

PI:	Title: Intermittent Hypoxia and Retinopathy of prematurity	
Received: 06/16/2009	FOA:	Council: 01/2010
Competition ID: ADOBE-FORMS-A	FOA Title: NIH SMALL RESEARCH GRANT PROGRAM (PARENT R03)	
1 R03 HD	Dual:	Accession Number:
IPF: 218601	Organization:	
Former Number:	Department: Pediatrics	
IRG/SRG: CHHD-A	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 50,000 Year 2: 50,000	Animals: N Humans: Y Clinical Trial: N Current HS Code: 30 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	Organization:	Role Category:
		PD/PI

**APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)**

2. DATE SUBMITTED	Applicant Identifier

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION

Pre-application Application Changed/Corrected Application

4. Federal Identifier

5. APPLICANT INFORMATION * Organizational DUNS: _____

* Legal Name: _____

Department: pediatrics Division: Neonatology

* Street1: _____

Street2: _____

* City: _____ County: _____

* State: _____ Province: _____

* Country: USA: UNITED STATES * ZIP / Postal Code: _____

Person to be contacted on matters involving this application

Prefix: Mrs. * First Name: _____ Middle Name: _____

* Last Name: _____ Suffix: _____

* Phone Number: _____ Fax Number: _____

Email: _____

6. * EMPLOYER IDENTIFICATION (EIN) or (TIN): _____

7. * TYPE OF APPLICANT: _____ O: Private Institution of Higher Education

Other (Specify): _____

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:

TITLE: _____

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

12. * AREAS AFFECTED BY PROJECT (cities, counties, states, etc.)

13. PROPOSED PROJECT:

* Start Date	* Ending Date
<u>04/01/2010</u>	<u>03/31/2012</u>

14. CONGRESSIONAL DISTRICTS OF:

a. * Applicant	b. * Project
<u>11</u>	_____

15. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: Dr. * First Name: _____ Middle Name: _____

* Last Name: _____ Suffix: _____

Position/Title: _____

* Organization Name: _____

Department: pediatrics Division: Neonatology

* Street1: _____

Street2: _____

* City: _____ County: _____

* State: _____ Province: _____

* Country: USA: UNITED STATES * ZIP / Postal Code: _____

* Phone Number: _____ Fax Number: _____

* Email: _____

<p>16. ESTIMATED PROJECT FUNDING</p> <p>a. * Total Estimated Project Funding <input type="text" value="157,000.00"/></p> <p>b. * Total Federal & Non-Federal Funds <input type="text" value="157,000.00"/></p> <p>c. * Estimated Program Income <input type="text" value="0.00"/></p>	<p>17. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?</p> <p>a. YES <input type="checkbox"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE: <input type="text"/></p> <p>b. NO <input checked="" type="checkbox"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="checkbox"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW</p>
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18. 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.

19. Authorized Representative

Prefix: * First Name: Middle Name:

* Last Name: Suffix:

* Position/Title:

* Organization:

Department: Division:

* Street1:

Street2:

* City: County:

* State: Province:

* Country: * ZIP / Postal Code:

* Phone Number: Fax Number:

* Email:

* Signature of Authorized Representative

* Date Signed

20. Pre-application

21. Attach an additional list of Project Congressional Districts if needed.

RESEARCH & RELATED Project/Performance Site Location(s)

Project/Performance Site Primary Location

Organization Name:

* Street1:

Street2:

* City: County:

* State: Province:

* Country: * ZIP / Postal Code:

Project/Performance Site Location 1

Organization Name:

* Street1:

Street2:

* City: County:

* State: Province:

* Country: * ZIP / Postal Code:

Additional Location(s)

OMB Number: 4040-0001
Expiration Date: 04/30/2008

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RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? Yes No

1.a If YES to Human Subjects

Is the IRB review Pending? Yes No

IRB Approval Date:

Exemption Number: 1 2 3 4 5 6

Human Subject Assurance Number:

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 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.a. * Does this project involve activities outside the U.S. or partnership with International Collaborators? Yes No

5.b. If yes, identify countries:

5.c. Optional Explanation:

6. * Project Summary/Abstract

7. * Project Narrative

8. Bibliography & References Cited

9. Facilities & Other Resources

10. Equipment

11. Other Attachments

OMB Number: 4040-0001
Expiration Date: 04/30/2008

Abstract

Intermittent desaturation episodes are a significant clinical problem in preterm infants as a consequence of immature respiratory control. These alterations in oxygenation are unpredictable and are probably due to sudden, dynamic changes in ventilatory drive. Hypoxia/hyperoxia events are difficult to control using threshold alarms in the neonatal intensive care unit and, although continuous pulse oximetry monitoring has been in use for many years, this technology has yet to be used to characterize the true incidence of intermittent hypoxic episodes in preterm infants and to further assess the relationship of these events to neonatal morbidity.

As part of a multicenter study of oxygen supplementation, [redacted] and [redacted] Hospital has generated two patient data sets that include long-term, high resolution monitoring of oxygen saturation via pulse oximetry. The two infant cohorts, comprising a total of 174 infants, include: 1) infants enrolled in the multicenter SUPPORT trial and 2) infants meeting enrollment criteria but not enrolled in the SUPPORT trial who received normal clinical care. Preliminary data analysis in the second cohort have revealed a significantly higher incidence of desaturation ($< 80\%$ SaO₂) events in infants developing ROP requiring laser therapy.

However, there is large inter- and intra-patient variability in the pattern of desaturation episodes over time; additionally, data in animal models has suggested an association between patterns of desaturation events and ROP severity. We hypothesize that repetitive desaturation/resaturation events will result in clustering of hypoxia and hyperoxia events and present a significant risk factor for ROP in extremely low birth weight infants younger than 28 weeks gestational age.

To test this hypothesis we will use our existing database of long-term measurements of oxygen saturation obtained via pulse-oximetry for all 174 infants gathered over 8 weeks of NICU care.

In Specific Aim 1, we will use temporal and spectral analysis methods to quantify the linear properties of this patient dataset; additionally we will quantify clustered intermittent hypoxia and hyperoxia events using both linear and non-linear statistical methods to quantify the signal components present in the data.

In Specific Aim 2, we will use a linear mixed model and discriminant analysis to distinguish patterns of desaturation, resaturation, and hypersaturation in infants who do and do not require laser treatment for ROP.

Project Narrative:

Intermittent desaturation episodes are a significant clinical problem in preterm infants as a consequence of immature respiratory control. Higher incidence of intermittent hypoxic (desaturation) episodes is associated with retinopathy of prematurity (ROP), a condition which can lead to life-long visual impairment and blindness.

However, animal models have suggested that variable patterns in the intervals between desaturation episodes are an additional risk factor for ROP. In this application we propose analysis methods to quantify clustered intermittent hypoxia and hyperoxia events in order to minimize risk for ROP in very low birth weight infants. Identification and elimination of these patterns of intermittent hypoxia may lead to reduced incidence of ROP.

