Published in final edited form as:

J Crit Care. 2015 June ; 30(3): 652.e1–652.e7. doi:10.1016/j.jcrc.2015.01.019.

ENGINEERING CONTROL INTO MEDICINE

David J. Stone^{1,2}, Leo Anthony Celi^{3,4}, and Marie Csete⁵

David J. Stone: djs4v@virginia.edu; Leo Anthony Celi: lceli@mit.edu; Marie Csete: csete@hmri.org

¹Departments of Anesthesiology and Neurosurgery, University of Virginia School of Medicine, 1215 Lee Street, Charlottesville, VA 22908, USA

²Center for Wireless Health, University of Virginia School of Engineering and Applied Science, 351 McCormick Road, Charlottesville, VA 22904, USA P.O. BSA

³Laboratory of Computational Physiology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, E25-505, Cambridge, MA 02139, USA

⁴Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, MA 02215, USA

⁵Huntington Medical Research Institutes, 99 North El Molino Ave, Pasadena, CA 91101, USA

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, i.e., 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, though 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.

Keywords

control systems; heart rate variability; autoimmune disease; artificial pancreas; sepsis

© 2015 Published by Elsevier Inc.

Corresponding Author: Leo Anthony Celi, +1 (617) 253-7937.

Conflict of Interest: The authors report no potential conflict of interest that exist with any companies/organizations whose products or services may be discussed in this paper.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 which accepts and analyzes inputs, and produces outputs. The systems of interest in medicine are generally dynamic i.e. 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. Though 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 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.

Figure 1a displays the components of a basic feedback in a control loop describing cruise control. Figure 1b uses the same format to display a sample feedback loop for physiological temperature control. The term ‘plant’ is generically utilized for that element of the system that is both actuator controlled and subject to disturbances e.g. 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. While 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 (VTE) 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]

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 ICUs, 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’ while 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 even though the rest of the circuitry (e.g. muscles to shiver, brown fat in babies for thermogenesis, behavioral modifications to cover up) is perfectly normal and able to respond to normal inputs.

PHYSIOLOGICAL CONTROL

Heart Rate Control

Heart rate (HR) is an example of an output of a physiologically controlled system that we have studied in the control context.[3] The system requirement in this case is to maintain (control) acceptably small errors in the critical provision of nutrient and oxygen delivery to vital organs, including muscle oxygen delivery in response to both external and internal (e.g. inspiratory and expiratory intrathoracic pressure changes) workload disturbances (Figure 2). Control is accomplished via autonomic nervous system actuators that regulate HR, minute ventilation, and vascular tone. The control of HR in the setting of healthy physiological variables and constraints results in predictable and necessary saturations in the involved actuators that lead to low mean HR with high variability at rest. With increased workload and stress, mean HR is greater with lower variability (Figure 3). Actuator saturations in hemodynamic control result from basic physiological limitations, system constraints (e.g. impact on CBF regulation), and tradeoffs that balance robust homeostasis and metabolic

efficiency. The analogies from the cruise control example are maintained velocity range for homeostasis, and use of fuel and computing power for metabolic efficiency. As the system approaches its theoretical limits of performance, the actuators that maintain this performance ‘saturate’, that is, they have no further capacity to increase their impact on system output. This phenomenon appears to be the general case for complex controlled systems, whether the system is a car accelerating on cruise control or a heart that is racing to meet metabolic demands. In the automotive case, saturation is manifest by the difficulty in controlling steering at high velocities (which qualifies car racing as a sport); for the heart, it is the loss of high HRV that is present in healthy individuals at rest.

Notably, this ‘low mean/high variability’ signature of health is consistent with a robustly controlled system, whereas the ‘high mean/low variability’ pattern represents a system in the throes of failure. The ‘low mean’ component indicates that the system is providing sufficient actuation at sustainable cost levels while a ‘high mean’ indicates that the system has to work beyond usual (and perhaps sustainable) levels to provide the required outputs (Table 1). Similarly, low variability is indicative of a control system that has reached or is approaching its constraint limits either due to reversibly high workload demands or to incipient intrinsic failure that may be catastrophic and irreversible.

