PI: **SCHIFF, STEVEN J.**	Title: Control of the Neonatal Septisome and Hydrocephalus in sub-Saharan Africa	
Received: 10/29/2013	FOA: RM13-006	Council: 05/2014
Competition ID: FORMS-C	FOA Title: 2014 NIH PIONEER AWARD PROGRAM (DP1)	
1 DP1 HD086071-01	Dual: OD,RM	Accession Number: 3631235
IPF: 1524204	Organization: PENNSYLVANIA STATE UNIV HERSHEY MED CTR	
Former Number: 1DP1OD019094-01	Department: Neurosurgery	
IRG/SRG: ZRG1 BCMB-N (50)R	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 2,500,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N HFT: N	New Investigator: Early Stage Investigator:
Senior/Key Personnel:	*Organization:*	*Role Category:*
Steven Schiff	PENNSYLVANIA STATE UNIV HERSHEY MED CTR	PD/PI

Reference Letters

[redacted]

OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. TYPE OF SUBMISSION*

❍ Pre-application ❍ Application ● Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number
3 CTR; 9 QCB

2. DATE SUBMITTED
2013-10-29

Application Identifier

c. Previous Grants.gov Tracking Number
GRANT11510535

5. APPLICANT INFORMATION

Organizational DUNS*: [redacted]

Legal Name*: PENNSYLVANIA STATE UNIV HERSHEY MED CTR
Department:
Division: College of Medicine
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]

Person to be contacted on matters involving this application
Prefix: First Name*: Stephanie Middle Name: Last Name*: Johnson Suffix:
Position/Title: Director, Grants Administration
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
ZIP / Postal Code*: [redacted]
Phone Number*: [redacted] Fax Number: [redacted] Email: [redacted]

6. EMPLOYER IDENTIFICATION NUMBER *(EIN) or (TIN)** [redacted]

7. TYPE OF APPLICANT* X: Other (specify)

Other (Specify): State-related Institution of Higher Education
Small Business Organization Type ❍ Women Owned ❍ Socially and Economically Disadvantaged

8. TYPE OF APPLICATION*

● New ❍ Resubmission
❍ Renewal ❍ Continuation ❍ Revision

If Revision, mark appropriate box(es).
❍ A. Increase Award ❍ B. Decrease Award ❍ C. Increase Duration
❍ D. Decrease Duration ❍ E. Other *(specify)* :

Is this application being submitted to other agencies?* ❍Yes ●No What other Agencies?

9. NAME OF FEDERAL AGENCY*
National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
93.310
TITLE: Trans-NIH Research Support

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Control of the Neonatal Septisome and Hydrocephalus in sub-Saharan Africa

12. PROPOSED PROJECT
Start Date* 09/30/2014
Ending Date* 07/31/2019

13. CONGRESSIONAL DISTRICTS OF APPLICANT
PA-017

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Steven Middle Name: J Last Name*: Schiff Suffix:

Position/Title: PROF NEURO,ESM & PHYSICS

Organization Name*: PENNSYLVANIA STATE UNIV HERSHEY MED CTR

Department: [redacted]

Division: [redacted]

Street1*: [redacted]

Street2: [redacted]

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: [redacted]

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: Email*: [redacted]

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$2,500,000.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$2,500,000.00
d. Estimated Program Income*	$0.00

16.IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?*

a. YES ○ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ● PROGRAM IS NOT COVERED BY E.O. 12372; OR

○ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)

● I agree*

** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.*

18. SFLLL or OTHER EXPLANATORY DOCUMENTATION File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Stephanie Middle Name: Last Name*: Johnson Suffix:

Position/Title*: Director, Grants Administration

Organization Name*: PENNSYLVANIA STATE UNIV HERSHEY MED CTR

Department: [redacted]

Division: [redacted]

Street1*: [redacted]

Street2: [redacted]

City*: [redacted]

County: [redacted]

State*: [redacted]

Province:

Country*: [redacted]

ZIP / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: [redacted] Email*: [redacted]

Signature of Authorized Representative*

Stephanie Johnson

Date Signed*

10/29/2013

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:0_Cover_Letter_1015131009842776.pdf

424 R&R and PHS-398 Specific
Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

Project/Performance Site Location(s)

Project/Performance Site Primary Location

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: The Pennsylvania State University
Duns Number: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: PA-005

Project/Performance Site Location 1

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Mbarara University of Science and Technology
DUNS Number: [redacted]
Street1*: [redacted]
Street2:
City*: [redacted]
County:
State*:
Province:
Country*: [redacted]
Zip / Postal Code*:
Project/Performance Site Congressional District*: 00-000

Project/Performance Site Location 2

❍ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: PENNSYLVANIA STATE UNIV HERSHEY MED CTR
DUNS Number: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]
Project/Performance Site Congressional District*: PA-017

Funding Opportunity Number: RFA-RM-13-006. Received Date: 2013-10-29T13:02:06.000-04:00

File Name

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Other Project Information

1. Are Human Subjects Involved?* ● **Yes** ○ **No**

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations? ○ Yes ● No

If YES, check appropriate exemption number: _ 1 _ 2 _ 3 _ 4 _ 5 _ 6

If NO, is the IRB review Pending? ○ **Yes** ● **No**

IRB Approval Date: [redacted]

Human Subject Assurance Number [redacted]

2. Are Vertebrate Animals Used?* ○ **Yes** ● **No**

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ○ Yes ○ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. Is proprietary/privileged information included in the application?* ○ **Yes** ● **No**

4.a. Does this project have an actual or potential impact - positive or negative - on the environment?* ○ **Yes** ● **No**

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ○ Yes ○ No

4.d. If yes, please explain:

5. Is the research performance site designated, or eligible to be designated, as a historic place?* ○ **Yes** ● **No**

5.a. If yes, please explain:

6. Does this project involve activities outside the United States or partnership with international collaborators?* ● **Yes** ○ **No**

6.a. If yes, identify countries: Uganda

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	2_Abstract_1018131009926216.pdf
8. Project Narrative*	1_Project_Narrative_1018131009926218.pdf
9. Bibliography & References Cited	
10.Facilities & Other Resources	8_Facilities_1018131009926226.pdf
11.Equipment	
12. Other Attachments	3_Most_Significant_Accomplishment_1022131009926227.pdf

Funding Opportunity Number: RFA-RM-13-006. Received Date: 2013-10-29T13:02:06.000-04:00

I propose a novel approach to institute model-based feedback control to seek a rational, and optimal, framework to reduce neonatal sepsis (NS) in developing countries. In addition to reducing deaths from NS, one of the leading global killers of children worldwide, this will reduce the sequelae in the survivors of NS such as postinfectious hydrocephalus (PIH) – likely the dominant cause of hydrocephalus in children worldwide. I presently am a PI on a Phase III NIH sponsored randomized controlled surgical trial in Africa seeking to optimize treatment of PIH (clinical trial # NCT01936272). However, as an alternative to surgical treatment of children with irreparable brain damage, I am now in a unique position to learn how to more effectively treat NS in this setting, and thereby better prevent the large numbers of infants with PIH in this part of the world that we would otherwise need to surgically palliate.

Although a pediatric neurosurgeon, I have acquired considerable expertise in both control engineering and physics. I recently wrote the first book on Neural Control Engineering, published by the MIT press in 2012. This Pioneer Award seeks to leverage my knowledge of control engineering and apply this to an entirely new avenue of research for me – seeking to impact in a sustainable way both the morbidity and mortality of NS.

I have put in place a unique infrastructure in Uganda to enable this project. I have secured Ugandan medical licensure. I have organized two pilot projects with two key institutions: a pediatric neurosurgery specialty hospital in Mbale (the CURE Children's Hospital of Uganda), and a major referral hospital in Mbarara (at the Mbarara University of Science and Technology). At Mbale, most of the hydrocephalus in Uganda is now treated, and the majority of these cases are postinfectious following NS. At Mbarara, the most common admission to their infant ward is NS, and all of their hydrocephalus is referred to Mbale. At each institution, I have negotiated IRB proposals to meet US standards. I have secured approval from the Ugandan National Council of Science and Technology, as well as the materials transfer agreement required to ship specimens to the US. Our preliminary data demonstrates that this proposed Pioneer Award project is feasible.

Reducing PIH will reduce the necessity for expensive neurosurgery that often is unable to alter the tragic outcome of severe hydrocephalus in such infants. Most importantly from a global health perspective, is that we can begin to create a rational framework to reduce the deaths from NS each year in regions such as sub-Saharan Africa where such infections remain out of control. The Pioneer Award would provide the resources to put into place in Uganda the proposed model-based feedback control framework. It would readily adapt to neighboring countries in East Africa, where we have colleagues treating large numbers of PIH. At the conclusion of this Pioneer Award, a template for implementing a similar framework in other developing countries will be the long-term outcome, with the potential for a substantial impact on global infant health.

