# Short-term Cardiovascular-Respiratory Control Mechanisms

organized by
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Workshop Summary

The overall objectives of this workshop were (i) to identify physiological mechanisms involved in short-term cardiovascular-respiratory regulation, (ii) to develop mathematical models to improve understanding, diagnosis, and treatment of clinical problems related to short-term cardiovascular-respiratory regulation, (iii) to discuss the methodological and computational framework for adapting complex mathematical models to clinical applications, and (iv) to develop new projects/collaborations. To tackle these objectives the organizers successfully brought together researchers representing a mixture of world-renowned experts and young, promising researchers, with expertise in physiology, mathematics, and statistics.

The organizers feel that the workshop was very successful, most notably in terms of shared knowledge and ideas generated. We have had very positive feedback from participants during and after the workshop, and new projects/collaborations have been formed as a direct result of this meeting.

**Scientific Advances:** Among the many interesting and promising ideas that have emerged from working group discussions, we emphasize the following ideas that, we believe, will potentially impact future developments and collaborations in this area.

- Ary Goldberger, in his plenary talk, alluded to a method whereby breathing activity can be inferred from changing heights of R waves. Dwain Eckberg added that this clearly could be useful if one expand the short-term cardiovascular-respiratory regulation modeling effort to understand vasovagal syncope. In addition, the discussions of the heart rate model as presented by Johnny Ottesen generated lively and productive discussions throughout the workshop. Dwain Eckberg suggested that as an alternative (or supplementary) approach to including baroreceptor nerve activities, one could consider incorporating an estimate of supine baroreflex gain for each subject. This can be derived readily from the spectral analysis of the data. Other suggestions for improvement of the heart rate model include the incorporation of central command, which according to both Dwain Eckberg and John Karemaker contributes to vagal withdrawal. This would be an accompanying signal from the central nervous system to the motor command that might show up as suppression of the baroreflex signal transmission from the nucleus tractus solitarii to the cardiac vagal motor nucleus. Moreover the pressure sensitive afferents from the contracting muscle itself can have the same effect. The ensemble of these muscle-heart reflex effects will show up as fast vagal withdrawal going together with the initiation of muscular effort. As a result of the workshop, new collaboration has evolved between Johnny Ottesen, John Karemaker, and Dwain Eckberg to incorporate these ideas to improve the heart rate model.

- The discussion on what modifications a deterministic model for the cardiovascular system should undergo in order to produce outputs, which when considered as time series would have similar characteristics to recorded time series, generated fruitful exchange of ideas throughout the week. Two possible ideas, which have emerged from the discussions, include (a) the introduction of stochastic components in the feedback loops of the model, in particular, in the baroreceptor loop and (b) modeling the input to the cardiovascular system from the central nervous system using stochastic components. To further pursue this investigation, it was agreed that data should be exchanged among various groups in order to determine the complexity of the recorded time series. In addition, if numerical simulations of the resulting stochastic differential equations indicate the important role of the feedback structure in the model, the role of the feedback structure from experimental data should be closely examined.
- Other suggestions for modeling include validation of models against a number of scenarios, e.g. head-up tilt, sit-to-stand, bicycling ergometer tests, and hand-grip. John Karemaker showed a dataset with differentiated input indicating contributions from both baroreceptors and modulation of atrial filling. Other topics for modeling include response to slow tilt, which will induce syncope if the subject is tilted for long periods. The suggestion was made by Dwain Eckberg to try to develop models that reproduce the scenario to try to understand what happens just before syncope. In addition, several discussions occurred during the week on possibilities to get information concerning the role of the feedback structure from experimental data. Data, which may be of importance, are data from patients with heart transplants or patients which have a carotid tumour removed. In both cases one has the baroreceptor loop more or less completely interrupted. Another issue that was discussed was the question if the antagonistic action of vagal and sympathetic control of heart rate plays a role in slow-tilt syncope. This could be checked by experiments, where one of the two actions is removed. This is possible for the sympathetic action, but seems to be not available for the vagal activity.
- ethodologies for model validation and parameter estimation were discussed by Kathleen Fowler and Genetha Gray. In particular, they discussed a range of derivative free optimization methods. The methods considered were for designed simulation-based or black-box minimization problems and these methods use only function values to guide the minimization process. In other words, derivatives are not required. These methods are well equipped to handle problems with low-amplitude noise, non-convexity, non-smoothness, and many local minima. More specifically, they are ideal for the problems of parameter calibration that arise from physiological models. Other ideas that were discussed include the meaning of validation as it relates to physiological models using examples from electrical engineering. Overall, it was agreed that the goal is to quantify the uncertainties and to explain the variations in the models. Some tools for validation and sensitivity analysis include Minitab sensitivity plots, interaction effects, the McKay correlation ratio, and comparison metrics and all these are methodologies could provide insight into the role and the importance of the model parameters. Kathleen Fowler and Genetha Gray have already started collaborating with Mette Olufsen and her students on utilizing these optimization

methods for model validation as well as applying the above tools for model analysis in the context of the heart rate model as presented by Johnny Ottesen.

- State estimator is an approach from system theory that is used to estimate the state of a system based on available measurement data. During the workshop, George Verghese, Hien Tran, Johnny Ottesen, and Vera Novak discussed two ideas of using state estimator to: (a) estimate the hidden variables (or the states that cannot be readily available from measurements) and (b) estimate the states which can then be used to provide additional measurement data for parameter identification. For example, Ursinos group has proposed in the past mathematical models for simulating, among other variables, the intracranial pressure, which cannot be measure non-invasively. These models are complex, containing many state variables and parameters. One idea that was discussed was to use one of Ursinos models to generate intracranial pressure that can then be used to validate a simpler/minimal model (as is termed by Michael Khoo). This minimal model can be formulated as a state estimator/observer using available data such as arterial and venous blood flows. By the end of the week, the new collaborating group already produced a simple model for the cerebral circulation described by an electrical circuit. This new collaboration, initiated at the workshop, if successful will be beneficial not only to this application but to the general biomathematics community as well.
- various open problems and collaborations.
- Springer has formally agreed to the project to publish articles generated from this workshop in Special Issues of Cardiovascular Engineering, an international journal (see the journal web link: http://www.springerlink.com/content/1573-6806/). These issues (one or two) will appear as regular issues of the journal but be devoted to a collection of articles written by well-known experts who participated in this workshop. These articles will reflect either new research or to provide a state-of-the-art review of key physiological, clinical, or modeling areas related to the topic of the workshop. The organizers have set up a deadline of March 1, 2007 for the submission of articles.

Finally, on behalf of all participants, we would like to thank AIM and NSF for sponsoring the workshop. We would also like to thank the entire staff at AIM for their guidance, assistance, and hospitality. The program structure of AIM conferences was clearly beneficial for creating the dynamics interactions at the meeting.