In any case, early detection of control dysfunction within the evolution of a pathophysiological process provides the potential for timelier and more informative monitors. The neonatal HeRO[®] (heart rate observation) system utilizes the detection of reduced HRV (and increased HR decelerations, unique to the fetus and premature neonates) to formulate a probability value that alerts the clinician to the possibility of an adverse physiological state.[4] In the NICU setting, the presumptive state is sepsis and blood cultures can be drawn earlier for diagnosis, and antibiotics started based on a pattern indicating a stressed cardiovascular system before classical signs of sepsis are apparent. Reported results include a 20% reduction in premature neonatal mortality when such monitoring is employed. [5] Chronically ill and elderly adults may demonstrate baseline control dysfunction (e.g. reduced HRV) making this approach more challenging in an important group of patients who have already exhausted some degree of reserve in their control systems, and are often taking drugs that mask normal control system outputs.[3]

The Immune System

The immune system can be considered a master controller of physiologic homeostasis, making us robust to a wide variety of pathogens and insults, but the same mechanisms that provide robustness, when hijacked, can lead to systems failure (as in the case of sepsis, discussed below). The development and functional outputs of the immune system are regulated by complex series of control loops, in a hierarchy of nested controls. Hematopoietic stem cells and their daughter immune cells, like other stem cell lineages, are controlled through negative feedback over proliferation of intermediate lineage stages (transit amplifying cells) and control of commitment to a more differentiated state.[6,7] Tight control over immune system homeostasis is important not only for dealing with infection but also for trauma and hemorrhage. The negative feedback (the ‘do not proliferate signal’) is under control of secreted factors. Polycythemia vera affects one of the switches

that control proliferation of erythroblasts, but the rest of the hematopoietic system is relatively unscathed because of the location of this control element in the hematopoietic lineage hierarchy.[8]

At steady state, the immune system is set to respond to an attack (by massive proliferation of immune cells) but with numbers of attack-ready cells and their toxic secreted products low. The low numbers of attack-ready cells are necessary to deal with normal wear and tear, as inflammation is essential for normal endogenous regeneration, and modulating inflammation is now recognized as a possible mechanism to control regenerative responses.[9] For example, M2 macrophages promote skeletal muscle regeneration after injury, and these cells also tamp down on M1 macrophages, part of a complex feedback between immune cells called to the site of injury.[10] This process works remarkably well for small injuries, such that overshoot of the damaging signals from M1 (and Th1) cells does not usually cause major problems after an injury. However, with aging, muscle repair and regeneration become less robust than in the young, due to a senescent immune system in which the controlled balance of pro-inflammatory and anti-inflammatory responses is pushed toward the pro-inflammatory spectrum. This degradation in control over the immune system highlights the need for understanding the molecular controls over the normal balance of immune cells at steady state and after injury in developing fundamentally new therapies. The molecular mediators of these responses are increasingly well-understood and the mathematical models of the system are also increasingly sophisticated, but critical interactions (controls) are still not completely understood in the way that provides control over the host (patient) immune response. For this reason, computational models using the engineering perspective can be used to make sophisticated predictions about outcome, but the various biologic, mathematic and computational frameworks for constructing the entire picture of control of inflammation have not yet come together in a way that affords physicians (or drug developers) practical information in dealing with individual patients.[11]

CONTROL SYSTEMS AND DISEASE

Physiologic systems control is dominated by control loops (glucose regulation, circadian rhythms, menstrual cycles, osmoregulation). Degradation in function of a controlled system may occur on the basis of failure of any of the system components, but loss of the controller invariably leads to systems failure (overt disease). As such, many disorders can be considered 'loopopathies' reflecting the importance of the controller (rather than its elements) in pathophysiology (Table 2). Diseases may result from faulty lines of communication within the control system loop or a faulty actuator or sensor. Control systems in physiology are linked in overlapping networks of systems (immunology and coagulation for example) making reverse engineering particularly difficult (Table 3). Network' here refers to an interconnected set of controlled systems. Engineers design the network 'architecture' and use mathematical protocols to optimize outputs of these more complex systems, in which time delays in sensing cause new challenges. [21,22]

