Chapter II
Systems and Control Theory for Medical Systems Biology

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ABSTRACT

In this chapter the authors describe systems and control theory concepts for systems biology and the corresponding implications for medicine. The context for a systems approach to the life sciences is outlined, followed by a brief history of systems and control theory. The technical aspects of systems and control theory are then described in a way oriented toward their biological and medical application. This description is then used as a reference base against which to indicate specific areas where systems and control theory aspects of systems biology have strong medical implications. Specifically, two systems biology projects are described as examples of where methods from systems and control theory play an important role.

INTRODUCTION

In this chapter the authors give their experiences gained working at the interface between the biological/medical sciences and the physical/engineering systems sciences. In doing so we attempt to convey the contributions that the physical, mathematical and engineering sciences have made, and will continue to make, to innovations in biology and medicine. In this context we stress the role played by systems and control theory in the development of general principles for biological systems, and in particular the understanding of dynamical phenomena in biology and medicine. According to our experiences, systems methods are influencing the biology research sector through a series of evolutionary scientific steps, as follows:

- **Stage 1:** High-throughput biochemical instrumentation was (and continues to be) developed to provide rapid measurement and generation of *data*.
- **Stage 2:** To meet the need to process data generated in stage 1, data processing methods are being developed to extract *information* from very large data records.
- **Stage 3:** The information from stage 2 is used to calibrate mathematical models with which to *visualise* an underlying biological process. This is the current evolutionary state in systems biology.
- **Stage 4:** Control and systems theory are applied to the mathematical models of stage 3 to provide *understanding* of biological behaviour and underlying principles.

In summary, the sequence goes from:

measurement → data → information → visualisation → understanding.

The current state of the art is that the value of *in-silico* simulation of biological phenomena is becoming appreciated. Even so, most biological measurement techniques are designed to collect static data, whereas time course data is required to develop mathematical models for visualising system dynamics by *in-silico* simulation. It is not always appreciated that, as a result of poor data, the calibration and structural correctness of mathematical models is often suspect. Likewise, there is currently little appreciation of the fundamental importance of control and systems theory in understanding biological and physiological phenomena and principles.

On the other hand, the role of systems and control theory is clearly established in the medical community through the understanding that it gives to physiological function. Under the historical influence of Claude Bernard's ideas, as embodied in Cannon's concept of homeostasis (Bayliss, 1966, Cannon, 1932), feedback control is central to many aspects of current medical understanding, although this is usually intuitive and non-theoretical in nature (Tortora, 2003). Since Cannon's work in the 1930's, other researchers have expanded upon the homeostatic feedback principle (Sterling, 2004) in its specific medical and physiological contexts. In the meantime however, systems and control theory has expanded scientifically and progressed to become a mature scientific discipline with fundamental relevance to all areas of scientific endeavour. Throughout this 70-year period of separate development, the medical concepts of control systems and the mathematical tools of control and systems theory have diverged. The aim of this chapter is to reconnect the medical ideas of feedback with mainstream theory by explaining areas where control and systems theory can contribute. We consider this to be vitally important to our scientific futures. For, as indicated above and documented in the recent report *Systems Biology: a vision for engineering and medicine* (Royal Academy, 2007), the use of systems theory and control concepts will be essential to our understanding of biological systems for medicine.

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