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator			
Prefix: Dr.	* First Name:	Middle Name:	
* Last Name:			Suffix:
Position/Title:	Department: Pediatrics		
Organization Name:			Division: Neonatology
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country: USA: UNITED STATES	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role: PD/PI	Other Project Role Category:		
* Attach Biographical Sketch	1234-09Junenihbio.pdf	Add Attachment	Delete Attachment View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment View Attachment

PROFILE - Senior/Key Person 1			
Prefix:	* First Name:	Middle Name:	
* Last Name:			Suffix:
Position/Title:	Department:		
Organization Name:			Division:
* Street1:			
Street2:			
* City:	County:		
* State:	Province:		
* Country: USA: UNITED STATES	* Zip / Postal Code:		
* Phone Number:	Fax Number:		
* E-Mail:			
Credential, e.g., agency login:			
* Project Role:	Other Project Role Category:		
* Attach Biographical Sketch		Add Attachment	Delete Attachment View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment View Attachment

ADDITIONAL SENIOR/KEY PERSON PROFILE(S)

	Add Attachment	Delete Attachment	View Attachment
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Additional Biographical Sketch(es) (Senior/Key Person)

	Add Attachment	Delete Attachment	View Attachment
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Additional Current and Pending Support(s)

	Add Attachment	Delete Attachment	View Attachment
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OMB Number: 4040-0001
Expiration Date: 04/30/2008

Principal Investigator/Program Director (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the 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 Assistant Professor	
eRA COMMONS USER NAME			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
A	BA	1984-1988	Biology, Chem, Russian
	PhD	1989-1996	Physiology, BioMed Eng
	postdoctoral	1996-2001	Neural Cntrl of Breathing

Please refer to the application instructions in order to complete sections A, B, and C of the Biographical Sketch.

Section A. Positions and Honors

Positions and Employment

2001-2002 Instructor, Dept. of Pediatrics, Div. Of Neonatology, ty,

2002- Assistant Professor, Dept. of Pediatrics, Div. of Neonatology, /e

Honors

1992-1995 Pre-Doctoral Fellow, NIH Training Grant,

1996-2001 IRTA Post-Doctoral Fellow, I

Section B. Selected peer-reviewed publications (in chronological order).

(Publications selected from 20 peer-reviewed publications)

RJ I

CA

CG

CA

CG

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Section C. Research Support

2006–Present NIH NHLBI : 010)
Investigator:

The major goal of this project is to quantify the role that astrocytes serve in the modulation of respiratory network activity in the CNS over the course of early development in rats and mice.

2001–2007 NIH NHLBI HL
Investigator:

The major goal for this project is characterization of central neural chemical pathways that contribute to impaired hypercapnic ventilatory response in early life.

2001–2005 NIH NHLBI HL5
Investigator:

The project seeks to characterize signaling pathways that mediate airway relaxin responses induced by nitric oxide and prostraglandins under normoxic and hyperoxic conditions.

2001–2002 Children's Health Foundation
Investigator:

Glial and neuron interactions in the in vitro respiratory slice preparation.

This project is focussed on determining the manner in which cell-to-cell interactions between neurons and glia modulate respiratory rhythm. My responsibilities include preparing the in vitro slice, performing dual whole-cell patch-clamp recordings, analyzing the data and writing and submitting any manuscripts from that data.

1999–2001 NINDS Ir

Systems Neurobiology
and electrophysiology.

Investigator:

In this project we isolated the pre-Bötzinger complex in stationary organotypic cultures that enabled us to image the respiratory rhythm generating kernel repeatedly over the course of many weeks. This pilot project is finished and the publication is being prepared for submission.

1999–2001 NINDS

section. A methodology for achieving high-speed rates for artificial conductance injection in electrically excitable biological cells.

Investigator:

Developed a high speed method of injecting mathematically modeled currents into real neurons using a computer interface with our laboratory amplifiers. This project has been summarized and published in the

7 001.

PHS 398 Cover Page Supplement

OMB Number: 0925-0001

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

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

* New Investigator? No Yes

Degrees:

2. Human Subjects

Clinical Trial? No Yes

* Agency-Defined Phase III Clinical Trial? No Yes

3. Applicant Organization Contact

Person to be contacted on matters involving this application

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

* Phone Number: Fax Number:

Email:

* Title:

* Street1:

Street2:

* City:

County:

* State:

Province:

* Country: * Zip / Postal Code:

PHS 398 Modular Budget, Periods 1 and 2

OMB Number: 0925-0001

Budget Period: 1 <input type="button" value="Reset Entries"/> Start Date: <input type="text" value="04/01/2010"/> End Date: <input type="text" value="03/31/2011"/>				
A. Direct Costs			* Funds Requested (\$)	
* Direct Cost less Consortium F&A			50,000.00	
Consortium F&A				
* Total Direct Costs			50,000.00	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	Modified Total Direct Costs	57	50,000.00	28,500.00
2.				
3.				
4.				
Cognizant Agency (Agency Name, POC Name and Phone Number)		Dept of Health & Human Services (DHHS) HHS Representative FAX.		
Indirect Cost Rate Agreement Date <input type="text" value="06/03/2008"/>		Total Indirect Costs <input type="text" value="28,500.00"/>		
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$) <input type="text" value="78,500.00"/>	
Budget Period: 2 <input type="button" value="Reset Entries"/> Start Date: <input type="text" value="04/01/2011"/> End Date: <input type="text" value="03/31/2012"/>				
A. Direct Costs			* Funds Requested (\$)	
* Direct Cost less Consortium F&A			50,000.00	
Consortium F&A				
* Total Direct Costs			50,000.00	
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	Modified Total Direct Costs	57	50,000.00	28,500.00
2.				
3.				
4.				
Cognizant Agency (Agency Name, POC Name and Phone Number)		Dept of Health & Human Services (DHHS) HHS Representative FAX.		
Indirect Cost Rate Agreement Date <input type="text" value="06/03/2008"/>		Total Indirect Costs <input type="text" value="28,500.00"/>		
C. Total Direct and Indirect Costs (A + B)			Funds Requested (\$) <input type="text" value="78,500.00"/>	

PHS 398 Modular Budget, Periods 3 and 4

Budget Period: 3	<u>Reset Entries</u>	Start Date: <input style="width: 80%;" type="text"/>	End Date: <input style="width: 80%;" type="text"/>
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A. Direct Costs	* Direct Cost less Consortium F&A	<input style="width: 95%;" type="text"/>
	Consortium F&A	<input style="width: 95%;" type="text"/>
	* Total Direct Costs	<input style="width: 95%;" type="text"/>

B. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>

Cognizant Agency (Agency Name, POC Name and Phone Number)	<input style="width: 95%;" type="text"/>
Indirect Cost Rate Agreement Date <input style="width: 80%;" type="text"/>	Total Indirect Costs <input style="width: 80%;" type="text"/>