Autoimmune disease may result from some combination of faulty input (incomplete deletion of self-reactive T cells), and computation (i.e. misidentification), resulting in inappropriate actuation against self-antigens that are misinterpreted as 'foreign'. In immune deficiencies,

the actuation element may be stuck in ‘off’ because of a lack of an imbalance of critical control elements: Mice lacking certain microRNAs lose normal infection-fighting ability, whereas mice that overproduce them develop a fatal autoimmune syndrome.[15] Allergy may be a variant of this kind of control dysfunction in which an excessive response (overshoot) to an ordinarily innocuous foreign substance leads to symptoms. The pathogenesis of chronic inflammation consists, at least in part, of “failed resolution of responses to initiating stimuli and the consequent perpetuating molecular feedback loops, particularly those of cytokines, which maintain inflammatory processes that impair organ integrity”. [16] Understanding the immune response is tremendously important because it is involved in so many acute and chronic disease processes, especially those associated with aging.

Real time control is quite evidently manifest in many therapeutic processes such as the administration of general anesthesia, the titration of intravenous fluids and vasoactive drugs to a target blood pressure range, and the modulation of the settings of a ventilator to the desired level of cardiorespiratory homeostasis. In these cases, the clinician represents the controller except for those instances in which automatic feedback control administration systems have been utilized for these purposes (e.g adaptive support ventilation mode).[23] Analyzing the problem in these cases by identifying the elements of a controlled system can potentially improve therapeutics, and blunt wide shifts in physiologic signals that come from overshooting or undertreating a critically ill patient.

Diabetes and the Artificial Pancreas- A control-based therapy

Blood glucose levels are under control of hormonal feedback loops familiar to all physicians. Despite huge differences in glucose and other carbohydrate intake and activity levels, healthy humans maintain blood glucose levels in a relatively tight range. Type 1 diabetes results in loss of one controller of glucose levels (the beta cell) with catastrophic results that can only be effectively reversed by replacing the controller with an islet cell transplantation or, more recently, an artificial engineered controller. The controlled interactions of insulin and glucagon in the glucose control system can be thought of as analogous to the cooling and heating functions of a room temperature controller that can supply both cooling and heating, as necessary (Figure 4). By contrast, patients with fatty liver and type 2 diabetes have a faulty sensor (insulin resistance) which does cause problems but not as severe as those manifested by loss of the beta cell controller, and one that can be reversed or significantly ameliorated with weight loss.

Type 1 diabetes is also important in the context of this paper because it is an example of a victory of control engineering over a complex disease. [24] A variety of controllers were tested in development of a wearable artificial pancreas to find optimal methods for glucose closed-loop control in patients with type 1 diabetes, including controllers that ‘learned’ from individual subject responses to glucose loads or various stressors.[25] For a detailed review of the control strategy in the wearable artificial pancreas, the reader is referred to an excellent recent review about control design in this setting.[26] Type 1 diabetes is relatively amenable to development of a controller to replace the lost endogenous controller because the major components of the system are known, unlike complex inflammatory response.

Systemic Inflammation and Sepsis

The inflammatory response to infection that manifests itself as the clinical syndrome of sepsis represents an extraordinarily complex sequence of (usually well-)controlled biological and chemical responses.[27,28] Sepsis is so defined when these systemic inflammatory changes accompany infection, but the changes may also occur as a result of non-infectious insults such as trauma. The systemic manifestations of the process may include delirium, gut dysfunction (motility, permeability), hemodynamic compromise, and single or multi-organ failure. While in the short term a hyper-inflammatory response can be life-saving, when sustained and amplified, the response is deleterious and can be fatal.[29] In addition to the inflammatory response, there also appears to be a mitochondria-mediated metabolic hibernation presumed to play a role in the ability to resist damage during tissue ischemia. [30] Clinical sensors of mitochondrial function are missing from our monitoring armamentarium, despite the need. Further confusion about the inflammatory system in sepsis comes from simultaneous hyper-inflammatory response from some parts of the immune system, and hypo-inflammatory responses from other parts of the system, as well as differences in responses based on species. [31]

