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Engineering control into medicine☆

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ABSTRACT

The human body is a tightly controlled engineering miracle. However, medical training generally does not cover "control" (in the engineering sense) in physiology, pathophysiology, and therapeutics. A better understanding of how evolved controls maintain normal homeostasis is critical for understanding the failure mode of controlled systems, that is, disease. We believe that teaching and research must incorporate an understanding of the control systems in physiology and take advantage of the quantitative tools used by engineering to understand complex systems.

Control systems are ubiquitous in physiology, although often unrecognized. Here we provide selected examples of the role of control in physiology (heart rate variability, immunity), pathophysiology (inflammation in sepsis), and therapeutic devices (diabetes and the artificial pancreas). We also present a high-level background to the concept of robustly controlled systems and examples of clinical insights using the controls framework.

1. Systems and control loops

The term *system* is often loosely applied. Using an engineering perspective, we define a system as a functional entity of interacting components that accepts and analyzes inputs, and produces outputs. The systems of interest in medicine are generally dynamic, that is, systems with changing inputs and outputs (often widely varying) over time. Control systems are all around us, but largely invisible when they work well: engineered controls maintain the output of our technologies within tolerable ranges. Although highly evolved physiologic systems are also tightly controlled, physiology is not usually taught as a system under engineered (evolved) control, and the lack of recognition of control engineering to "reverse engineer" complex disease processes seems a lost opportunity.

We use engineered feedback control systems daily—from system thermostats to automotive cruise control—and when functioning well, we are unaware of the computational complexity that keeps us comfortable. Cruise control is a very useful way to understand the concept of a controller: one sets a desired speed, then the throttle setting (the "actuator" in engineering terminology) is adjusted by a computer on the basis of the detected speed (feedback) in order to meet the grading demands (disturbances) of the road. The control is sufficiently "robust" in an imperfect environment so as to maintain a speed that is reasonably close to the desired set speed, even when faced with frequent grading changes. The controller is also adjusted for "efficiency" in the use of computational power and gasoline (the system's "constraints") and is optimized at the recognized tradeoff cost of less-than-precise maintenance of the set speed. The precision of control required depends on the exact task at hand with a calculable price to be paid for additional precision in terms of energetic and design (additional complexity) costs.

Fig. 1A displays the components of a basic feedback in a control loop describing cruise control. Fig. 1B uses the same format to display a sample feedback loop for physiologic temperature control. The term *plant* is generically used for that element of the system that is both actuator controlled and subject to disturbances, for example, the moving car under cruise control. In the medical example, the patient constitutes the "plant" with the state of the plant (temperature) controlled by feedback loops. Although feedback control involves sensing the net effect of the disturbance on the plant (or disease process on a patient), feedforward control directly senses the disturbance itself. In the car analogy, slamming on the brakes after seeing activation of the brake lights of the car in front (even recognizing that the car is slowing down) is a feedforward response. In medicine, situations in which perceived risk is "sensed" before it actually happens cause feedforward actions, for example, venous thromboembolism prophylaxis. Many clinical protocols are examples of feedforward control as they are initiated on the basis of the clinical equivalent of direct sensing of a "disturbance" alone. Note that in engineering, the term *protocol* refers generically to the rules that organize system components or parts into a functional system [1].