C. Total Direct and Indirect Costs (A + B)	Funds Requested (\$) <input style="width: 95%;" type="text"/>
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Budget Period: 4	<u>Reset Entries</u>	Start Date: <input style="width: 80%;" type="text"/>	End Date: <input style="width: 80%;" type="text"/>
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A. Direct Costs	* Direct Cost less Consortium F&A	<input style="width: 95%;" type="text"/>
	Consortium F&A	<input style="width: 95%;" type="text"/>
	* Total Direct Costs	<input style="width: 95%;" type="text"/>

B. Indirect Costs	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>	<input style="width: 80%;" type="text"/>

Cognizant Agency (Agency Name, POC Name and Phone Number)	<input style="width: 95%;" type="text"/>
Indirect Cost Rate Agreement Date <input style="width: 80%;" type="text"/>	Total Indirect Costs <input style="width: 80%;" type="text"/>

C. Total Direct and Indirect Costs (A + B)	Funds Requested (\$) <input style="width: 95%;" type="text"/>
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PHS 398 Modular Budget, Periods 5 and Cumulative

Budget Period: 5 <input type="button" value="Reset Entries"/> Start Date: <input style="width: 100px;" type="text"/> End Date: <input style="width: 100px;" type="text"/>				
A. Direct Costs				* Funds Requested (\$)
			* Direct Cost less Consortium F&A	<input style="width: 100px;" type="text"/>
			Consortium F&A	<input style="width: 100px;" type="text"/>
			* Total Direct Costs	<input style="width: 100px;" type="text"/>
B. Indirect Costs				
	Indirect Cost Type	Indirect Cost Rate (%)	Indirect Cost Base (\$)	* Funds Requested (\$)
1.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
2.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
3.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
4.	<input style="width: 95%;" type="text"/>	<input style="width: 50px;" type="text"/>	<input style="width: 100px;" type="text"/>	<input style="width: 100px;" type="text"/>
Cognizant Agency (Agency Name, POC Name and Phone Number) <input style="width: 95%;" type="text"/>				
Indirect Cost Rate Agreement Date <input style="width: 100px;" type="text"/>			Total Indirect Costs <input style="width: 100px;" type="text"/>	
C. Total Direct and Indirect Costs (A + B)				Funds Requested (\$) <input style="width: 100px;" type="text"/>
Cumulative Budget Information				
1. Total Costs, Entire Project Period				
*Section A, Total Direct Cost less Consortium F&A for Entire Project Period		\$	<input style="width: 150px;" type="text" value="100,000.00"/>	
Section A, Total Consortium F&A for Entire Project Period		\$	<input style="width: 150px;" type="text"/>	
*Section A, Total Direct Costs for Entire Project Period		\$	<input style="width: 150px;" type="text" value="100,000.00"/>	
*Section B, Total Indirect Costs for Entire Project Period		\$	<input style="width: 150px;" type="text" value="57,000.00"/>	
*Section C, Total Direct and Indirect Costs (A+B) for Entire Project Period		\$	<input style="width: 150px;" type="text" value="157,000.00"/>	
2. Budget Justifications				
Personnel Justification	<input style="width: 200px;" type="text" value="1239-BudgetJustification.pdf"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
Consortium Justification	<input style="width: 200px;" type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>
Additional Narrative Justification	<input style="width: 200px;" type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	<input type="button" value="View Attachment"/>

Budget Justification:

(0 months) will serve as PI for the proposed study.

(0 months) will serve as Co-PI for the proposed study.

Engineer (4.8 months) will perform data analysis.

Engineer (2.4 months) will perform data analysis

Support is requested for the two engineers on this project and as they will perform the actual data analysis and for supplies related to the data analysis and storage related to this project. Drs. and will supervise and co-direct the interpretation and publication of the projects results.

Drs. and will serve as consultants.

PHS 398 Research Plan

1. Application Type:

From SF 424 (R&R) Cover Page and PHS398 Checklist. The responses provided on these pages, regarding the type of application being submitted, are repeated for your reference, as you attach the appropriate sections of the research plan.

*Type of Application:

New Resubmission Renewal Continuation Revision

2. Research Plan Attachments:

Please attach applicable sections of the research plan, below.

1. Introduction to Application <small>(for RESUBMISSION or REVISION only)</small>	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
2. Specific Aims	1240-SpecificAims.pdf	Add Attachment	Delete Attachment	View Attachment
3. Background and Significance	1241-Background_Significanc	Add Attachment	Delete Attachment	View Attachment
4. Preliminary Studies / Progress Report	1242-Preliminary_Studies.pd	Add Attachment	Delete Attachment	View Attachment
5. Research Design and Methods	1243-ResearchDesignMethods.p	Add Attachment	Delete Attachment	View Attachment
6. Inclusion Enrollment Report	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
7. Progress Report Publication List	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment

Human Subjects Sections

Attachments 8-11 apply only when you have answered "yes" to the question "are human subjects involved" on the R&R Other Project Information Form. In this case, attachments 8-11 may be required, and you are encouraged to consult the Application guide instructions and/or the specific Funding Opportunity Announcement to determine which sections must be submitted with this application.

8. Protection of Human Subjects	1244-HumanSubjects.pdf	Add Attachment	Delete Attachment	View Attachment
9. Inclusion of Women and Minorities	1245-InclusionOfWomen&Minor	Add Attachment	Delete Attachment	View Attachment
10. Targeted/Planned Enrollment	1246-TargetedEnrollment.pdf	Add Attachment	Delete Attachment	View Attachment
11. Inclusion of Children	1247-InclusionOfChildren.pd	Add Attachment	Delete Attachment	View Attachment

Other Research Plan Sections

12. Vertebrate Animals	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
13. Select Agent Research	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
14. Multiple PI Leadership Plan	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
15. Consortium/Contractual Arrangements	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
16. Letters of Support	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment
17. Resource Sharing Plan(s)	<input type="text"/>	Add Attachment	Delete Attachment	View Attachment

18. Appendix [Add Attachments](#) [Remove Attachments](#) [View Attachments](#)

A Specific Aims

Premature infants are subject to a number of debilitating problems that result in impaired quality of life including cerebral palsy, neurodevelopmental disabilities, bronchopulmonary dysplasia, and retinopathy of prematurity. Clinical protocols include the use of supplemental O₂ to alleviate respiratory morbidities, however, high O₂ saturation in neonates is implicated in retinopathy of prematurity (ROP). Strict management of oxygen levels and attempts to reduce baseline hyperoxia have been partially successful in combating ROP in preterm infants, yet this disorder remains a significant problem. Fluctuations in oxygenation as measured by bedside charting and intermittent blood gas or transcutaneous measurements—all of which underestimate the true number of events—have also been implicated in ROP. Hypoxic and hyperoxic fluctuations in human infants are unpredictable and likely due to sudden, non-linear changes in ventilatory drive, thus, they are difficult to control using threshold alarms in the neonatal intensive care unit. Compelling data from recent animal studies suggest that the high variability, resulting in clustering, of hypoxic events is associated with increased ROP severity. Although continuous pulse oximetry monitoring has been in use for many years, this technology has yet to be used to characterize the true incidence of intermittent hypoxic episodes in preterm infants and to further assess the relationship of these events to neonatal morbidity.