Neonatal sepsis kills over 1 million newborn infants each year, with cases highly concentrated between sub-Saharan Africa and southern Asia, and in survivors accounts for most of the world's infant hydrocephalus requiring neurosurgery. I am a pediatric neurosurgeon who has acquired a considerable amount of expertise in control engineering, and have created a unique infrastructure to enable a project in a sub-Saharan African country employing control engineering to reduce the mortality from neonatal sepsis and lessen hydrocephalus in the survivors. The framework created from carrying out this project can be sustainably adapted to other countries, with the potential for a substantial impact on global infant health.

Facilities & Other Resources

Penn State University - Center for Neural Engineering

Laboratory

The Center for Neural Engineering laboratories occupies 22,000 square feet in the Millennium Science Complex at the University Park campus of Penn State, and is fully equipped for the transdisciplinary research crossing the boundaries of experimental and computational science, medicine, and engineering.

Critical for this Pioneer Award, is that the Center for Neural Engineering is directly above the Center for Infectious Disease Dynamics faculty in the same building (floors 3 and 2 respectively). Dr Schiff collaborates closely with these infectious disease faculty, including Professors Kapur (bacteriology) and Poss (virology), all of whom are clustered in close proximity for fluid collaboration.

Animal

There is a large animal care facility on the ground floor of the Millennium Science Center where we have custom designed instrumented animal recording rooms as required for the long-term monitoring of feedback control. Pertinent to this Pioneer Award project on infectious disease, we have special facilities for the housing of animals with infectious disease and the study of pathogens. We have a new BSL3 containment facility if necessary that is also available. These facilities meet AALAC requirements to care for monitored and infected animals. If the needs of this Pioneer Award dictate that we pursue animal experiments in the later stages of the project, we are very well set up to pursue such investigations.

Computer

Dr Schiff's laboratory houses 25 PCs, a 2-node 3.5Tb server, as well as access to a range of high performance Unix clusters on the Penn State campus.

Office

Dr. Schiff has an office adjacent to the Neural Engineering laboratories. Additional student and post doc office space is provided for personnel working on this project. The office space of the Center for Neural Engineering encompasses 11,000 square feet of faculty, student, and postdoc office areas, state of the art conference facilities, a brain machine interface teaching laboratory, and an administrative suite.

Clinical

Clinical facilities at Hershey are a 2-hour ride away by shuttle bus. We will not make use of these clinical facilities during this Pioneer Award.

Other

One full-time staff administrator is provided for the Center. The Center adjoins 3 floors of the Materials Research Institute, with extensive facilities for construction of electrodes, photonics, nanofabrication, and electron microscopy.

Most significant accomplishment.

I consider my most significant accomplishment to be the fusion, over the past 7 years at Penn State, of computational neuroscience with control theory.

This synthesis was published as a full-length solo authored book in 2012 by the MIT Press, as Neural Control Engineering: The Emerging Intersection Between Control Theory and Neuroscience.

The book represents a culmination for me a physician-scientist. I left full-time medical practice in 1998 in quest of a better way of treating dynamical disease of the brain. I could not see that our present path, treating children with intractable epilepsy with mutilative resection of their brains, was the best we could do even if outcomes appeared acceptable. From a medical device perspective for diseases such as Parkinson's disease and epilepsy, I could not see that all we had learned about neuroscience would be ignored as we developed deep brain stimulation therapies that typically reproduced the physiological effect of the brain lesions we hoped to move beyond.

My goal was to ask how to take advantage of our growing knowledge of neuroscience to learn to intelligently interact with the brain. The embodiment of that knowledge, as for any discipline where ‘laws’ governing the elemental dynamics are uncovered, is to create mathematical models of those laws. But although computational neuroscience models of neuronal elements had been thriving since the 1950s, we had no clear structure to adapt those models to control dynamical diseases of the brain.

In parallel with computational neuroscience, since the 1950s we have progressively developed the modern version of control theory. This theory used computational models to replicate the dynamics of the system to be controlled, and we developed the theoretical framework to fuse such models with real-time sensing of robotic systems to achieve many of the most spectacular advances in engineering – airplane autolanders and Google cars. The same principles of control theory fusion of models with natural systems has brought us numerical weather prediction of unprecedented accuracy (albeit without control). But these developments required substantial advances in our numerical frameworks to fuse models with highly nonlinear and complex systems, and that framework did not appear until the late 1990s.

I have recently accomplished what is the first comprehensive approach to the fusion of these two disciplines. I achieved this by showing how to use the canonical models of computational neuroscience – Hodgkin-Huxley, Fitzhugh-Nagumo, and Wilson-Cowan equations – and placed them within a control theoretic framework. That these models adapted so well in such a setting was a complete surprise to all of us. I then laid out the adaptation of this strategy to dynamical diseases of the brain such as epilepsy and Parkinson’s disease. I handled some of the deep theoretical issues such as formalizing model inadequacy in this setting, a subject at the cutting edge of numerical weather prediction geophysics, and showed how this would translate into neural systems. And I showed how to design neuronal controllers based upon these principles. Based upon this work, I was recently appointed to the Neurological Devices Panel of the Medical Devices Advisory Committee of the FDA.

I thus have constructed through this fusion of fields what will likely lead the design of the next generation of neuronal feedback control devices for treating diseases of the brain. A broad US Patent for model-based control of neuronal diseases will issue within weeks of this writing (I am the sole inventor). These principles will readily adapt to a wide variety of other medical devices, including smart cardiac pacemakers, ventilator control, blood pressure control, glucose regulation, etc.

I leveraged the experience I gained through this fusion of fields to enable me to carry out my recent African climate study in 2012, where I was able to perform all of the numerical analysis required (and wrote the codes) fusing climate dynamics with surgical case data. The results of this study are a foundation of this present proposal.

My acquisition of control engineering expertise has prepared me to credibly make this Pioneer Award proposal. I can see how to leverage all that I have learned towards a very novel model-based control framework for the treatment of neonatal sepsis in Africa. Such an approach will be inexpensive, scalable, and sustainable in the developing world where neonatal sepsis is a global killer of considerable magnitude. And I see clearly the links to my clinical roots – that the possibility of making a substantial reduction in the world’s burden of infantile hydrocephalus would be an immediate consequence to this present project.

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Steven Middle Name J Last Name*: Schiff Suffix:

Position/Title*: PROF NEURO,ESM & PHYSICS
Organization Name*: PENNSYLVANIA STATE UNIV HERSHEY MED CTR
Department: [redacted]
Division: [redacted]
Street1*: [redacted]
Street2: [redacted]
City*: [redacted]
County: [redacted]
State*: [redacted]
Province:
Country*: [redacted]
Zip / Postal Code*: [redacted]

Phone Number*: [redacted] Fax Number: E-Mail*: [redacted]

Credential, e.g., agency login: [redacted]

Project Role*: PD/PI Other Project Role Category:

Degree Type: MD/PhD Degree Year: 1985

	File Name
Attach Biographical Sketch*:	6_SCHIFF_Biosketch_2_Page_Format_Pioneer_1028131009926491.pdf
Attach Current & Pending Support:	7_SCHIFF_Current_and_Pending_Support_1022131009926231.pdf

Tracking Number: GRANT11511156
Funding Opportunity Number: RFA-RM-13-006 . Received Date: 2013-10-29T13:02:06.000-04:00

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Schiff, Steven J.	Director, Center for Neural Engineering Brush Chair Professor of Engineering
eRA COMMONS USER NAME (credential, e.g., agency login) [redacted]	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
M.I.T.	S.B.	1977	Biology
Duke University School of Medicine	M.D.	1980	Medicine
Duke University School of Medicine	Ph.D.	1985	Physiology