The apparent initial inflammatory response and its control, as well as subsequent responses, including metabolic down-regulation, depend on a number of heterogeneous factors such as the infecting organism and the site of infection (or the degree and duration of the physiologic insult); the timing of the diagnosis in the evolution of the inflammatory response; and patient factors such as genetics, co-morbidities, and therapies.[32] Immunomodulatory therapy represents a potential exogenous mechanism for control of infection-induced inflammation. However, there has been a notable historic failure of immunomodulatory therapy in sepsis in spite of immense efforts in this area. For many years, basic research utilizing a highly simplified version of the inflammatory cascade has driven clinical trials evaluating biologicals. Most, but not all of the trials involved agents that block some element of the early, pro-inflammatory response.[32] In view of the complexity and dynamic nature of the overall inflammatory response in sepsis, it is no surprise that individual therapeutic agents crudely timed and targeted toward individual elements of the pro-inflammatory response have not resulted in outcome improvements. Mathematical modeling up to and including *in silico* clinical trials is likely the way to capture the immune response to infection in ways that help identify important control elements and potential new therapies.[33] As the parts of the hyper- and hypoinflammatory pathology leading to sepsis are identified, they can be incorporated into models of sepsis evolution to predict outcome and response to therapy. In the meantime, the models are useful for tweaking these components (such as unknowns in mitochondrial function) to develop a better picture of the systemic response to changes in inputs.

Ultimately, perhaps a kind of ‘inflammation control device’ employing new technologies will be constructed to enable real time sensing of the levels of the inflammatory elements involved as well as modulation of the appropriate compensatory effectors to augment or blunt a pathologic inflammatory response (Figure 5). A recent study of postoperative inflammation indicates that this kind of approach should be feasible, noting that “mechanistically derived immune correlates point to diagnostic signatures, and potential

therapeutic targets”.[34] The goal would be to maintain inflammatory factors at the levels required for successful eradication of the infection without resulting in- an overwhelming and fatal acute hyperinflammatory response; a long term, counterproductive hyperinflammatory response resulting in damage such as lung fibrosis after ARDS; or a hypoinflammatory response resulting in immune suppression and another infection taking over a compromised host. These patterns might be obtained by examination of the ‘diagnostic signatures’ in prior patients in similar situations who had good outcomes.[35] Exhaustion of intrinsic cellular and biochemical resources might require regenerative therapies and to take advantage of the immunomodulatory properties of some stem cells. [36,37]

CONCLUSION

Control engineers are experts at designing and analyzing complex systems but have traditionally had little contact with clinicians. Clinicians generally do not consider the control strategies that fail in pathologies they face daily. We maintain that collaboration between engineers and clinicians is now required for the achievement of selected significant advances in medicine. For example, the collaboration of data engineers and clinicians will be required for the design and production of better data systems. The collaboration of clinicians with engineers with expertise in control issues will be useful if not essential for advances in understanding that complex system of systems- the diseased human. With the notable exception of the artificial pancreas, we simply have not leveraged the brain power and expertise of some very smart people, i.e. the control engineers, in the analysis of the medical problems we face. New approaches utilizing such long-term collaboration have enormous potential for breakthrough concepts that would not be conceived without a dialogue between clinicians and engineers.

Acknowledgments

The authors would like to thank Professor John C. Doyle of Caltech for his insightful comments and discussion, and Yuan Lai for his assistance with the figures. Leo Anthony Celi is funded through Grant R01 EB017205-01A1 from the National Institutes of Health.

References

1. Csete ME, Doyle JC. Reverse engineering of biological complexity. *Science*. 2002; 295:1664–9. [PubMed: 11872830]
2. Chandra FA, Buzi G, Doyle JC. Glycolytic oscillations and limits on robust efficiency. *Science*. 2011; 333(6039):187–192. [PubMed: 21737735]
3. Li N, Cruz J, Chien SC, Sojoudi S, Recht B, Stone D, et al. Robust efficiency and actuator saturation explain healthy heart rate control and variability. *Proc Natl Acad Sci USA*. 2014; 111(33):E3476–85. [PubMed: 25092335]
4. [Last Accessed 29 October 2014] HeRO®. <http://www.heroscore.com/>
5. Moorman JR, Carlo WA, Kattwinkel J, Schelonka RL, Porcelli PJ, Navarrete CT, et al. Mortality reduction by heart rate characteristic monitoring in very low birth weight neonates: a randomized trial. *J Pediatrics*. 2011; 159(6):900–6.
6. Lo WC, Chou CS, Gokoffski KK, Wan FY, Lander AD, Calof AL, et al. Feedback regulation in multistage cell lineages. *Math Biosci Eng*. 2009; 6(1):59–82. [PubMed: 19292508]