As part of a multicenter study of oxygen supplementation, we have access to two patient data sets that include long-term, high resolution monitoring of O₂ saturation via pulse oximetry. The two infant cohorts include: 1) infants enrolled in the multicenter SUPPORT trial (randomized to high, 91–95%, and low, 85–89%, baseline SaO₂ levels) and 2) infants meeting enrollment criteria but not enrolled in the SUPPORT trial who received normal clinical care. Preliminary data in the second cohort have revealed a significantly higher incidence of desaturation (<80%) events in infants developing ROP requiring laser therapy. However, there is large inter- and intra-patient variability in the number of desaturation episodes over time. Based on animal data suggesting that variability in timing of saturation events is a risk factor for ROP incidence and severity, *we hypothesize that repetitive desaturation results in clusters of hypoxia and the pattern of these cycles is a significant risk factor for ROP in infants younger than 28 weeks of gestational age.* To test this hypothesis we will use an existing database of long-term measurements of SaO₂ obtained via pulse-oximetry for the entire cohort of 174 infants gathered over 8 weeks of treatment in our NICU. We will use temporal and spectral analysis methods to quantify the linear and non-linear properties of this patient dataset.

Specific Aim 1 *To analyze SaO₂ using a suite of linear and non-linear analysis algorithms to quantify patterns of intermittent hypoxia and hyperoxia. We will use variance-based statistical measurements (mean, standard deviation, and coefficient of variation) to quantify changes in frequency and variability of desaturation events. In addition to these tools, we propose the use of algorithms derived from information theory (including Shannon entropy, power spectral density, approximate entropy, and spatial statistics) to quantify the non-linear variability associated with desaturation events in our human patient database.*

Specific Aim 2 *To utilize a linear mixed model and discriminant analysis techniques to characterize and quantify patterns of desaturation, and hypersaturation between infants with and without ROP requiring laser therapy. This will allow us to quantify the role that these events play in relation to ROP outcome. To do this we will use the analyses developed in Aim 1 to build a statistical model for identifying infants at risk for ROP requiring laser treatment. Our goal is to identify early patterns that are predictive of ROP requiring laser treatment.*

B Background and Significance

Intermittent hypoxic (IH) episodes, recognized by the use of non-invasive monitoring techniques such as transcutaneous pO₂ and pulse oximetry, are almost universal in very low birth weight infants. However, there is currently no reliable documentation of these hypoxic events over time. Preterm infants often exhibit spontaneous apnea and shorter respiratory pauses associated with periodic breathing. These events can be central, obstructive or mixed in nature [1] with obstructive efforts often undetected by standard impedance monitoring. Hypoventilation and resulting desaturation are also frequent occurrences in preterm infants during mechanical ventilation [15, 5, 19]. Fortunately, pulse oximetry allows us to quantify the impairment of oxygenation that results from these diverse events. Several studies have proposed that persistent apnea and accompanying bradycardia in preterm infants are associated with an increase in neurodevelopmental disabilities [8, 32]. Episodic desaturation, a common consequence of apnea, was not documented in these studies and may be a strong risk factor for neurodevelopmental impairment. This would be consistent with data from neonatal rat pup models suggesting that IH exposures during an early vulnerable developmental period may have long-lasting effects on respiratory control and neurobehavioral responses [37, 29]. *These observations all point to the need for documentation and quantification of IH episodes in preterm neonates if we are to establish a relationship with current and future morbidity.*

Intermittent Hypoxia and Development of Retinopathy of Prematurity [ROP]: Recently completed and ongoing studies are evaluating the effect of targeted baseline oxygen saturation on various neonatal morbidities, including retinopathy of prematurity (ROP). These studies have demonstrated no clear benefit to targeting baseline SaO₂ above 95% [27, 4] and current investigation is focused on targeting baseline SaO₂ between approximately 85% and 95%. Several non-randomized reports encompassing changes in practice at various sites have reported a decrease in ROP rates when high levels of SaO₂ were avoided [43, 9, 38]. This is consistent with the concept that excessive oxygen contributes to the first phase of ROP by oxygen-induced suppression of vascular endothelial growth factor [VEGF] which, in turn, inhibits normal vessel growth in the immature retina [6]. While avoidance of baseline hyperoxia reduces the incidence and severity of ROP, the problem has clearly not been eliminated.

The second phase of ROP is characterized by hypoxia-induced retinal neovascularization induced by VEGF and other growth factors with the neovascularization potentially resulting in retinal scarring and detachment. Therefore, intermittent hypoxia (see preliminary data) is also a likely etiologic factor in the pathogenesis of ROP, even when hyperoxia is minimized [14]. Apnea, especially if associated with ventilatory support, was reported as a possible risk factor for retrolental fibroplasia [now known as ROP] nearly 30 years ago [40, 24, 22]. Subsequent anecdotal and retrospective reviews of arterial blood gas and transcutaneous pO₂ data from preterm infants suggest that fluctuations in PaO₂ are risk factors for ROP [46, 13]. The potential relationship between baseline hyperoxia and IH in the genesis of ROP is further complicated by the suggestion that spontaneous episodes of desaturation are more common when a lower baseline SaO₂ is targeted [26].

Patterns of Fluctuation in Oxygenation and ROP Development: Newborn rat models have demonstrated that exposure to cycles of hyperoxia alternating with hypoxia [50% fluctuating with 10% O₂] is more critical for the development of ROP than exposure to cycles of variable hyperoxia [80% fluctuating with 40% O₂]. The authors speculate that avoidance of hypoxic episodes is important for prevention of ROP in infants [30, 31]. Recent data from an oxygen-induced rat pup model of retinopathy have demonstrated that clustered episodes of hypoxia result in a more severe form of ROP than equally distributed episodes of hypoxia [12]. Rat pups exposed to clustered hypoxic episodes also exhibited the highest serum vitreous and retinal VEGF levels.

Variability in Cardiac and Respiratory Rhythm: Measures of pattern irregularity (such as Approximate and Shannon Entropy) have been applied, by ourselves and others, to estimate the complexity of patterns in including EEG, ECG and respiratory rhythmogenesis [34, 33, 36, 35, 18, 23, 7]. These measures have the ability to reveal information that linear measures (such as standard deviation or variance) may not capture. Pincus and Goldberger (1994) have shown that a decrease in Approximate Entropy (ApEn) is an indicator of human pathological progression. Others have shown in both animal and human infant models [18, 7, 23, 42, 17] that similar methods can distinguish changes in respiratory pattern and timing. This ability to capture additional subtleties may prove useful for identifying neonatal disease progression and identify problematic patterns of oxygen saturation (and supplemental O₂ levels) which could have future implications on clinical decision making.