B. Positions and Honors

Positions and Employment

1981 Internship, General Surgery, Duke University School of Medicine
1982-1989 Neurosurgery Residency, Duke University School of Medicine
1989-1990 Fellowship, Pediatric Neurosurg, Children's Hosp of Philadelphia (Instructor, U Penn Med Sch)
1990-1994 Assistant Prof. Neurosurgery and Pediatrics, George Washington Univ. Sch. of Med. (GWUSM)
1993-1997 Co-Director, Epilepsy Surgery Program, Children's National Medical Center (CNMC)
1994-1998 Associate Prof. of Neurosurgery, Pediatrics, and Physiology, GWUSM,
1996-1998 Assoc Director, Ctr for Neurosci and Behavioral Medicine, Children's Res Inst, CNMC
1998- Adjunct Professor of Pharmacology, GWUSM,
1998-2006 Chief, Laboratory of Neural Dynamics, Krasnow Institute, George Mason University (GMU),
1998-2006 Krasnow Professor of Neurobiology, Krasnow Institute, George Mason University,
1998-2006 Professor of Psychology, George Mason University (Tenured 1999)
2005-2006 Director, Center for Neural Dynamics, George Mason University
2006- Brush Chair Professor of Engineering, Penn State University
2006 - Professor of Neurosurgery, Engineering Sciences and Mechanics, and Physics (Courtesy Appt)
2007- Director, Penn State Center for Neural Engineering
2013- US Food and Drug Administration, Neurological Devices Panel, 7/28/2013 - 7/27/2017

Other Experience and Professional Memberships

1992- Diplomat, American Board of Neurological Surgery; 1996-2008 American Board of Pediatric Neurological Surgery; 1996- American Society for Pediatric Neurosurgery (Elected to Membership), 1995-1996 Biological Physics Prize Selection Committee, American Physical Society; 1998-04 NIH Study Section member, Integrative Functional Cognitive Neuroscience (IFCN)-8; 2000-2 Program Committee, Annual Computational Neuroscience Meeting; 2000-6 Editorial Board, Physical Review E; 2002-2 Translational Clinical Research Task Force, American Epilepsy Society; 2002-4 Chair, IFCN-8/Cog Study Section; 2005 Chair, Conte Center Study Section; 2005-8 Board of Directors, Annual Computational Neurosci Meeting; Journal of Computational Neuroscience, Action Editor, 2006-; Physical Review Letters, Divisional Associate Editor (Biological Physics), 2006-2012; PRX Editorial Board 2012-; Editorial Board Journal of Neural Engineering 2013-; Temporary Ugandan Med Lic 2008-.

Honors: 1979-1984 James B. Duke Graduate Fellowship, Duke Univ; 1994- Fellow, American College of Surgeons; 2005- Fellow, American Physical Soc.; 2010- Fellow, American Association of Neurological Surgeons; Guide to America's Top Physicians (2005) /Surgeons (2006, 2011); Fellow, Am Association for the Advancement of Science 2012-

C. Publications Most Relevant to Control Engineering (selected from over 140 articles and patents)

1. Schiff, SJ. Neural Control Engineering. MIT Press, Cambridge, 2012.
2. Schiff SJ, Jerger K, Duong DH, Chang T, Spano ML, Ditto WL, Controlling Chaos in the Brain, Nature 370(1994) 615-20. PMID: 8065447
3. Schiff SJ. Forecasting brain storms. Nature Medicine 1998 Oct;4(10):1117-8. PMID: 9771736
4. Schiff, SJ, Huang, X, Wu, JY, Dynamical Evolution of Spatiotemporal Patterns in Mammalian Middle Cortex, Physical Review Letters, 98, 178102, 2007. PMID: 17501537
5. Schiff SJ, Sauer T, Kalman Filter Control of a Model of Spatiotemporal Cortical Dynamics, Journal of Neural Engineering 5: 1-8, 2008. PMID: 18310806
6. Ullah G, Schiff SJ, Tracking and Control of Neuronal Hodgkin-Huxley Dynamics, Physical Review E, 79, 040901(R), 2009. PMID: 19518166
7. Schiff SJ. Towards Model Based Control of Parkinson's Disease. Philosophical Transactions of the Royal Society A, 368:2269-2308, 2010. PMID: 20368246
8. Ullah G, Schiff SJ. Assimilating Seizure Dynamics. PLoS Computational Biology, 6(5): e1000776, 2010. PMID: 20463875
9. Gorzelic P, Schiff SJ, Sinha A. Model-based rational feedback controller design for closed-loop deep brain stimulation of Parkinson's disease. Journal of Neural Engineering, 10: 026016, 2013. PMID: 23449002

Publications Most Relevant to Neurosurgery

10. Drake, J. M., Kestle, J. R. W., Milner, R., Cinalli, G., Boop, F., Piatt, J., Haines, S., Schiff, S. J., Cochrane, D., Steinbok, T., MacNeil, N., and the collaborators, Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus, Neurosurgery, 1998 Aug;43(2):294-30. PMID: 9696082
11. Li L, Padhi A, Ranjeva SL, Donaldson SC, Warf BC, Mugamba J, Johnson D, Opio Z, Jayarao B, Kapur V, Poss M, Schiff SJ, Association of Bacteria with Hydrocephalus in Ugandan Infants, Journal of Neurosurgery: Pediatrics 7:73-87, 2011 [Cover Article]. PMID: 21194290
12. Warf BC, Dagi AR, Nsubuga B, Schiff SJ. Five year survival and outcome of treatment for post-infectious hydrocephalus in Ugandan infants, Journal Neurosurgery: Pediatrics, 8: 502-508, 2011. PMID: 22044377
13. Warf BC, Alkire BC, Bhai S, Hughes C, Schiff SJ, Vincent JR, Meara JG. The costs and benefits of neurosurgical intervention for infant hydrocephalus in sub-Saharan Africa. Journal Neurosurgery: Pediatrics 8: 509-521, 2011. PMID: 22044378
14. Schiff SJ, Ranjeva S, Sauer T, and Warf BC. Rainfall Drives Hydrocephalus in East Africa. Journal of Neurosurgery: Pediatrics 10: 161-167, 2012 [Cover and lead article September, 2012 issue]. PMID: 22768966
15. Mandell JG, Kulkarni AV, Warf BC, Schiff, SJ. Volumetric Brain Analysis in Neurosurgery: II. Brain and CSF Volumes Discriminate Neurocognitive Outcomes in Hydrocephalus. Journal of Neurosurgery: Pediatrics, in press 2013.

Current and Pending Support

Ongoing Research Support

1R01EB014641-01, NIBIB, US-German Collaborative Research in Computational Neuroscience (CRCNS):
"Model-Based Control of Spreading Depression", PI (contact, multiple with Gluckman, Dahlem).
$191,127 (US), 8/15/2011 – 7/31/2014
Model-based control of spreading depression waves in cortical brain slices. 1.0 mos

[redacted]

R01NS065096 Gluckman(PI) $250,000 5/15/2009-4/30/2014 0.6 mos
"Perturbative Seizure Prediction and Detection of a Seizure Permissive State"
A study utilizing polarizing low frequency electrical fields to probe brain state to detect preseizure states and investigate the nature of apparent false seizure predictions.
Role: Co-Investigator

1 K25 NS061001-01A2 Kamrunnahar (PI) $100,000 11/2008 – 10/2013 0 mos
"Brain-Robot Interface: A Robust, High Performance Predictive Control Algorithm".
Role: Mentor

NIH Fogarty International Center and NINDS, 1R21TW009612-01A1, 9/14/2012 – 9/30/2014, 0.6 mos
"Neurocognitive outcomes and changes in brain and CSF volume after treatment of post infectious hydrocephalus in Ugandan infants by shunting or ETV/CPC", $50,183 (Total Costs), PI (multiple with Warf and Kulkarni).

[redacted]

Pending Support (total costs)

[redacted]

Overlap

The focus of the Pioneer Award is on feedback control optimization of treatment through predictive modeling, using climate and microbial surveillance, none of which are in the NICHD project. The NICHD application is entirely focused on routine microbial discovery, with exhaustive follow-up of cases of neonatal sepsis to identify sentinel cases of postinfectious hydrocephalus, and exhaustive microbial discovery in hydrocephalus, neither of which are part of the Pioneer Award. If both awards are funded, they would strongly leverage each other in terms of the medical science that would result. Modest cuts to the NICHD aims would be negotiated with NIH staff to eliminate this overlap were both to be awarded.

Note on effort for Pioneer Award: If funded, I can devote 51% effort to the Pioneer Award. If all other grants are funded, they will account for 2.0 months effort (16%) when the Pioneer Award is made.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

1. Project Director / Principal Investigator (PD/PI)

Prefix:
First Name*: Steven
Middle Name: J
Last Name*: Schiff
Suffix:

2. Human Subjects

Clinical Trial? ● No ○ Yes
Agency-Defined Phase III Clinical Trial?* ○ No ○ Yes

3. Permission Statement*

If this application does not result in an award, is the Government permitted to disclose the title of your proposed project, and the name, address, telephone number and e-mail address of the official signing for the applicant organization, to organizations that may be interested in contacting you for further information (e.g., possible collaborations, investment)?