7. Manesso E, Teles J, Bryder D, Peterson C. Dynamical modelling of haematopoiesis: an integrated view over the system in homeostasis and under perturbation. *J R Soc Interface*. 2013; 10(80): 20120817. [PubMed: 23256190]
8. Soriano G, Heaney M. Polycythemia vera and essential thrombocythemia: new developments in biology with therapeutic implications. *Curr Opin Hematol*. 2013; 20(2):169–75. [PubMed: 23298878]
9. Aurora AB, Porrello ER, Tan W, Mahmoud AI, Hill JA, Bassel-Duby R, et al. Macrophages are required for neonatal heart regeneration. *J Clin Invest*. 2014; 124(3):1382–92. [PubMed: 24569380]
10. Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. *Am J Physiol Regul Integr Comp Physiol*. 2010; 298(5):R1173–85. [PubMed: 20219869]
11. Wolfram D, Starzl R, Hackl H, Barclay D, Hautz T, Zelger B, et al. Insights from computational modeling in inflammation and acute rejection in limb transplantation. *PLoS ONE*. 2014; 9(6):e99926. [PubMed: 24926998]
12. Cobelli C, Renard E, Kovatchev B. Artificial pancreas: past, present, future. *Diabetes*. 2011; 60:2672–82. [PubMed: 22025773]
13. Suzuki K, Jayasena CN, Bloom SR. Obesity and appetite control. *Experimental Diabetes Res*. 2012; 2012:824305.
14. Fuchs S, Feferman T, Meidler R, Margalit R, Sicsic C, et al. Immunosuppression of EAMG by IVIG Is Mediated by a Disease-specific Anti-immunoglobulin Fraction. *Ann N Y Acad Sci*. 2008; 1132:244–8. [PubMed: 18567875]
15. Kang SG, Liu WH, Lu P, Jin HY, Lim HW, Shepherd J, et al. MicroRNAs of the miR-17~92 family are critical regulators of T(FH) differentiation. *Nature Immunology*. 2013; 14(8):849–57. [PubMed: 23812097]
16. Schett G, Elewaut D, McInnes IB, et al. Toward a cytokine-based disease taxonomy. *Nature Medicine*. 2013; 19:822–4.
17. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti PD-1 antibody in cancer. *N Eng J Med*. 2012; 366:2443–54.
18. Hazarika S, Farber CR, Dokun AO, Pitsillides AN, Wang T, Lye RJ, et al. MicroRNA-93 controls perfusion recovery after hindlimb ischemia by modulating expression of multiple genes in the cell cycle pathway. *Circulation*. 2013; 127:1818–28. [PubMed: 23559675]
19. Stegmeier F, Warmuth M, Sellers WR, Dorsch M. Targeted cancer therapies in the twenty-first century: lessons from imatinib. *Clin Pharmacol Ther*. 2010; 87(5):543–52. [PubMed: 20237469]
20. Chakkalakal SA, Zhang D, Culbert AL, Convente MR, Caron RJ, Wright AC, et al. An Acvr1 R206H knock-in mouse has fibrodysplasia ossificans progressiva. *J Bone Miner Res*. 2012; 27(8): 1746–56. [PubMed: 22508565]
21. Doyle JC, Csete M. Architecture, constraints, and behavior. *Proc Natl Acad Sci U S A*. 2011; 108 (Suppl 3):15624–30. [PubMed: 21788505]
22. Sinopoli B, Sharp C, Schenato L, Schaffert S, Sastry SS. Distributed control applications within sensor networks. *Proc IEEE*. 2003; 91(8):1235–46.
23. Iotti GA, Polito A, Belliato M, et al. Adaptive support ventilation versus conventional ventilation for total ventilatory support in acute respiratory failure. *Intensive Care Med*. 2010; 36 (8):1371–1379. [PubMed: 20502870]
24. Csete M, Doyle J. The mathematician's control toolbox for management of type 1 diabetes. *Interface Focus*. 2014; 4:20142242.
25. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, et al. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care*. 2014; 37(7):1789–96. [PubMed: 24929429]
26. Doyle FJ 3rd, Huyett JM, Lee JB, Zisser HC, Dassau E. Closed-loop artificial pancreas systems: engineering the algorithms. *Diabetes Care*. 2014; 37(5):1191–7. [PubMed: 24757226]
27. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008; 454(7203):428–435. [PubMed: 18650913]