Significance: The majority of risk factors for ROP *cannot* be controlled (e.g. gestational age, gender, early weight gain) but the potential opportunity to control desaturation/hypersaturation allows us to decrease a risk factor for this potentially blinding disease. Yet even with the ability to control only that one risk factor, the importance for ROP outcome cannot be overstated. ***We are now in a unique position and are able—for the first time—to characterize patterning of IH hypoxic episodes from a preterm human cohort, and relate these patterns to the development of ROP, a major cause of morbidity in this population. These data are of particular relevance at this time as there is increasing interest in clinical testing of algorithm-controlled adjustment of inspired oxygen concentration in preterm infants [41, 45, 11, 10]. Automated control of oxygen saturation could significantly affect the pattern of IH episodes in this population and the implications of such changes on neonatal morbidity need to be clearly understood.***

C Preliminary Studies

Preliminary data analysis was performed in 79 infants receiving normal clinical care. Thirty seven (47%) males, 32 (43%) caucasians, and 17 (22%) multiple births. Sixteen of 79 infants developed ROP requiring laser therapy. The mean gestational age at birth was 26 ± 1 weeks and birth weight was 836 ± 183 gms (mean \pm SD). Infants requiring laser treatment for ROP (LaserROP) were of younger gestational age (25.5 ± 0.7 vs 26.4 ± 1.2 weeks, $p < 0.001$), smaller birth weight (730 ± 157 vs 863 ± 180 gms, $p < 0.005$), and more likely to be males (11 (69%) vs 26 (41%), $p < 0.05$). Severity of illness during the first 12 hours of life, as measured by the SNAPPE-II score, revealed a higher degree of illness in the infants with LaserROP (55 ± 15 vs 40 ± 12 , $p = 0.008$). There were no significant differences in race or multiple births between infant groups.

A linear mixed model for repeated measures including the covariates listed above showed an overall higher incidence of desaturation events in the LaserROP group ($p < 0.05$), with differences at weeks 5, 7 and 8 (all $p < 0.05$) (Figure 1). A higher incidence of desaturation episodes was seen in males ($p < 0.02$) and younger gestational age infants ($p < 0.003$).

During the first week of life less than 100 hypoxic events per week were noted with minimal variability between infants. However, beyond week one, there was an increase in variability of hypoxic events both within and between infants. The increase in variability can readily be seen over successive weeks in the summary data (Figure 1) and the individual infant graphs (Figure 2). We anticipate similar variability in the hypersaturation events.

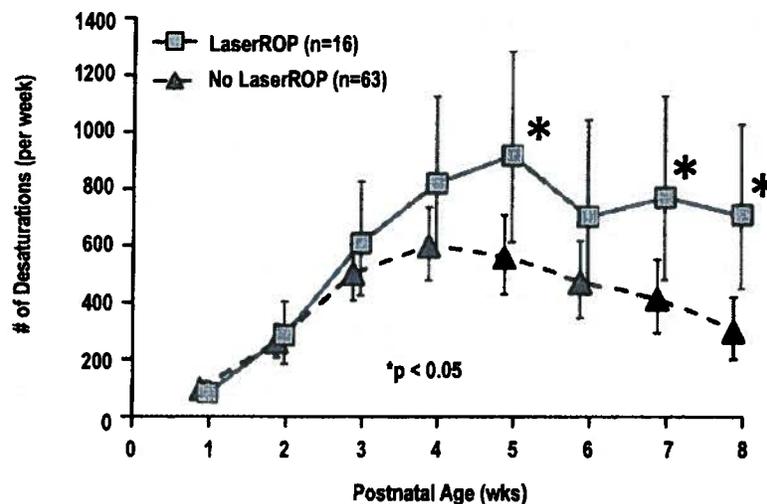


Figure 1 – The model based estimate of desaturation episodes in infants with ROP requiring laser treatment (LaserROP) versus infants with mild or not requiring ROP (No LaserROP) controlling for gestational age, gender, race, severity of illness (SNAPPE-II score) and multiple births. ROP requiring laser treatment was associated with a higher incidence of desaturation episodes ($p = 0.03$) with significant differences at 5, 7, and 8 weeks postnatal age ($p < 0.05$). Error bars are $\pm 95\%$ confidence interval.

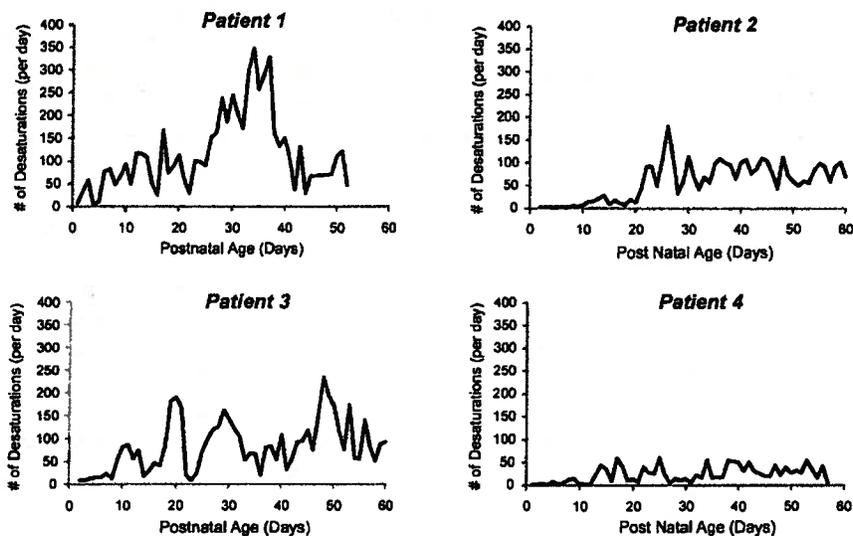


Figure 2 – Although there is an increase in the incidence of desaturation episodes over time for all infants, as shown in the four individual patients depicted here, there is a wide variation in the number of events per day and the range of variability in the pattern of occurrence of these events.

Variability in our data set: To quantify the variability in timing (both interval and duration) of desaturation episodes with increasing postnatal age, we have begun to develop and implement a series of analysis methods from the cohort receiving normal clinical care. Examples of these analyses are shown in Figures 3–5. Over the funding period we will expand the selection of analyses as described in the *Design and Methods* section of this proposal. We will evaluate multiple temporal windows (total dataset, by week, by day, by hour) to identify differences in desaturation event timing.

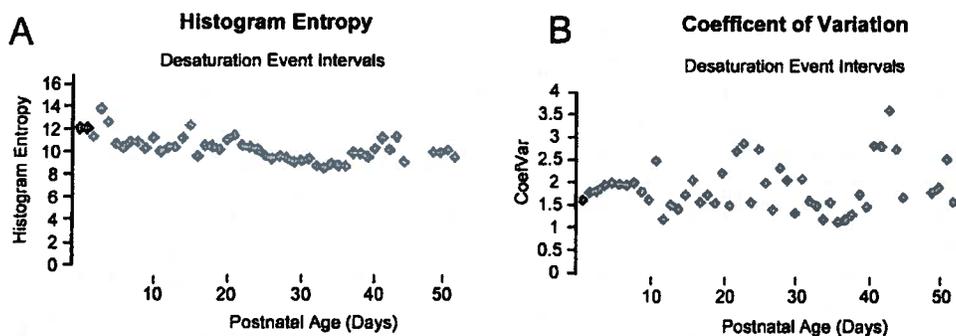


Figure 3 – Patient 1: Patterns of the interval between desaturation episodes over time as expressed by *Histogram Entropy* and *Coefficient of Variation*. A) Measurements of histogram entropy showed a slight decrease in complexity of the intervals between desaturation events with increasing postnatal age. Measurements of the coefficient of variation revealed minimal dispersion of the intervals between desaturation events during the first week of life with large daily variations thereafter.