● Yes ○ No

4. Program Income*

Is program income anticipated during the periods for which the grant support is requested? ○ Yes ● No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

Budget Period*	Anticipated Amount ($)*	Source(s)*

Funding Opportunity Number: RFA-RM-13-006. Received Date: 2013-10-29T13:02:06.000-04:00

PHS 398 Cover Page Supplement

5. Human Embryonic Stem Cells

Does the proposed project involve human embryonic stem cells?* ● No ❍ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://grants.nih.gov/stem_cells/registry/current.htm. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the registry will be used:

Cell Line(s): Specific stem cell line cannot be referenced at this time. One from the registry will be used.

6. Inventions and Patents (For renewal applications only)

Inventions and Patents*: ❍ Yes ❍ No

If the answer is "Yes" then please answer the following:

Previously Reported*: ❍ Yes ❍ No

7. Change of Investigator / Change of Institution Questions

❑ Change of principal investigator / program director

Name of former principal investigator / program director:

Prefix:

First Name*:

Middle Name:

Last Name*:

Suffix:

❑ Change of Grantee Institution

Name of former institution*:

PHS 398 Research Plan

Please attach applicable sections of the research plan, below.

OMB Number: 0925-0001

1. Introduction to Application (for RESUBMISSION or REVISION only)	
2. Specific Aims	
3. Research Strategy*	4_Research_Plan_1023131009926374.pdf
4. Progress Report Publication List	
Human Subjects Sections	
5. Protection of Human Subjects	10a_Human_Subjects_Pioneer_1018131009926234.pdf
6. Inclusion of Women and Minorities	10c_Inclusion_of_Women_and_Minorities_1018131009926235.pdf
7. Inclusion of Children	10b_Inclusion_of_Children_1018131009926236.pdf
Other Research Plan Sections	
8. Vertebrate Animals	
9. Select Agent Research	
10. Multiple PD/PI Leadership Plan	
11. Consortium/Contractual Arrangements	
12. Letters of Support	
13. Resource Sharing Plan(s)	
Appendix (if applicable)	
14. Appendix	

Science Areas: 3 CTR; 9 QCB. Clinical and Translational Research; Quantitative and Computational Biology
Project Title: Control of the Neonatal Septisome and Hydrocephalus in sub-Saharan Africa
Project description: The World Health Organization and United Nations data demonstrate that neonatal sepsis (NS) leads to the yearly deaths of over 1 million infants, more than half in sub-Saharan Africa (SSA). In the US, the rates of NS were as high as 2-3/1000 live births during the 1970s, which substantially abated with maternal screening for group B streptococcus. In SSA group B streptococcus is uncommon in NS. Centers in the developing world often report a spectrum of responsible bacteria heavily weighted in favor of gram-negative coliforms, but derives this estimate from typically less than 1/3 positive cultures in neonates with NS.

Hydrocephalus is the most common condition in children requiring neurosurgery world-wide. In SSA there has until recently been little availability of neurosurgery. With the introduction of technically high-quality pediatric neurosurgery in Uganda at Mbale (The CURE Children's Hospital of Uganda, CCHU), it became apparent that, in stark contrast to the industrialized countries, the majority of infant hydrocephalus in East Africa appeared postinfectious (Warf J Neurosurg 102(1S):1-15, 2005). At CCHU the first 1000 consecutive cases yielded no positive bacterial cultures – their infections had largely burned out in the weeks prior to presentation. The one salient feature of these children was that the majority acquired their hydrocephalus following a severe infection in the neonatal period typically accompanied by convulsive seizures. These East African cases of infantile hydrocephalus are largely comprised of survivors of neonatal sepsis (NS).

Thus NS leads to postinfectious hydrocephalus (PIH), and the world's medical community has no idea what the majority of the causative organisms are for either condition.

Hydrocephalus has not been considered a high priority for global health. But it was also largely under the radar screen of organized medicine – most developing countries had no children's neurosurgery. So most of these infants died unrecognized early in life. When facilities acquire the capability for pediatric neurosurgery (e.g. where we have trained surgeons in Vietnam, Nepal, Zambia, Nigeria, Ghana, Ethiopia, and Tanzania), they can become rapidly swamped by the influx of infantile hydrocephalus cases. At the US-run hospital in Kijabe, Kenya, they are seeing over 600 cases of hydrocephalus per year, and the case load at Mbale, Uganda is similar – all are nearly uniformly culture negative. So in East Africa there are tens of thousands of cases of PIH from unknown origin deriving from NS of unknown origin, which we at present need to expend considerable resources to treat surgically. And as we do so, our recent work demonstrates that the 5-year survival of PIH patients with optimal surgical intervention in Uganda remains disturbingly low (J Neurosurg Peds 8:509-521, 2011). We will never surgically operate our way out of this problem.

We recently performed an Economic Burden of Disease analysis for PIH in SSA. There are about 100,000 postinfectious hydrocephalus (PIH) cases per year in SSA, generated from a pool of 1,000,000-2,000,000 cases of NS (J Neurosurg Peds 8:502-508, 2011). The brains of children with PIH are devastated, with values of statistical lives lost of $26-48 billion per year. As we now complete our economic analysis for NS, the numbers are substantially larger than for PIH. The potential economic benefits from a modest 10-20% reduction of NS cases would be extraordinary. This Pioneer Award proposal seeks to lay the foundation for the capability to prevent the majority of these cases.

After jointly negotiating IRB protocols between the CCHU and Penn State, I began a pilot project with my colleague John Mugamba, the medical director of CCHU, and Benjamin Warf, the former Medical Director (now at Harvard). We collected samples of cerebrospinal fluid (CSF) from the brains of these infants at surgery in Mbale, and shipped them to the US using culture transport systems. Collaborating with the microbiologists at our agricultural diagnostic laboratory, we threw the book at these samples, yet as with our African colleagues, grew out no organisms. These infections are largely burned out by the time the infants develop PIH.

I then set up a DNA collection facility at Mbale, and collected 50 specimens. I formed a collaboration with 2 of our renowned infectious disease scientists: Vivek Kapur (bacteriology) and Mary Poss (virology). Sequencing the 16S ribosomal bacterial gene gave us evidence of pathogenic bacterial fragments within the sterile CSF collected at surgery in nearly all of these infants. The predominant types were gram-negative coliforms, and the most common species were Acinetobacter (J Neurosurg Peds 7:73-87, 2011).
I then organized the fieldwork to track down the home villages of the infants who had evidence of Acinetobacter infection. We found 8 of these infants in northern and central Uganda, and showed close genetic matches of Acinetobacter sequences from their huts or nearby cow dung and the sequences of 16S rRNA recovered from these same infants' brains (J Neurosurg Peds 7:73-87, 2011).

Since we do not know whether these bacterial fragments were from bacteria causal to the NS, I organized a separate pilot trial contrasting specimens from a cohort of infants with hydrocephalus unrelated to infection (congenital malformations), with a matched set of patients with typical infectious histories. No one knows what

organisms the typical child in these settings acquires in early life given typical living conditions in rural East Africa, and this is a critical control for further interpreting our findings.

I noticed that there appeared to be seasonality in the bacterial spectrum being sequenced from these infants at the time of surgery. I then fused 10 years of satellite case data with 10 years of case data calculated monthly for each of the 77 districts in Uganda. Incredibly, there is a powerful climate drive of these cases (Schiff et al J Neurosurg Peds 10:161-167, 2012). Like seasonal cholera, these infections appear quenched at peak rainfall. With 2 rainy seasons in Uganda, we resolve 4 peaks in cases each year, straddling the 2 rainfall peaks (Figure 1A, 1B). As with melioidosis in southeast Asia and northern Australia, organisms can be exquisitely sensitive to soil wetness and temperature, and infectivity peaks with optimal surface conditions.

Thus PIH has an antecedent in NS. We do not know which organisms in NS lead to PIH. But in the much broader sense, we do not understand the spectrum of organisms that inhabit or infect infants in SSA, nor do we understand which ones have the apparent predilection for the brain we observe on endoscopic treatment. On endoscopy, the typical brain of a PIH infant has considerable purulence within the ventricles, but pristine basal cisterns beneath the brain. This is a very different picture than expected following typical bacterial meningitis, and raises our concerns about primary brain ventricular seeding (well described for several bacterial species), and potential that there may be viral involvement.

The first step is then to define the bacterial and viral agents associated with NS - the **Neonatal Septisome**.

