School of biomedical engineering, science and health systems

A.B. Kogan Research Institute for Neurocybernetics

KRINC

Rostov State University

PROJECT OF SCIENCE AND TECHNOLOGY CO-OPERATION

BETWEEN

SCHOOL OF BIOMEDICAL ENGINEERING, SCIENCE AND HEALTH SYSTEMS

DREXEL UNIVERSITY

PHILADALPHIA, PA
USA

AND

A. B. KOGAN RESEARCH INSTITUTE FOR NEUROCYBERNETICS

ROSTOV STATE UNIVERSITY

ROSOV-ON-DON
RUSSIA

MODELING NEURAL MECHANISMS FOR RESPIRATORY PATTERN GENERATION AND CONTROL OF BREATHING

2004 - 2006

PHILADELPHIA – ROSTOV-ON-DON

1 - Title of the project:

MODELING NEURAL MECHANISMS FOR RESPIRATORY PATTERN GENERATION AND CONTROL OF BREATHING

2 - Partners:

Drexel University:

Project Director: Research Professor, Dr. Ilya Rybak, PhD
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Rostov State University:

Project Director: Senior Researcher, Dr. Natalia Shevtsova, PhD
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3 - Goal of the Project:

The main goal of this collaborative Project is to increase the understanding the neural mechanisms for generation of the respiratory rhythm and pattern and performing neural control of breathing. The project has the following 3 objectives.

4 – Objectives and expected results:

Objective 1: ***Development of a computational model of the ponto-medullary respiratory network***
Expected results and significance: The model will integrate existing experimental data and will be able to generate the robust eupneic respiratory rhythm, demonstrate the realistic firing patterns and membrane potential trajectories of respiratory neurons under normal conditions and reproduce various changes in the respiratory rhythm and neuronal firing patterns produced by different perturbations applied to the ponto-medullary network. This study will allow us to define the basic architecture of the ponto-medullary respiratory network and phase switching mechanisms. Moreover, the model will provide insights into a state-dependent reconfiguration of the respiratory rhythmogenesis from network-based to pacemaker-driven mechanisms and may consolidate two major theoretical concepts in the field of neural control of respiration, the network-based and pacemaker-based theories.

Objective 2: ***Investigation and evaluation of the role of the pons and ponto-medullary interactions in generation, shaping and control of the respiratory pattern***
Expected results and significance: The proposed study will provide important insights into the critical role of the pons in the control of breathing. We will evaluate multiple key hypotheses concerning the contribution of the pons to the neurogenesis of eupnea. We will investigate the influence of pontine stimulation upon the firing patterns of different medullary respiratory neurons, the durations of inspiration and expiration, and the discharges of hypoglossal and phrenic nerves. We will also investigate the alterations of firing patterns of medullary and pontine neurons following other perturbations, including pharmacological blockade or removal of different pontine regions. The experimental data obtained in these studies will be incorporated in our computational model (see Objective 1) and used for model testing and elaboration.

Objective 3: ***Characterization of the mechanisms whereby activation of pulmonary afferents alters the firing patterns of medullary and pontine respiratory neurons, the durations of inspiration and expiration, and the discharge patterns of hypoglossal and phrenic nerves.***
Expected results and significance: These studies will provide important insights into the systems mechanisms for control of the respiratory rhythm and pattern by pulmonary feedback. They also provide additional data concerning the particular neural mechanisms involved in feedback regulation of breathing under different conditions. These data will be incorporated in our computational model (see Objective 1) and used for model testing and elaboration.

5 - Preliminary joint work:

Dr. Rybak is the author of the first models of neural control of respiration based neuron models developed in the Hodgkin-Huxley (HH) style. In 1997, he published a series of papers devoted to the modeling of the respiratory rhythm generation at several levels (Rybak et al., 1997a,b,c). Later, he developed a series of models supporting the "switching concept" of respiratory rhythm generation (Rybak et al., 2001, 2002). According to the this concept respiratory rhythm may be generated by either a network mechanism operating in the ponto-medullary network or a hybrid mechanism with a pacemaker-driven kernel in the pre-Botzinger Complex (pBC), which depends on the conditions.

