# Modeling and Analysis of the Respiratory Control System: Trends an Challenges

(Z. Topor and J. Remmers, Faculty of Medicine, University of Calgary)

Modeling and simulation of physiological systems is a complex and poorly defined subject. The endeavor has its roots in several fields and derives its strength from the concepts, theories, and techniques developed in several disciplines of science.

Respiratory control is one of the first areas within physiology to which dynamic modeling and computer simulation methods were applied. The use of dynamic models based on difference or differential equations is well established in this field.

An important factor, which has provided a stimulus for simulation and dynamic modeling activities in respiratory physiology, is that key variables, such as the gas flow rate at the mouth as well as partial pressures of respiratory gases in lungs and blood, are readily measured in animals and in man. Therefore, the model can be subjected to direct testing and validation not feasible in many other physiological systems.

As our knowledge about physiological control systems grows we become more aware of how complex and highly nonlinear they are. Therefore, an appropriate and sophisticated mathematical description is required to capture an essence of their dynamic behavior.

In case of the respiratory control system any realistic model has to employ a time-delayed differential equations as a foundation of plant description and propagation of chemical stimuli from the lungs to central and peripheral chemoreceptors. This has to be coupled with a realistic description of a controller consisting of a central and peripheral feedback loops separated by a variable, state dependant time delay.

More and more detailed description of the plant requires a modular approach to its structure. Each module should capture functional characteristics of one part of the plant such as upper airways mechanics, cerebral blood flow control, carrying capacity of blood for the respiratory gases, etc. The modular strategy is very effective in facilitating further development of the model and provides the modeler with an option of including only the necessary modules into the functional model depending on the investigated problem. For example, investigation into the causes of central sleep apnea may not require a detailed description of the upper airways mechanics or chemoreflex control during wakefulness.

We expect that the models of increased complexity will generate a complex data defying simple and intuitive interpretation. Development of new methods of data interpretation and processing is required to generate a useful summary of the global behavior of the system.

In the light of all the trends described above a set of new challenges emerges. We believe that the progress in the area of modeling and analysis of the respiratory control system will depend on:

- Development of a Markup Language to facilitate a modular approach to model development and possible exchange of an accurate description of specific components between existing models
- Development of intuitive graphical methods for interpretation of complex data obtained from computer simulations especially regarding the issue of a global stability analysis of the system.

- Closer multidisciplinary collaboration between modelers and mathematicians aimed at development of an analytical analysis of complex systems governed by multiple feedback loops where temporal separation between the feedback responses is a function of state variables
- Closer multidisciplinary collaboration between modelers and experimental physiologists. The model, as any correlational study, cannot establish a causal relationship but only suggest that one exists. Therefore, hypothesis emerging from computer simulations should be explicitly stated and experimentally tested.

In the past, mathematical models of complex physiological systems have commonly been used to test the plausibility of mechanistic hypotheses. However, it is increasingly apparent that the complexity of some systems defies intuitive understanding. Consequently, the model serves as a beacon or a guide for the physiologist. The model frequently predicts a counterintuitive global behavior of the system. While this is a humbling experience, the model is becoming a necessary partner in investigating the integrative behavior of complex system with highly nonlinear components.