28. Xiao W, Mindrinos MN, Seok J. A genomic storm in critically injured humans. *J Exp Med*. 2011; 208(13):2581–2590. [PubMed: 22110166]
29. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *New Engl J Med*. 2003; 348(2):138–150. [PubMed: 12519925]
30. Levy RJ. Mitochondrial dysfunction, bioenergetic impairment, and metabolic down-regulation in sepsis. *Shock*. 2007; 28(1):24–8. [PubMed: 17483747]
31. Seok J, Warren HS, Cuenca AG, Cuenca AG, Mindrinos MN, Baker HV, Xu W, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Nat Acad Sci*. 2013; 110(9):3507–3512. [PubMed: 23401516]
32. Marshall JC. Why have clinical trials in sepsis failed? *Trends Mol Med*. 2014; 20(4):195–203. [PubMed: 24581450]
33. Vodovotz Y, Billiar TR. In silico modeling: methods and applications to trauma and sepsis. *Crit Care Med*. 2013; 41(8):2008–14. [PubMed: 23863232]
34. Gaudillière B, Fragiadakis GK, Bruggner RV, Nicolau M, Finck R, Tingle M, et al. Clinical recovery from surgery correlates with single-cell immune signatures. *Sci Transl Med*. 2014; 6:255ra131.
35. Celi LA, Zimolzak AJ, Stone DJ. Dynamic clinical data mining: search engine-based clinical decision support. *JMIR Med Inform*. 2014; 2(1):e13. [PubMed: 25600664]
36. Forbes SJ, Rosenthal N. Preparing the ground for tissue regeneration: from mechanism to therapy. *Nature Med*. 2014; 20(8):857–69. [PubMed: 25100531]
37. Hotchkiss RS, Moldawer LL. Parallels between cancer and infectious disease. *New Engl J Med*. 2014; 371(4):380–383. [PubMed: 25054723]

Figure 1. Control loop elements in automotive cruise control (1A) and temperature homeostasis (1B). Inner labels describe specific elements for each domain e.g. 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.

Figure 2.

Schematic for cardiovascular control of aerobic metabolism. Blue arrows represent venous beds, red arrows are arterial beds, and dashed lines represent controls. Four types of signals, distinct in both functional role and time series behavior, together define the required elements for robust efficiency. The main control requirement is to maintain (i) small errors in internal variables for brain homeostasis (e.g., arterial O₂ saturation SaO₂, mean arterial blood pressure P_{as}, and cerebral blood flow CBF), and muscle efficiency (oxygen extraction O₂ across working muscle) despite (ii) external disturbances (muscle work rate W), and (iii) internal sensor noise and perturbations (e.g., pressure changes from different respiratory patterns due to pulsatile ventilation V) using (iv) actuators (heart rate H, minute ventilation VE, vasodilation and peripheral resistance R, and local cerebral autoregulation).

Reproduced with permission from reference 3.

Figure 3.

Heart rate HR responses (red) to simple changes in muscle workload (blue) collected from subjects on a stationary bicycle. Each subject performed separate exercises of 10 min for each workload profile, with different means but nearly identical square wave fluctuations around the mean. A typical result is shown from a subject for three workload profiles with time on the horizontal axis (zoomed in to focus on a 6-min window). *Reproduced with permission from reference 3.*

Figure 4.

Low granularity view of the glucose control system (top) and a room temperature controller (bottom), emphasizing similar system structures. Controllers used in industry applications have been applied in development of the wearable artificial pancreas. *Reproduced with permission from reference 24.*

Figure 5.