Dr. Natalia Shevtsova started collaboration with Dr. Rybak in 2001 when she was invited to do her research at the School of Biomedical Engineering, Science and Health Systems, Drexel University. During her work at Drexel, a series of realistic models of a single bursting pacemaker neuron and neuron populations were jointly developed based on experimental characterization of ionic currents in neurons of rostroventrolateral medulla and pBC (see Rybak et al., 2003a; Shevtsova et al., 2002). These studies were focused on the investigation of the possible role of endogenous bursting activity in the pBC in the respiratory rhythm generation in vivo vs. in vitro and during normal breathing in vivo vs. gasping (Rybak et al., 2003b, Rybak et al., 2004). As a result of modeling study, several important predictions about the mechanisms for the respiratory rhythm generation were made and verified in neurophysiological experiments (Rybak et al., 2003b). The results of a preliminary joint work are published in 4 papers and presented at 4 international conferences. Two proposals were submitted to NSF.

The results of the above joint studies have created a basis for the development a more realistic model of the ponto-medullary respiratory network which accumulates all available experimental data on respiratory neurons both in the medulla and the pons and their connectivity.

6 - Stages of the Project and the role to be played by each research team:

The research will be carried out by using mathematical modeling and computer simulations. All simulations will be performed using a special simulation package NSM 2.0 developed at Drexel University by Dr. Rybak's research group. The following stages of the Project correspond to the research Objectives above. The results obtained jointly in the previous studies (Rybak et al., 2003a,b; Rybak et al., 2004; Shevtsova et al., 2002) will be used as a basis.

KRINC, Rostov State University (RUSSIA):

Stage 1. Development of a computer model of the ponto-medullary network using available neurophysiological data on neuronal properties and neural connectivity in the medulla and pons.
Stage 2. Computer experiments with the model to reproduce respiratory reflexes.
Stage 3. Modification of the model on the base of the results of computer simulations and their comparison with the data of neurophysiological experiments.

School of Biomedical Engineering, Science and Health Systems, Drexel University (USA):

Stage 1. Accumulation of neurophysiological data on neuron properties and their connectivity in the medulla and the pons. Creation of the conceptual ponto-medullary model of respiratory rhythm generation.
Stage 2. Computer experiments with the model, formulating predictions from the results of modeling study and their verification in collaborative neurophysiological experiments.
Stage 3. Modification of the conceptual ponto-medullary model on the base of computer and neurophysiological experiments.

7 - Organization and financial statement:

In the framework of the present Project, each partner has its own financial support. Additional financial support may be searched from different national and international foundations by applying joint proposals.

8 - Exchange of research documents and papers:

The partners will send each other scientific reports, papers and demonstration data. They will prepare joint publications and present joint results in national and international scientific conferences and educational seminars.

9 – Lists of participants:

From KRINC, RSU:

Project Director	Dr. NATALIA A. SHEVTSOVA	Senior Researcher
Principal Investigator:	Dr. SERGEY N. MARKIN	Senior Researcher

From the School of Biomedical Engineering, Science and Health Systems, Drexel University

Project Director:	Dr. ILYA A. RYBAK	Research Professor

10 - Duration of the Project:

This agreement will be in force upon signing and will continue for a three year period, from May 1, 2004 through April 30, 2006, renewable by a further agreement. This agreement can be cancelled by either of the two partners with a six months advance notice.

Signed, from **Drexel University**: Date

Professor Ilya A. Rybak
Project Director

Ilya Rybak

May 1, 2004

Professor Banu Onaral,
Director of the School of Biomedical Engineering, Science and Health Systems,
Drexel University, USA

Signed, from **Rostov State University**: Date

Dr. Natalia A. Shevtsova
Project Director

Professor Boris M. Vladimirsky
Director of A. B. Kogan Research Institute for Neurocybernetics,
Rostov State University, Russia.