To begin to define the Neonatal Septisome, I set up a collaboration with the Mbarara University of Science and Technology (MUST) and their head of pediatrics, Julius Kiwanuka. This is the major teaching and referral hospital in Southwest Uganda, where they see typically 1 case of NS each day – it accounts for 40% of admissions to their infant ward. Following careful IRB negotiations, and translation of informed consent documents into Runyankore, I supplied proper equipment for blood culture and infant lumbar puncture, and trained the physicians in sample collection. We have so far recruited 193 mother-infant pairs with NS, collecting blood and CSF from neonates presenting with strict criteria for NS, and blood and vaginal specimens from their mothers. A fraction of these infants must acquire early NS during the birth process, and we are stratifying cases as early and late onset based on the number days from birth to infection. Mothers who are HIV positive are staged for AIDS, and we find that HIV involvement is not overrepresented in these cases. We performed superb bacteriology onsite at MUST, with my colleague Joel Bazira, an MD-PhD microbiologist – and consistent with other reports we only recovered 32% positive cultures from these infants. We have just published our first joint bacteriological study (Kiwanuka et al PLoS ONE 8:e72775, 2013), finding a nearly identical neonatal bacterial spectrum as another high-quality laboratory in Uganda at the National hospital in Kampala, but most importantly, demonstrating the strength of the team effort I organized in Mbarara to carry out, analyze, and publish meticulous quality microbiological data.

All of the cases of hydrocephalus that present to MUST are referred to CCHU at Mbale, whose staff holds a clinic at MUST every 8 weeks. So it is a matter of numbers. If I can capture sufficient numbers of mother-infant NS pairs at MUST, and track the cases that develop PIH, then I can prove which agents are responsible. We are approved for 400 mother-infant pairs, out of which I estimate yielding about 20 cases of PIH in survivors. Although I have nearly 200 sets of mother-infant samples in hand, I lack the resources from seed funding to suitably analyze all but a fraction of these invaluable specimens. Based on our preliminary microbiology, the IRB at MUST, and the Ugandan National Council for Science and Technology (which oversees IRBs in Uganda, with whom I have negotiated a Materials Transfer Agreement for this study, and which approved my Ugandan security clearance for performing this work), has given us approval to collect this full enrollment.

Thus I am in a unique position in East Africa. I have the collaborators on the ground, the IRB protocols in place, and government approval, to define the microbial origins of NS (bacterial and viral) in a country in SSA to a level not previously performed, and to determine which of these agents are responsible for causing PIH.

However, the climate link demonstrates that the causal agents will not be stationary with time. At present, the pediatricians at hospitals in SSA tend to treat NS without the benefit of bacteriology, and typical broad spectrum antibiotics are administered (e.g. ampicillin and gentamicin). Were we to merely average our microbial findings throughout the year, it would be inapplicable much of the time.

The Neonatal Septisome is a living ecosystem that varies over time and geographical locale – it is a spatiotemporal dynamic biological system that we can at best sparsely measure. I will therefore adapt the effective strategy used in numerical weather prediction and probabilistic robotics – a model-based predictive control observer. We will fuse this computational model with real-time (scale of weeks) microbiological and climate satellite sensing data available from the National Oceanographic and Atmospheric Agency. This will give us the next generation of therapeutics for NS – predictive real-time guidance of antibiotic (and possibly

antiviral) therapy. Such a control theoretic approach to infectious disease treatment can incorporate antimicrobial resistance into the surveillance and model data. We must answer the question: On a given day, when a sick infant arrives at point-of-treatment with NS, what antimicrobials are immediately instituted to lessen the damage to the infant? Such urgent therapy is required whether or not the organisms causing that particular infant's infection are identified. Reality needs to be predicted and reconstructed when it cannot be directly and immediately sensed – this principle is the foundation of modern model-based control engineering. This approach would reduce the number of deaths from NS, and reduce the number of cases of PIH in survivors of NS. To complete the control engineering picture, by following up the outcome of cases in surveillance, we will close the feedback loop on this system and adjust the model as done in all modern feedback control systems. I illustrate my vision for this in Figure 1C.

A blend of bacteriology and metagenomics will play an important role in untangling the complexities of NS in such settings. In our present analysis workflow, we use control FTA cards to generate background controls for both African sample collection sites, and our US laboratory and sequencing center. Using high-quality matches at the genus level and below, we are able to validate our sequences against in-country organism recovery with bacteriological identification of isolates, and then to demonstrate the appropriate distribution of copy numbers within patients (e.g. higher copy numbers in CSF during meningitis, but lower copy numbers of the same genus in blood when blood cultures were negative). Furthermore, we are now identifying patients with dual or sequential infections where S. pneumoniae is the primary organism, but in a subset of these patients we recover Leptospira DNA. Leptospirosis may be the world's most common zoonosis, but is not culturable in our African settings, is climate linked and can affect the brain. It has never been described in neonates before. It is very treatable if we know it is present. These are the slowly emerging findings from our preliminary work that supports our strategy of combining bacteriology with metagenomics in an effort to characterize the neonatal septisome. These are the microbial surveillance data to be entered into our predictive model in Figure 1C.

Control theory has not yet had a substantial role in sustainable predictive care of infectious diseases. NS and meningitis require immediate treatment before bacteriological identification of organisms is performed, in developed or developing countries. Thus my strategy is broadly applicable to a wide range of infectious disease applications, where the spectrum of organisms or resistance patterns are shifting with time.

Furthermore, I wish to develop a sustainable strategy to enter other countries and perform a similar analysis, but at low cost and in much shorter periods of time than we will require for this first effort in Uganda. One ideally needs to perform the initial organism identification in-country – it is infeasible to have major research institutions in the US performing massive sequence analysis efforts for each country in the world. I have been in close contact with the CEO of Life Technologies, Greg Lucier, and I would like to collaborate with such biotechnology companies in order to create a more effective computational framework for validating organism discovery using a combination of bacteriology and metagenomic analysis as done here. Such a framework would be used to optimize surveillance once the initial intensive organism discovery phase was completed. The predictive modeling is straightforward to adapt once we have done this in Uganda (substitute surveillance data from the new country and fuse with the appropriate satellite grid data).

Lastly, once an infant presents with NS, it is in many cases already too late to prevent morbidity and mortality. I have done enough field work in Uganda to know that I would be able to organize an effort to comprehensively evaluate the villages of the children with NS that we study, in an effort to identify the likely sources and routes of infection. The climate data supports a strong environmental component, and the rainfall link points to soil hydrology. In future work, rational public health strategies can be developed using a similar strategy of control feedback optimization based upon NS case numbers, in the style of Figure 1C.

Following definition of the Neonatal Septisome for a given region, the design of rational public health strategies, such as water supply improvement or animal husbandry practice changes, will face all of the monetary, inertial, and cultural barriers that force the kinetics of such improvements to be much slower than the needs that millions of sick neonates dictate. If we knew what the most common organisms were, maternal screening using low-cost diagnostics might be highly cost-effective. Once we have the first definitions of the Septisome in hand we can consider whether maternal vaccination strategies might be feasible for certain agents (our increasing documentation of S. pneumoniae at Mbarara is an example of an organism where safe and effective vaccination strategies are possible). I note that neonatal tetanus in Africa melted away once mothers were routinely inoculated against tetanus.

It is my opinion that we, as a global medical community, have failed to adequately address the burden of NS in the developing world. There are more NS deaths each year than global deaths from malaria, and comparable to world-wide numbers of deaths from tuberculosis. I was invited in 2011 to testify to the US House

Foreign Relations subcommittee on Africa, Global Health, and Human Rights (http://www.c-spanvideo.org/program/Ugand). In my testimony, I expressed my opinion that one reason for this knowledge gap is that newborn infants dying in developing countries have no political voice. I very much hope to begin to address this gap with support from this NIH Pioneer Award.

Evidence of PD/PI's innovativeness:

I have had a rather unorthodox career. Armed with a few too many math and physics courses as an undergraduate at MIT, I pursued a PhD in physiology along with my MD, and following completion of my training in adult and pediatric neurosurgery at Duke and the Children's Hospital of Philadelphia, I practiced Pediatric Neurosurgery for 8 years at the Children's National Medical Center. I co-founded their Epilepsy Surgery Program, and for 5 of those years also treated the children requiring epilepsy surgery from the Intramural program at NIH. Highly motivated to seek better alternatives to resection for epilepsy in children, I founded and directed the Center for Neural Dynamics at the Krasnow Institute for Advanced Studies at George Mason University, bringing an amalgamation of physicists and mathematicians to work together with me to explore the physics of the nervous system. I became what is, to my knowledge, the only person who is both a Fellow of the American College of Surgeons and the American Physical Society. I have served for 14 years on the Editorial Boards of the journals of the American Physical Society (6 years Physical Review E, 6 years as Divisional Associate Editor for Physical Review Letters, the premier journal for high impact physics in the US, and now with the new open access Physical Review X). I negotiated getting the biological physics articles from these journals indexed in Medline/Pubmed, and wrote the policies for the American Physical Society on human and animal investigations. Most recently, I founded and direct the Center for Neural Engineering at Penn State, a physical unit of 20 physicians, engineers, physicists, mathematicians, and neuroscientists, seeking transdisciplinary solutions to important medical problems that none of us could solve individually.