D Research Design and Methods

Population: The study population entails 174 preterm infants with a gestational age of 24 to 27 $\frac{6}{7}$ weeks admitted to the NICU from June 2005 to April 2009. High resolution pulse oximetry data (2 second average, 2 second sample rate) were acquired from birth to 8 wks postnatal age. Patients were stratified into two infant cohorts which include: 1) Infants enrolled in the multicenter SUPPORT trial (n = 95) who were randomized to high (91 to 95%) or low (85 to 89%) baseline SaO₂ levels and, 2) Infants meeting enrollment criteria but not enrolled in the SUPPORT trial (n=79) who received normal clinical care with the NICU protocol target range of 85–95%. The preliminary data (Figures 1–4) were derived from this dataset.

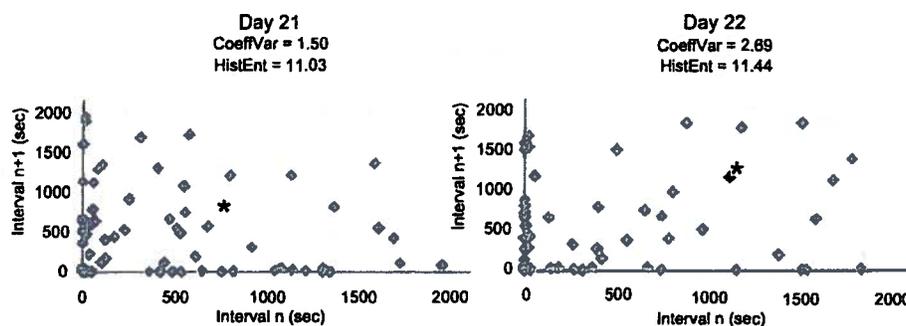


Figure 4 – Distributions for the time interval between sequential desaturation episodes during Day 21 and Day 22 in patient 1 as presented by Poincaré maps, values of coefficient of variation, and of histogram entropy. A shift in the center of mass (denoted by asterisks in each Poincaré plot) can be seen on the distributions with a corresponding elevation in dispersion as shown by the increased coefficient of variation from day 21 to 22. In contrast, no change in the distribution of events is seen as shown by a minimal change in histogram entropy.

Rationale for Specific Aim 1 experiments: There is very little available information published on the variability and clustering of desaturation events in preterm infants despite their abundance in this population. The application of our analysis suite has the potential to provide correlation between pathophysiology and patterning of desaturation events in early postnatal life.

Data analyses to address Specific Aim 1: This project involves the development and application of a number of linear and non-linear data analysis methods with the intention of applying these methods to a patient cohort exhibiting complex, dynamic changes in desaturation events. We will expand our current development of a unified data analysis suite of software tools that will allow investigators to perform extensive analyses on their patient data with an integrated, freely-available set of tools hosted on our laboratory website.

Definition of Events and Data Collection: Data analysis will expand to include the SUPPORT infants and will be composed of the number of desaturation (<80%) and hypersaturation (>95% and >98%) events. To distinguish intermittent hypoxic/hyperoxic events and distinguish them from changes in baseline, duration thresholds were set to events ≥ 10 seconds and ≤ 3 minutes. Our event detection algorithms were developed using *Matlab* and *Igor Pro* and can be easily modified for varying detection parameters.

Birth weight, gestational age, multiple births, race, gender, ROP requiring laser therapy, and severity of illness (SNAPPE-II score) will be noted [16]. Severity of illness will be quantified using the standardized scoring method of SNAPPE-II score [16]. To minimize disparities in diagnosis with less severe

forms of ROP, we will stratify infants into 2 groups: 1) requiring laser treatment for ROP and 2) not requiring laser treatment for ROP. Need for laser treatment will be based on the guidelines of the *Early Treatment for ROP Study* [44]. These guidelines state the need for laser therapy to include: *Zone I*—any stage with plus disease, *Zone I*—stage 3 without plus disease, *Zone II*—stage 2 or 3 with plus disease, where “plus disease” is defined as dilation and tortuosity of the posterior retinal blood vessels that meets/exceeds previously established photographic standards.

Analysis Strategy for Intermittent Hypoxia Datasets

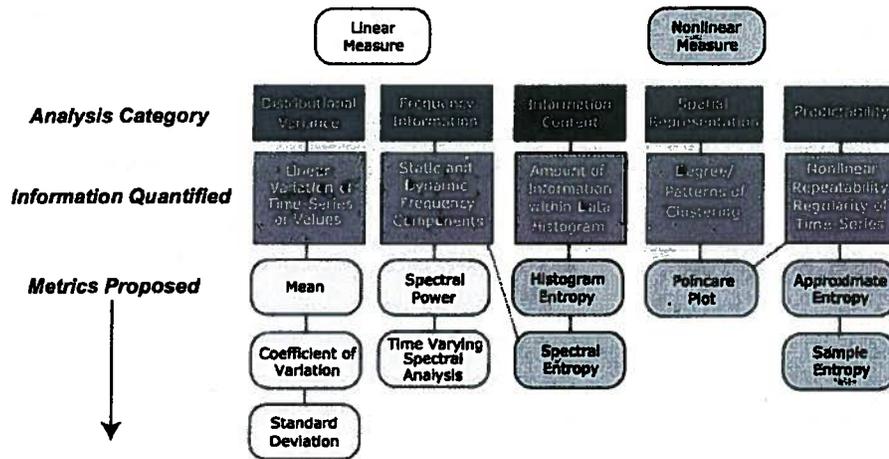


Figure 5 – A flowchart detailing the analyses we will apply to our patient desaturation datasets. Here we show the categories of analyses, the information we will be obtaining, and the metrics (reported numbers) for each analysis path.

Overview of Analysis methods: Our proposed measures and previous work are designed to distinguish between linear and non-linear sources of variability in signals. Proper use and segregation of linear/non-linear aspects of a signal can provide useful insight into changes in patient condition and may offer identifiers of changing health condition. Our data analysis strategy is summarized in Figure 5. We will begin our characterization of patient desaturation data using variance-based measures. The non-linear measures including information content, spatial representation of data, and predictability measures are part of our data analysis suite and designed to complement, not replace, more commonly-used variance-based measures. Each analysis category is designed to quantify different features of the data. The team of investigators have experience using these metrics on animal data collected in our laboratory and we continue to collaborate with internationally recognized experts in signal analysis here at

Linear analysis—Frequency Information: We plan to examine both the static and dynamic frequency components of the raw SaO₂ recordings. Power spectral analysis of the complete dataset will provide visual representation of the frequency bands of long time-scale recordings. We plan to use Fast-Fourier Transforms (FFTs) optimized for the data interval of interest and calculate Power Spectral Density (PSD) for each patient data set. We also will employ time varying spectral analysis (or spectrograms) [28] to identify changes in spectral power over time.