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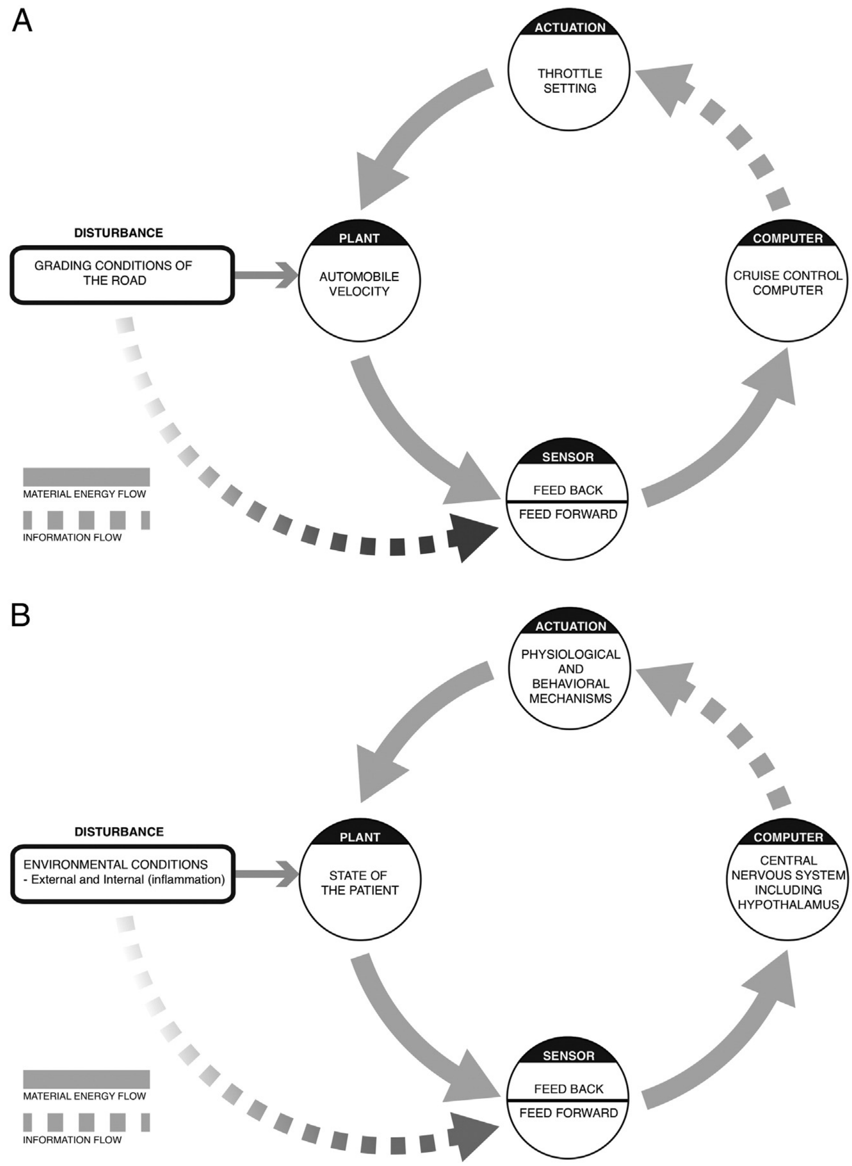

Fig. 1. Control loop elements in automotive cruise control (A) and temperature homeostasis (B). Inner labels describe specific elements for each domain; for example, the throttle setting is the actuator in automotive cruise control. The examples highlight the similarities between the systems that maintain automotive cruise control and temperature homeostasis in humans. Figure courtesy of Yuan Lai.

Using the cruise control analogy again, one can imagine how at higher velocities and more demanding road conditions, a control system has to "work harder" to maintain desired speed. In designing controllers, it is often useful to define the worst-case scenario to fully test the controller. If the demand for speed is great under conditions that are not anticipated in the design, the control system will fail and take all its component parts with it, producing a catastrophic system failure (or crash). Some important concepts underlying control deserve emphasis for considering physiologic controls:

- Controls are essential to the robust functionality of a complex system but are fragile to unmodeled conditions, that is, conditions that have not been taken into consideration during the engineering design process or for which the biological system has not evolved.
  - Example: Ventilation patterns are generated in response to a series of physiologic control loops based around oxygen and pH sensing, requiring (and modeled for) fully differentiated neuron components acting as chemosensors. In neonatal intensive care units, periodic breathing is likely the result of incomplete maturity of the neuronal ventilatory control system: the oscillatory behavior noted in breathing (including apneas) is a typical output for a dysfunctional feedback control system evolved to balance robustness and efficiency [2].
- Control systems may be extremely stressed "under the covers," whereas system output appears to remain normal to the external observer (Table 1).
  - Example: Glycemic control in normal individuals is well maintained even after periods of stressing the system with high carbohydrate intake or periods of starvation, similarly for serum sodium levels after high intake or some degree of relative deprivation.
- Failure of a (designed or evolved) controller can lead to catastrophic failure of an entire complex system even if all the component parts are functioning normally.
  - Example: Take the hypothalamus out of the loop and temperature regulation becomes impossible, although the rest of the circuitry (eg, muscles to shiver, brown fat in babies for thermogenesis, and behavioral modifications to cover up) is perfectly normal and able to respond to normal inputs.

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