Specific examples of my innovativeness include the first demonstration of chaos control in the brain (an Article in Nature in 1994, and US patent), the first application of wavelet transforms to EEG (1994), the first demonstration of electrical field suppression of seizure activity (1996), the first demonstration of stochastic resonance in the brain (1996), the first demonstration generalized synchronization in the nervous system (1996), the first demonstration of adaptive seizure control in brain (2001), the establishment of the experimental threshold of neurons to electrical fields (2003), the discovery of spiral waves in the brain (2004), the first demonstration of electrical modulation of cortical wave propagation (2005), the discrimination of seizure stages (2005), the first incorporation of micro-electro-mechanical (MEMS) accelerometers to improve EEG sleep stage discrimination (Sunderam et al 2007), the first adaptation of control theory to spatio-temporal control of neuronal circuitry (Schiff and Sauer 2008), the first demonstration of seizure entrainment (Sunderam et al 2009), the first validation of model-predictive reconstruction of neuronal microcircuit activity (Ullah and Schiff 2010), the first characterization of bacteria in African PIH (Li et al 2011), and the first demonstration that climate drives a neurosurgical condition in the form of PIH in Africa (Schiff et al 2012). Clinically, I have shown innovativeness by defining a safe approach to brainstem abscesses (1988), described a model for the surgeon's risk of AIDS (1990), shown that hemispherectomy without blood transfusion was possible for the Jehova's Witness patient (1993), redefined the physiology of selective rhizotomy surgery for cerebral palsy (1993-1994), served on the executive committee that designed the randomized Shunt Design Trail (1992-2000), and most recently constructed the first complete human brain growth curves (2013) and shown that such volumetrics can improve our surgical management for hydrocephalus (2013) and epilepsy (2013). The volumetric findings are a key component of an NIH funded Phase III randomized controlled surgical trial in Africa of which I am one of the PIs. My most innovative accomplishment, the one I discuss separately in this application, is the successful fusion of computational neuroscience with control theory, embodied in the first book on this topic published in 2012 by the MIT press, Neural Control Engineering.

My goal in this Pioneer Award is to leverage all that I have learned about control engineering to create a novel, and potentially transformative, framework to improve the efficacy of treatment of NS in the developing world, and simultaneously reduce the global burden of hydrocephalus.

How the planned research differs from the PD/PI's past or current work:

I have had no past publication track record or NIH funding for infectious disease research. On the other hand, it was never apparent until very recently that most of the world's hydrocephalus might stem from infections. As a Pediatric Neurosurgeon teaching the world to better treat hydrocephalus, when most of it is preventable, requires that we shift our focus from palliative surgery to prevention. Along the way, there is an opportunity to substantially affect the horrendous toll that NS takes on infants world-wide. I have supported my preliminary work described above from my endowed chair funds, and seed grants from Penn State and the

Pennsylvania Department of Health to get collection and analysis started. I published my first papers on PIH starting in 2011, and most recently published my bacteriology paper from work performed entirely in Africa – demonstrating my ability to organize collaborators to conduct very high-quality microbiology in some difficult circumstances. These recent papers help establish several things to support my credibility for this project. First, I have brought together effective teams to begin to address this problem. In the US, I have a collaboration formed with infectious disease experts Vivek Kapur (bacteriology) and Mary Poss (virology), along with the world's expert on the treatment of PIH in the developing world (Benjamin Warf from Harvard). I have worked with several groups on metagenomic sequencing, but optimizing the extractions and controlling for contamination have been the most important aspect for this now routine technology. Critically, I am now using bacteriology at Mbarara to validate our metagenomic speciation results. The point is that although I am not a microbiologist, I can work effectively to design the internal controls and validity checks and organize the collaborative efforts to ensure that our microbiological analysis is optimized and valid.

I have negotiated multiinstitution IRB proposals with both Mbarara and Mbale, bringing their IRB members and investigators up to US standards and training, and negotiated final agreements approved by all sites and the government of Uganda. I brought into our collaborative net a renowned mathematician with numerical weather prediction expertise to assist in my climate analysis (Tim Sauer, with consultation from the former head of NCAR – Eugenia Kalnay). And I organized the team that enabled me to conduct fieldwork in rural Africa. To support my efforts overseas, I now maintain Ugandan medical licensure. I have thus laid down all of the infrastructure required, in the US and in East Africa, to carry out this project if I can now secure funding at an adequate level and for sufficient numbers of years to carry this out.

Suitability for Pioneer Award program:

This project is well suited for the Pioneer mechanism. It represents a substantially new direction for my professional work. The transdiciplinary mixture of infectious disease, pediatric medicine and neurosurgery, control engineering, and climate dynamics are such that there are no single disciplinary study section or IC at NIH that accommodate the project. The problem is immense and global, and I am uniquely positioned in an African country to test hypotheses and create potentially transformative solutions within the scope of this grant.

Obvious questions for the Pioneer mechanism are whether this is ongoing work in search of funding. I have been laying the foundation for this project with about 5 years of preliminary effort supported by small seed grants. If one were to just carve out the microbiological organism discovery, as in my pending NICHD R01 application, this should be fundable through routine channels if I can escape the overarching issue that I have no credible track record (yet) in infectious disease. And this would be a narrowly defined microbiological study whose impact would be potentially limited outside of Uganda. On the other hand, this Pioneer Award is focused on control of NS through engineering principles and seeks sustainability and scalability – this project has no home in routine NIH channels.

I have shown that I can develop effective collaborations to support the medicine and science of this interdisciplinary effort, but I remain the clear project leader and PI for this effort. Although a new direction for me, it leverages all of my professional expertise in neurosurgery, physiology, physics, and control engineering. The effort, 51%, is exactly the percentage of my professional effort that I would wish to devote to this work. This project was a finalist for the Pioneer Awards in 2011, scored well for the Transformative award in 2012, and I am now following the recommendation to re-apply for the Pioneer Award for 2014 as my preliminary data more convincingly demonstrate that my vision of this project is feasible.

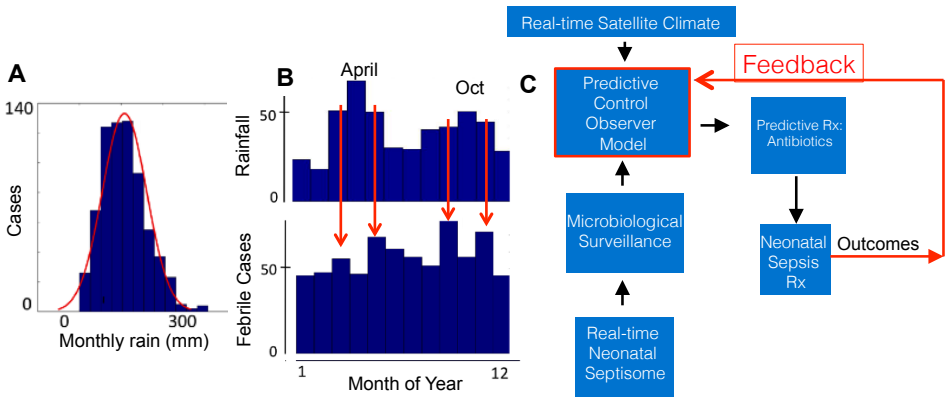

Figure 1. A) PIH cases (n=696) peak at intermediate levels of rainfall, and B), which straddle the two rainy season peaks in each year (6 years data). C: Structurally controllable diagram for feedback control for treatment optimization using predictive modeling. A similar feedback diagram is constructed for public health optimization of NS.

Protection of Human Subjects
Risks to Human Subjects

a. ***Human Subjects Involvement and Characteristics***

We will study blood and cerebrospinal fluid (CSF) collected during the course of treatment of neonates with neonatal sepsis (NS) at Mbarara University of Science and Technology (MUST) in order to determine the microbial cause of this condition.

At MUST, procedures on neonates presenting with NS consist of a blood draw for culture and a lumbar puncture. Under no circumstances are procedures performed to retrieve additional volume of blood or CSF for any experimental sampling – all sampling is performed for clinical indications.