A simplified control device in sepsis with time moving from top to bottom. The top image displays a representation of a limited number of the many inter-related chemical and cellular factors involved in the inflammatory response. The balloons represent the individual factors with their values represented by their position relative to the orbital network. The middle image displays an example of what might be detected in an index septic patient. The control device would sense the anomalies in these values and act to restore the levels of the factors to target values, as represented in the bottom image. The target values would depend on a number of factors such as their timing in the inflammatory sequence and the nature of the inciting trigger. Figure courtesy of Yuan Lai.

Table 1

Temporal evolution of systems dysfunction and failure

STAGE	STATE OF CONTROLS	STATE OF OTHER SYSTEM COMPONENTS
1. Normal functionality	Functional for unlimited duration with availability of required biochemical elements	Intact
2. Increase in system output requirement	Functional at increased capacity depending on level of imposed stress; duration potentially limited but changes are gradual	Intact
3. Control system capacity exceeded	Transition to failure may be sudden or gradual	Superficially intact with increasing potential fragility dependent on controls state
4. Control system failure	Failure	Initial phases of cascading failure; robustness lost
5. Total System failure	Failure	Failure that may be sudden, irreversible and catastrophic

Table 2

Potential control element dysfunctions manifesting as disease

CONTROL COMPONENT	CLINICAL EXAMPLE
Feedback input sensor	Keloid formation
Feedforward	Coagulation cascade amplification
Communication channels	<ul style="list-style-type: none"> • Dementia, Epilepsy, Autism, Aphasias • Drug-related suppression e.g. general anesthesia • Delirium, hallucinations
Computation	<ul style="list-style-type: none"> • Dementia • Schizophrenia
Actuation	<ul style="list-style-type: none"> • Stroke volume in CHF • insulin secretion in Type I DM
• Limitation	
• High mean/low variability	Reduced Heart Rate Variability in a variety of conditions e.g. neonatal sepsis
• Excessive variability	Fibrillatory dysrhythmias
• Stuck in 'on'	<ul style="list-style-type: none"> • Neoplastic disease; • Selected dysrhythmias; • Hormonal hypersecretion e.g Cushing's • Epilepsy
• Stuck in 'off'	<ul style="list-style-type: none"> • Immune deficiency disorders; • Hormonal hyposecretion e.g Addison's • Selected cases of infertility on hormonal basis; • Cardiac conduction blocks

Table 3

Control Elements in Disease.

SYSTEM	DISEASE	CONTROL ISSUE	CURRENT OR (POTENTIAL) CONTROL THERAPIES
Metabolic	Diabetes mellitus	Glycemic	Artificial pancreas[12]
	Obesity	Appetite and caloric utilization	Appetite suppressants and gut microbiome modification[13]
	Hormonal hyper and hyposecretion syndromes	Level of specific hormone	Agents that inhibit or replace/ stimulate production or secretion
Immunologic	Autoimmune	Immune recognition of self vs non-self	Gamma globulin for myasthenia gravis[14] (microRNA therapy) [15]
	Allergy	Aberrant response to environmental substance	Hyposensitization therapy
	Systemic inflammation e.g. sepsis, chronic inflammatory states	Timing and modulation of intrinsic inflammatory response	(Cytokine modulation)[16]
	Cancer (also see genomic section below)	Negative feedback control of immune response	(Anti PD-1 antibodies)[17]
Cardiovascular	Hypertension	Blood pressure increase, mainly due to increased vascular resistance	None that directly act on control system
	Localized inflammation e.g. peripheral vascular disease	microRNA gene suppression	(microRNA therapy)[18]
Genomic	Cancer	Cell division and metastasis	Targeted therapy e.g. CML- Restore feedback control of cellular replication by blocking aberrant enzyme[19]
	Inherited disease	Metabolic pathways	(genomic approach)
Musculoskeletal	Craniosynostosis	Bony growth and closure of sutures	none
	Fibrodysplasia ossificans progressiva	Repair of muscle injury	(modulation of Acvr1 genetic activity)[20]
Neurologic (speculative)	Dementia	Faulty sensors and computation	(prevent deposition of biochemical network disruptors)
	Psychosis	Faulty feedforward control and computation	(block deleterious feedforward phenomena)
	Epilepsy	Faulty network communication and feedback control	(replicate the pathological network disruption/resection as currently achieved by neurosurgery)