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Methods of Sensitivity Identifiability Analysis in Modeling Human Physiological Systems

In this talk we discuss techniques to quantify the parameter estimation problem in models that characterize human physiological systems. In general, the issue is to balance model complexity and parameter number with available data, data that is often restricted by such constraints as accessibility to measurement sites, the degree of error in measurements, cost of collecting data, and in the clinical setting, the need to screen patients with tests that are minimally invasive.

As a template example we will present a mathematical model of the cardiovascular control system of mid-level complexity that reflects the various pathways for short-term blood pressure control in response to various cardiovascular stresses. The model includes 10 vascular compartments and baroreflex feedback control that can alter resistance, heart rate and heart contractility, and unstressed volume to counteract a perturbation in blood pressure, returning the pressure to its more or less steady state of operation. The unstressed blood volume of a vascular element is the natural filling volume that can be accommodated before stretching of the vascular wall begins. Additional volume generates transmural pressures that stretch the vascular wall (stressed volume). Unstressed volume does not contribute to the dynamic pressure which determines blood flow. It is therefore a reservoir (particularly venous unstressed volume) that can be transferred (mobilized) by control mechanisms (through constriction of vessels) to stressed volume when blood volume is reduced. The model presented is sufficiently complex to characterize responses to a variety of system stresses including reduction in blood volume.

Orthostatic stress is caused by blood pooling in the lower limbs when standing upright, a consequence of gravity. This pooling removes a percentage of blood from the dynamic circulation. In changing from the prone to standing position, the control system must compensate for what is in effect a reduction in blood volume. A number of experimental protocols such as head up tilt (HUT) and lower body negative pressure (LBNP) are used to examine system response to orthostatic stress. To illustrate the difficulties that arise in assessing control response via diagnostic testing, we note that the HUT and LBNP protocols each have specific effects on overall physiology which can obscure the examination and characterization of system response. For example, unstressed blood volume is mobilized in different ways during LBNP, HUT, and orthostasis [2].

Several aspects and problems of model validation will be discussed. Various tools derived from sensitivity analysis will be applied, including both classical and generalized sensitivities and subset selection [1, 3]. Applied jointly, these tools can provide insight into how specific experimental protocols such as HUT and LBNP impact model response and the potential for parameter estimation.

References

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