Withdrawal of blood volumes in the range of 1% for analysis is well below the volumes expected to have any chance of significant affect on the cardiovascular system. Similarly, our suggested volumes below of less than 5% of total CSF volume are routinely withdrawn from neonates that meet the size criteria below without adverse consequences.

Note on body weight. In order not to expose these infants to any significant risk beyond that of routine medical care, we restrict our study at MUST to infants greater than 2 Kg. Lower birth weight infants pose technical difficulties with both blood and CSF withdrawal, and have smaller blood and CSF reservoirs to sample. There are, unfortunately, relatively few low birth weight infants in Uganda where the facilities to salvage them early in life are lacking.

In addition, with maternal consent at MUST, a vaginal smear will be collected, cultured, and placed on DNA/RNA collection cards. Maternal blood will be drawn as well, with consent, for malaria smear, HIV testing (CD4 counts if HIV+), and additional immunological testing.

• Characteristics of the subject population

We will study neonates (one month or less in age) with clinical sepsis and mothers of neonates with sepsis. Mothers will be at least 18 years old to be able to give informed consent.

MUST has an IRB in the US style. **We iterated all versions of this multiinstitution IRB proposal with each site so that all sites are in agreement with the detailed structure of the human investigations.** All investigators, US and Ugandan, have passed human studies ethics training as investigators for human studies projects through the Collaborative Institutional Training Initiative online program at the University of Miami that Penn State requires of it's investigators on IRB proposals.

• Criteria for inclusion or exclusion

Mbarara Inclusion

1) Neonates with Presumed Sepsis
    a. Entrance Criteria (i, ii, or iii)
        i. fever, lethargy, poor feeding
        ii. hypothermia, lethargy, poor feeding
        iii. full fontanel, fever, poor feeding
2) Age less than one month
3) Weight greater than 2.0 Kg
4) Mother at least 18 years old to give informed consent

Mbarara Exclusion

1) Known infection other than sepsis
2) Known congenital malformation
3) Known cutaneous or GI fistula
4) Known birth trauma such as wounds or fractures

• Rationale for the involvement of special classes of subjects, such as neonates

The rationale for involvement of neonates is that NS is a widespread and highly lethal condition of such children in the developing world. There are no alternatives to studying the neonatal patient population for diseases inherent only within that population. Our study design does not expose these children to risks beyond the risks of routine medical care.

• Collaborating sites where human subjects research will be performed, and the role of those sites and collaborating investigators in performing the proposed research.

The collaborating site is the Mbarara University of Science and Technology (MUST).

At MUST, the Chairman (Dr. Kiwanuka) of Pediatrics will direct the clinical management of neonates with sepsis. With the resources from this project, we will enable them to perform routine blood and CSF cultures on these infants (Dr. Bazira is the microbiologist), which they would perform as part of their clinical care were the resources available. They will further obtain blood and vaginal specimens from the patient's mothers upon informed consent, and process small amounts of excess blood and CSF from the infants if consent is obtained.

b. **Sources of Materials**

At MUST, we will collect specimens of blood and CSF urgently from 400 consecutive neonates that arrive with clinical sepsis and meet the clinical criteria above. **We have received approval from the IRB at MUST, the Ugandan Council of Science and Technology (oversees human investigations in Uganda, and grants materials transfer agreements), to proceed with this full 400 patient recruitment.** We will consider cultures of blood and CSF to be routine analysis, albeit one that is often not performed at MUST due to resource constraints. We will then seek Maternal Consent to a) process the additional blood and CSF specimens previously placed on Whatman FTA cards for DNA/RNA analysis, and b) perform sampling of the maternal birth canal for culture and DNA analysis, and c) test maternal blood for malaria, HIV, and CD4 counts. If maternal consent is not obtained, the neonatal DNA/RNA cards will be destroyed, although the clinical culture results of blood and CSF will be available to the clinicians.

A note on specimen volumes. We need to collect specimens in ways that offer no significant risk from the volume of blood or spinal fluid withdrawn. Ideally, we would collect for analysis 100 uL specimens for DNA, and 400 uL specimens for viral RNA. Because of the risks of transport of such invaluable specimens, we will to collect backup specimens in case the primary specimens are lost in shipment to the US. Accordingly, at MUST, we set a minimal neonatal weight of 2 Kg for entrance into the study. This is a weight often used clinically for elective surgical procedures on young infants (such as permanent CSF shunt insertion in hydrocephalic infants). At this weight, the technical difficulties of withdrawing blood and performing lumbar punctures are less than in lower weight neonates. Since blood volume is 8% of body weight, there are 160 mL of blood in the typical 2 Kg infant. Intracranial CSF volume is on average equal to $4W^{0.697}$, where W is body weight in Kg (Robson et al 2004). Total CSF including the spinal subarachnoid space is on the order of twice this volume (a 70 Kg adult has approximately 150 mL of CSF). Accordingly, we have adjusted our volumes of blood and CSF withdrawn at MUST so that the volumes withdrawn for this study will not affect the infant. We use the following calculations to base our recommendations upon:

	Kg	Blood Vol mL		Cx, Malaria, HIV	Viral	DNA	Total mL	Fraction of Total
Blood	2.00	160.00		0.40	0.40	0.20	1.00	0.01
	Kg	IC CSF v	total CSF v	routine Cx+GS				
CSF	2.00	6.52	13.03	0.20	0.20	0.20	0.60	0.05

We will withdraw 1 mL of blood, sending 0.2 mL for culture, and 0.1 mL each for malaria smear and HIV test. We will place 0.2 mL each on a viral FTA card and a backup viral FTA card. We will place 0.1 mL each on a DNA FTA card and on a backup DNA FTA card. This 1 mL of blood in a 2 Kg infant is less than 1% of blood volume. If less than 1 mL is obtained, we will eliminate in order: the backup cards, the viral card, and finally the DNA card, leaving the routine test volumes. No additional blood venipunctures will be performed if the volumes for routine clinical testing have been obtained. For CSF, in contrast to blood, we typically remove more relative volume without clinical effect, and we propose withdrawing 0.6 mL (less than 5% of CSF volume in the 2 Kg infant). CSF will only be withdrawn as free flow from a spinal needle within 1 minute after insertion, without suction, and only so long as free flow is obtained. We will use 0.2 mL for gram stain and culture, 0.1 mL each for DNA FTA and backup DNA FTA specimens, and 0.1 mL each for viral FTA and backup viral FTA specimens. If less than 1 mL is withdrawn, we will eliminate in order: the backup cards, the viral card, and finally the DNA card, leaving the routine test volumes. If excess volumes are obtained, we will use additional specimen volume on the viral FTA cards (4 x 100 mL collection sites per card) and the backup viral card.

A note on maternal birth canal flora. Following identification of the bacteria in the infants with neonatal sepsis, we seek to match the DNA from the infecting organism with DNA probes to that same organism in the maternal specimens to determine whether the mothers were potential sources for these organisms. We will begin culturing such specimens as well at MUST, in expectation that, as in the industrialized countries, the use of selective culture can be an effective screen for bacterial agents (such as group B Streptococcus) that are causal of serious NS and meningitis. Positive pathogen cultures at MUST will be placed on FTA cards for DNA matching with pathogens from infants.

• Data that will be collected from human subjects

Demographic data. We will seek maternal consent for potential future home visits in our quest to characterize the environmental origin of infections, and utilize this in follow-up studies under IRB oversight.

Basic demographic information will be collected including: age, sex, medical record numbers, dates of birth when available. The results of the CSF cell count, Gram's stain, India ink, and culture will be collected several days later. The result of malaria smear and HIV testing, performed routinely on such children, will be recorded.

In addition to these basic demographics, we will collect information on 1) Villages where these infants were born, 2) Maternal language, and 3) Any tribal or cultural affiliation if noted. Seeking information on potential clustering, whether geographic or cultural, is critical to seeking to determine the role of these infectious agents in this disease process.

All such children will have a routine clinical blood sample collected. The results of the cell count and differential on the peripheral blood will be recorded.

All of the above patient data will be labeled with a unique code number.

Maternal malarial smear results, HIV status, and CD4 counts will be recorded following consent.

• Who will have access to individually identifiable private information about human subjects.

We will keep all records under physical lock at the participating institutions, and password encrypt computer files containing patient identifiers.

All non-clinical samples will be alphanumerically coded and be analyzed without patient identifiers. Access to the linkage codes for these samples will be restricted to the principal investigators.

