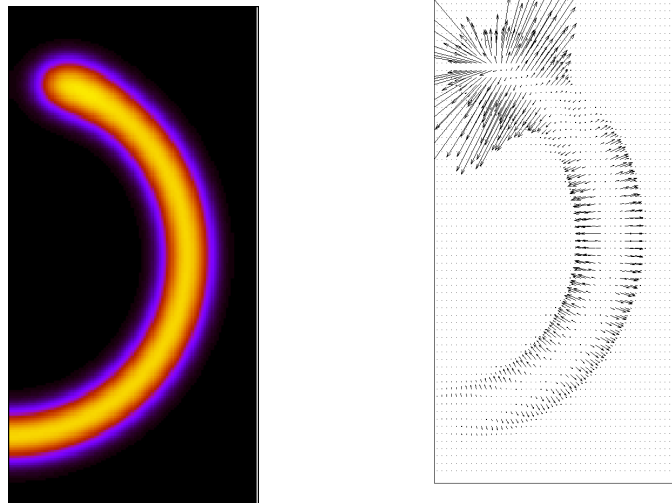
Figure 1: A calculated axially symmetric vesicle with pore (left) and the force it generates on the fluid (right). The concentration of the force at the rim of the pore–typically called line tension, an input in traditional membrane mechanics–as an output of the model.
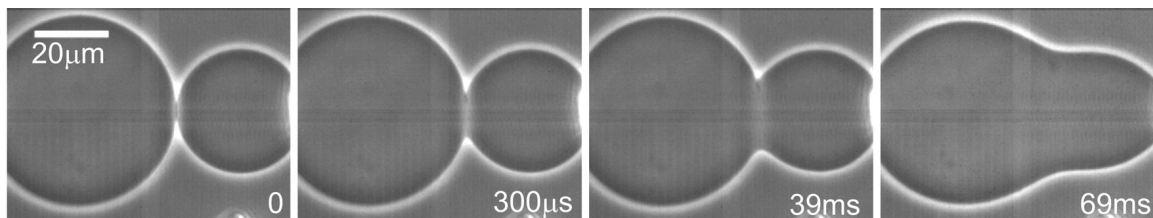

Figure 2: The merging of giant vesicles (taken from [11].) Fusion has already occurred in the first image frame.

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