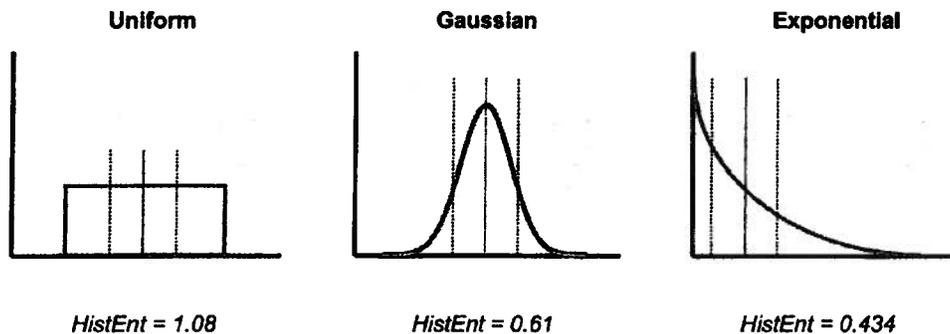


Figure 6 – Graphical representation of three different distributions: Uniform, Gaussian (normal), and Exponential. The mean of the distributions are represented by the red lines. The variances are equal for all three situations and denoted by the dotted lines. This illustrates that distributions with the same variance can portray clear differences in the structure of the dataset. HistEnt values listed are for the three sample distributions with equal variances, clearly capturing the different degrees of “information density” inherent in each dataset.

Nonlinear analysis—Information content/complexity: In order to further understand how the patterning of hypoxic occurrence may influence development of ROP, we plan to use Histogram Entropy (HistEnt), a measure of “information density” based on Shannon Entropy [39]. Such a metric provides a significant advantage over a variance based measure and allows us to capture the differences in the *distribution* of the data, not just the variance or “spread” of the data points (see Figure 6). We plan to use Histogram Entropy analysis on the desaturation and hypersaturation intervals and durations. Our method consists of creating the histogram of data events (e.g. the intervals between desaturation episodes), then applying the continuous form of Shannon Entropy to the histogram. This measure quantifies the amount of “information” contained within the distribution. A signal with more information (higher entropy) has a wider distribution of values, meaning the event intervals are more variable (less predictable). Since accurate measurement of HistEnt requires a reliable distribution of the dataset, days with < 50 events, or > 2 hours of missing data points (e.g. oximeter or computer malfunction or other difficulties) will be excluded from this analysis; we have performed a preliminary robustness analysis on our patient data set to set these exclusion criteria.

Nonlinear analysis—Measures of predictability:

Measures such as Approximate (ApEn) and Sample Entropy (SampEn) have been characterized as measures of “predictability”, “irregularity” and “complexity.” The essence of these computations is a determination of the likelihood a given range of data will, over time, remain close to the last delimited data window—that is, given a *range* of data, for example, 30 minutes of desaturation data, will the next 30 minute window of data be similar in extent and variability? We have previously published entropy analyses of “fictive” breathing *in vitro* slices that intrinsically generate a rhythm very similar in timing to that seen in a human [18]. The theoretical foundation and practical application of these measures is well-described in the literature, though previous work has concentrated on cardiac variability [34, 33, 36, 35, 21, 2, 3, 23, 17]. However, only recently have investigators begun to apply these *complexity measures* to respiratory data [17]. We have been very involved in systematic and thorough application of these models [23, 20] and our ApEn/SampEn parameters are consistent with previous work [7]. We plan to focus these predictability measures on the raw SaO₂ recordings, using a daily data exclusion criteria of >2hr missing data, in order to identify entropy fluctuations attributable to pathophysiology (or improvement) of the patient.

The essence of these computations is the determination of the “likelihood” that a m -dimensional vector within a tolerance, r , is likely to remain within the tolerance, r , when extended to a $m+1$ -dimensional vector for the same set of computational parameters. More precisely, ApEn is a measure of the logarithmic likelihood that patterns of length m that are close to each other will remain close in the next incremental comparisons, $m+1$. Higher pattern regularity is associated with a greater likelihood of remaining close and yields smaller values of ApEn values when compared with low regularity patterns that produce higher ApEn values. Examining this measure across groups offers a relative comparison of the “complexity” of the time series with higher values of ApEn (SampEn) associated with less predictability, in other words, higher system complexity.

To our knowledge, these analyses have not been performed on data such as ours and by examining ApEn and SampEn across days, patients and medical conditions we can provide details about non-linear changes within a complex physiologic system.

Nonlinear analysis—Spatial Representation: We will include qualitative measures of dataset variability, including Poincaré maps (circle-return maps). Qualitative and quantitative display of cycle times or intervals between desaturation events provides a compact and readily understandable way to characterize variability in a subject. We have previously used Poincaré maps to observe transitions from regular, periodic breathing to multi-periodic and chaotic breathing patterns across multiple species (including humans). From Poincaré plots—which essentially provide a qualitative view of variability in pattern—we have developed or adopted analyses that allow us to visualize spectral content over time as breathing patterns change [28]. Our Poincaré technique includes identification of the center of mass and examining changes with varying time-delays (e.g. n vs. $n+1$, $n+2$...). In collaboration with [redacted], an internationally recognized expert on signal theory and analysis, we will use quantitative visual tools to characterize patterns of desaturations.

Potential Difficulties and Limitations [Specific Aim 1]: We anticipate minimal difficulties in the application of our analysis methods as many of these have been formally tested and implemented in our basic science work on rats and mice [18, 23, 20]. However, the most significant problem would be an inability to discern correlated changes in desaturation events or missing events. Our data set includes time periods in which, due to motion artifact or other acquisition-related problems, there are gaps in recorded data. We will address this problem for each analysis method and we have already performed initial robustness tests to determine the effects of missing data on Histogram Entropy. For example, only days with < 2 hours of missing data and > 50 events have been used for our Histogram Entropy analyses. However, as time-varying spectral analysis will utilize the raw SaO₂ waveforms, this analysis will be limited by the number of desaturation events in a given patient’s data set. We may need to expand our analyses to incorporate algorithms or methods we have not proposed as we analyze additional data from both datasets. We continually seek out and critically evaluate new approaches in collaboration with our consulting engineer, [redacted].

Anticipated Results [Specific Aim 1]: We anticipate that, using the linear and nonlinear analysis tools we have proposed, we will be able to quantify changes in desaturation patterns with increasing postnatal age and the suite of analytic methods we have described will allow us to identify correlative relationships between desaturation and hypersaturation events in our cohort of infants.