We will seek a Data Management plan, whereby data will be keyed into the database by personnel supervised by the data manager with write only access for new patient documentation. Only one person at each institution, the person keying in data, will be assigned write access by the data managers. Only the data managers and PIs will automatically have read access to confidential data within the database. Other investigators will be designated for read access when data analysis is justified. In the US, all samples will be worked on using an alphanumeric code assigned at the time of patient admission

• Information about how the specimens, records, or data are collected and whether material or data will be collected specifically for the proposed research project.

Specimens, records, and data are being collected specifically for the proposed research project, and will be handled as above under IRB oversight. **Note that a unified IRB protocol has been negotiated and approved so that each of the project sites agrees to the entire IRB project.**

c. ***Potential Risks***

There are no significant additional risks to neonates in this study beyond the risks of routine collection of blood and CSF during the course of clinical care.

Mothers will additionally have a blood draw and vaginal smear collected by physician, which are minimal risk.

The other risk is that we will keep the patient identification and demographic data and there is a risk of loss of confidentiality if such records were not properly handled. We will keep all records under physical lock at MUST, and password encrypt computer files containing patient identifiers with restricted access only to those investigators who require this for conduct of the study.

All samples for non-clinical use (DNA/RNA analysis) will be alphanumerically coded and be analyzed without patient identifiers. Access to the patient linkage for the codes for these samples will be restricted to the principal investigators.

• Alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

This project will not affect state of the art treatment for these neonates and infants. We will not consider alternatives to the standard of care applied by our US and UK trained physicians adhering to the standards of US and UK medical systems. The results of this study may suggest improvements in strategies to treat or prevent NS, and such future studies will be conducted under future IRB oversight.

4.1.2 Adequacy of Protection Against Risks

a. ***Recruitment and Informed Consent***

• Plans for recruitment of subjects and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

Patients meeting the inclusion criteria will have specimens drawn during the routine clinical care and treatment of neonatal sepsis.

Additional DNA and RNA specimens will be collected at the time of initial treatment if this presents no harm to the infants. The reason to collect without initial consent are that mothers may not be present at initial presentation when specimens must be collected, and that treating neonatal sepsis is an urgent condition. We will, however, not analyze any specimens not used in routine clinical care without maternal consent.

One of the treating physicians will approach the mothers for informed consent.

The recruitment will be based upon explaining to the mother that their infant has a very serious condition. We are trying to find the cause of these illnesses, and would like to 1) analyze specimens in the United States to try to help the African doctors identify the cause, and at Mbarara, additionally 2) to see if the infant might have gotten ill during birth. We will explain that because the infant might have gotten ill at home, that we would like permission to visit in the future to gather specimens and try to find the cause, as well check to be sure that the infant is doing well.

• Description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver.

Full informed consent will be obtained as described above. At Mbarara, the local IRB has requested written consent, in English and Runyankore, the national and predominant local language respectively – the referral base at Mbarara is mostly southwest Uganda. We have translated our consent into Runyankore and the IRB at MUST has approved this translation.

A parent can request withdrawal from the study at any time. If withdrawal is requested, all non-clinical specimens collected from that patient (and mother if applicable) will be destroyed, and the subject data removed from the study.

b. ***Protections Against Risk***

• Planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.

There are no significant additional risks to neonates or infants in this study beyond the risks of routine collection of blood and CSF during the course of clinical care.

Mothers of infants with neonatal sepsis will additionally have a blood draw and vaginal smear collected, which are minimal risk.

The other risk is that we will keep the patient identification and demographic data and there is a risk of loss of confidentiality if such records were not properly handled. We will keep all records under physical lock at the participating institutions, password encrypt computer files containing patient identifiers, and as described above, be very strict about read and write access to these files.

All samples for non-clinical use (DNA/RNA analysis) will be alphanumerically coded and be analyzed without patient identifiers openly available. Access to the patient linkage for the codes for these samples will be restricted to the principal investigators.

• Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections.

It is unlikely that any of the mothers will be pregnant at Mbarara, because the infants will be neonates within the first month after birth.

This proposal studies neonates with life threatening sepsis, but only studies excess fluids collected during the course of routine medical therapy for the neonates.

• Additional Protections for Children:

Assent will not be obtained since all children will be 1 month or less in age.

This is Category 1 research in children – the study poses no greater than minimal risk to children. We are using excess blood and CSF specimens obtained in the course of clinical care for this research.

• Medical or professional intervention in the event of adverse effects to the subjects.

Adverse events or unanticipated problems will be reported to the principal investigators and communicated to the IRBs of each institution within a week of any such events.

The persons responsible for identification, documentation and reporting adverse events and unanticipated problems at each institution will be:

- Dr. Kiwanuka (Mbarara)
- Dr. Schiff (Penn State)

• Potential benefits of the research to research participants and others.

There are no direct benefits to the infants or mothers for participation in this research.

• Why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

There is minimal risk to subjects.

• Importance of the knowledge gained or to be gained as a result of the proposed research.

NS is a life threatening conditions, and those children who survive often suffer substantial morbidity. The knowledge gained in this study will very likely have an impact on the morbidity and mortality of these conditions for future children, and lead to more effective treatment and prevention strategies.

• Why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

This study poses no more than minimal risk above and beyond the risks of treatment of this condition.

• Data and Safety Monitoring Plan

This is a minimal risk study and as such does not require a formal data safety monitoring plan.

Nevertheless, we have agreed to the following policies: **1)** serious adverse events will be reported to the local PI and overall project PI within 1 week, **2)** The local PI will communicate with the project PI on a weekly basis, and **3)** The local PI will perform on-site auditing and monitoring.

• Sample Size Justifications

We wish to have sufficient numbers of patients recruited to study that have meningitis accompanying their sepsis, in order to both fully account for patients whose sepsis consists of invasive infection in the CSF without positive blood culture, both to establish the need for lumbar puncture in this setting, and to account for sequelae that are common in this setting such as postinfectious hydrocephalus. Using the formula of Kish and Lesler, $N = \frac{z^2 p(1-p)}{d^2}$, where N = the required sample size, z = 1.96 (the value from the standard normal curve corresponding to the 95%), p = the estimated proportion of patients with meningitis, and d = precision (5%), we can estimate how many patients we need to recruit. Setting p = 5-50%, which includes our maximal uncertainty and corresponds to the worst-case scenario, our calculations indicate that a sample size of 384 patients would be sufficient with a 95% confidence interval no wider than ±5%. At MUST, approximately 300 neonates with presumed NS are seen each year (about one admitted per day). We will therefore set our patient recruitment targets at 400 patients. A 2-year time horizon will ensure an adequate opportunity for recruitment. We have 120 patients already recruited and samples collected but without research genomic analysis. If we reach our recruitment cap during the course of this study, we will apply to amend our protocol and request additional recruitments to complete the real-time predictive component of this project.

• Inclusion of Women and Minorities

This study will involve consent from all mothers of neonates with sepsis recruited, and we will collect specimens from both the neonates and the mothers.

Neonates with NS will be recruited without regard to gender.

Almost all subjects recruited into this study will be black Africans, and the ethnic diversity will reflect the substantial African diversity of the peoples of Uganda. No patient with NS is turned away from MUST for race, ethnicity, or socioeconomic status.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: The Origin of Neonatal Sepsis in Uganda (Mbarara, local project title)

Domestic/Foreign: Foreign

Comments: N/A

Racial Categories	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	200	200	0	0	**400**
White	0	0	0	0	**0**
More than One Race	0	0	0	0	**0**
Total	**200**	**200**	**0**	**0**	**400**

Study 1 of 1

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• Inclusion of Children

This study will focus on neonates with neonatal sepsis.

• Rationale for selecting a specific age range of children. Description of the expertise of the investigative team for dealing with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.

The rationale for the ages of these children, less than 1 month for neonates with NS, is that this is the age at which this syndrome occurs.

At the Ugandan site in this project, physicians have extensive experience with treating neonates. The PI at Mbarara will be Dr. Julius Kiwanuka, Chairman of Pediatrics, who has degrees in Paediatrics from Leeds, and Tropical Paediatrics as well as Tropical Child Health from Liverpool (School of Tropical Medicine), and is certified in Pediatrics by the Royal College of Paediatrics and Child Health. The US PI, Dr. Schiff, is a Pediatric Neurosurgeon who, in addition to Board Certification in Neurosurgery and a license to practice medicine in the State of Pennsylvania, also maintains a temporary Ugandan medical license. Facilities for the treatment of NS at MUST are among the best in Uganda.

Sample size justifications are discussed in the main Human Studies section – sufficient numbers of children will be recruited to contribute to a meaningful analysis.