Rationale for Specific Aim 2: Specific Aim 2 will focus on the application of statistical models to identify which algorithms are associated with, and may be used as, a predictor of ROP requiring laser therapy. Using the methods from Specific Aim 1, we will be able to compare the relative significance of each measure as a discriminating factor for a predictive model of ROP requiring laser therapy and

the possible modulation of ROP development by controlling desaturation episodes. As current clinical practice requires repeated retinal screening for ROP which is both stressful to the neonate and time consuming for the ophthalmologist, these findings would be extremely beneficial in identifying which specific infants may be at greater risk for requiring laser treatment.

Data analyses to address Specific Aim 2: In the preliminary data analysis using infant cohort 1, a linear mixed model for repeated measures was used to identify the association between ROP requiring laser therapy and the number of desaturation episodes for each infant measured longitudinally. Considering the normality assumptions of a linear mixed model, we modeled the square root transformation of the number of desaturation episodes in an infant per week as a function of ROP requiring laser therapy and other covariates. Postnatal age was modeled as a categorical variable. Gender, race, multiple births, gestational age, and SNAPPE-II (initial severity of illness) score were included as covariates. Birth weight was not considered since it is included in the calculation of the SNAPPE-II score. Since repeated measurements of the number of desaturation episodes per week, are correlated, we chose a first order Antependence residual covariance structure, based on the lowest Akaike's Information Criterion (AIC), to account for the correlated repeated measurements on the same infant. In summary, the linear mixed model for repeated measurements was fit with ROP requiring laser therapy as the main factor in the model, postnatal age as a repeated measure and infant as the unit of analysis. A similar strategy will be applied to the SUPPORT infant data and the results will be combined into a single cohort dataset.

To assess differences in variability of desaturation patterns between infants with and without ROP requiring laser therapy, we anticipate using a similar linear mixed model design for each individual analysis algorithm (i.e., coefficient of variation, histogram entropy, etc.) with the transformation of the data to be determined by the distribution of each data set to fit normality assumptions. We will increase the resolution of the data set to daily measurements, as opposed to weekly, to identify more rapid changes in desaturation patterns. As each algorithm in this proposal uses a different approach to quantify desaturation patterns, application of a separate linear mixed model analysis for each algorithm will allow us to identify which analysis algorithms are useful in identifying differences in desaturation patterns between infant groups. Each analysis will be performed with and without the covariates of gender, race, multiple births, gestational age and SNAPPE-II score.

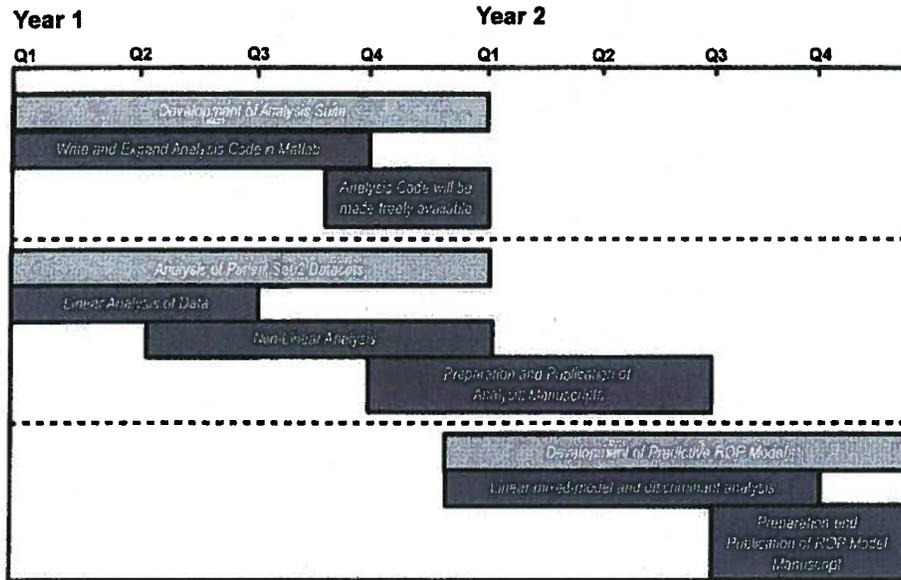
As the linear mixed model identifies mean differences between infant groups, we will expand our data analysis to include a linear discriminant model [25] to identify early patterns that are predictive of ROP requiring laser treatment. This analysis will be repeated for each individual analysis algorithm (ie coefficient of variation, histogram entropy, etc.) with the transformation of the data to be determined by the distribution of each data set to fit normality assumptions.

Potential Difficulties and Limitations [Specific Aim 2]: Our data set is very large with resolution as fine as 2 second collection intervals over multiple days. We will focus on an initial analysis of variables across one 24 hour period and we do not anticipate this large data set to be a limiting factor for our statistical software (SAS). As the number of observations varies between patients this may result in deletion of a small number of data points in some infants that extend beyond the other infants. In addition, there are random days with missing data due to oximeter/hard drive malfunction or other difficulties. However, both the linear mixed model and resulting linear discriminant function are robust and designed to be capable of handling missing observations.

Anticipated Results [Specific Aim 2]: We anticipate that we will be able to identify differences in patterns of desaturation episodes between the infant groups with one or more of the analysis algorithms listed in this proposal. We also anticipate being able to use the data generated from one or more of

these algorithms as an early predictor of those infants who may develop ROP requiring laser therapy.

Timeline



E Human Subjects

We have previously collected SaO₂, ROP, and demographic data under an IRB approved protocol. As data collection is complete the current proposal will include data analysis and application of mathematical models to the acquired data with all patients de-identified.

Inclusion of Women: There are no women enrolled in the study and infants of minority groups have been included in the original patient cohort.

Inclusion of Minorities: Infants of minority groups have been included in the original patient cohort.

Targeted Enrollment

This study is closed for enrollment and the purpose of this study is analysis of data that was collected previously into an existing patient database.

Inclusion of Children: The patient cohort includes preterm infants of gestational age 25 to 27 and six-sevenths weeks. All data from infants has already been collected we are analyzing this data post hoc.

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PHS 398 Checklist

OMB Number: 0925-0001

Expiration Date: 9/30/2007

1. Application Type:

From SF 424 (R&R) Cover Page. The responses provided on the R&R cover page are repeated here for your reference, as you answer the questions that are specific to the PHS398.

* Type of Application:

New Resubmission Renewal Continuation Revision

Federal Identifier:

2. 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:

3. 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

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)
<input type="text"/>	<input type="text"/>	<input type="text"/>
<input type="text"/>	<input type="text"/>	<input type="text"/>
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<input type="text"/>	<input type="text"/>	<input type="text"/>

5. Assurances/Certifications (see instructions)

In agreeing to the assurances/certification section 18 on the SF424 (R&R) form, the authorized organizational representative agrees to comply with the policies, assurances and/or certifications listed in the agency's application guide, when applicable. Descriptions of individual assurances/certifications are provided at: <http://grants.nih.gov/grants/funding/424>

If unable to certify compliance, where applicable, provide an explanation and attach below.

Explanation: