Biological Control Systems:
Systems Biology of Diseases and the Design of Effective Treatments

ABSTRACT

The mammalian organism maintains stable, efficient and "near-optimal" performance and *homeostasis* in the face of external and internal perturbations via distinct biological systems ranging from the large-scale *physiological* (nervous, endocrine, immune, circulatory, respiratory, etc.), to the *cellular* (growth and proliferation regulation, DNA damage repair, etc.), and the *sub-cellular* (gene expression, protein synthesis, metabolite regulation, etc). "Biological Control Systems," a sub-topic of Control Theory, arises from a control engineering perspective of the function, organization, and coordination of these multi-scale biological systems and the control mechanisms that enable them to carry out their functions effectively.

In this presentation, we provide an overview of *how* physiological life is made possible by control, and demonstrate the usefulness of a control engineering perspective of pathologies for diagnosis, design, and implementation of effective treatments. The concepts and principles will be illustrated using specific examples with significant research and clinical implications.

OVERVIEW

This is a presentation in three parts:

- In Part 1 (Introduction) is where I make the central point that "control" is everywhere in biological systems; in fact, physiological life as we know it is not possible without control.
- In Part 2 (Pathologies & Control Engineering Perspectives) is where I follow up with another important point: that if control is involved in a biological system and one is unaware of this, a naïve analysis of input/output data will quite likely lead to erroneous conclusions, especially when one wants to diagnose anomalous behavior. Using a control engineering perspective protects us from such errors, and helps clarify potential confusion
- In Part 3 (Engineering Control Systems and Disease Treatment) is where I make the final point: that when a biological control system fails, engineering control systems can provide viable alternatives.

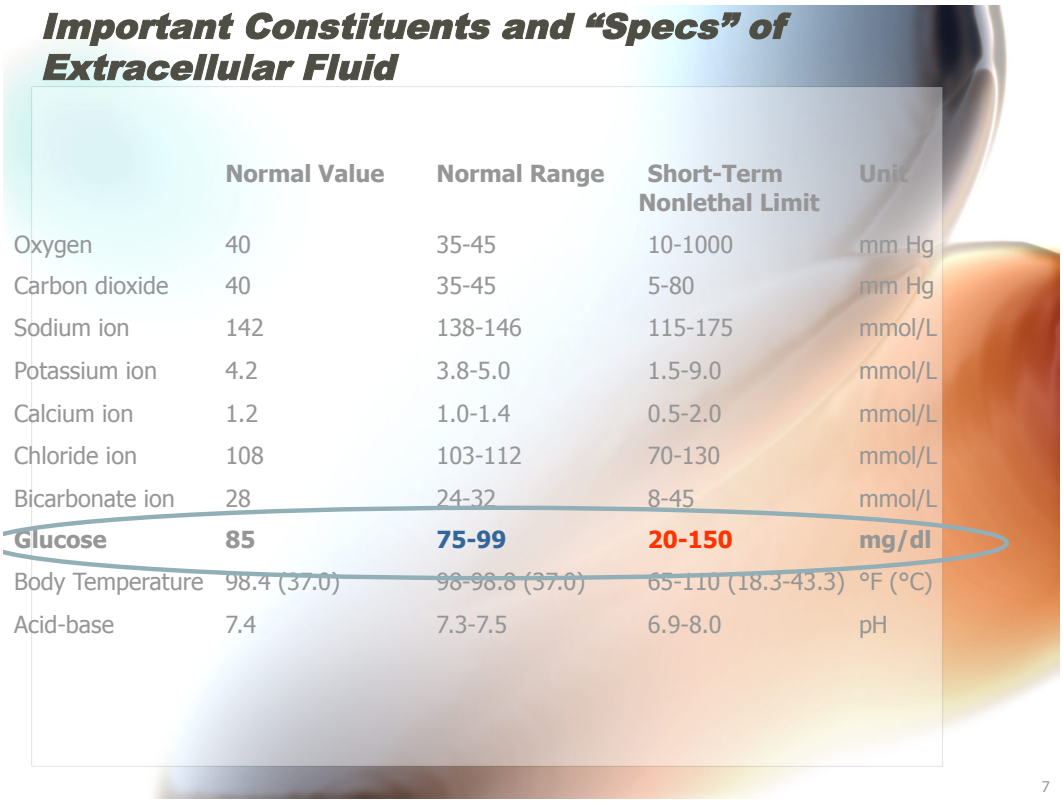
1. INTRODUCTION

In 1775, Charles Blagden (1748-1820), and some research associates, performed a seminal experiment: some human subjects, a dog and a piece of beefsteak were confined for 45 minutes in a chamber heated up to 127°F, with the following results: over this period, the human subjects sweated, the dog panted, but all survived; the beefsteak, on the other hand, cooked. The central conclusion was that living organisms are able to adapt to the external conditions and thereby maintain what became known as "homeostasis"; dead organism could not.

It is now well established that, overall, the mammalian system consists of a hierarchical organization of multiple levels of physiological systems at different length scales: from the *chemical level* (with atoms C, H, O, N, P, and DNA) to the *cellular level* consisting of an organization of atoms and molecules; to the *tissue level*, consisting of a systematic collection of cells; to the *organ level*, which is a collection of tissues, to the *system level*

which is a collection of organs and tissues organized into a coherent unit system with a specific task and objective (for example, the digestive system); to the final overall organismal level. With an overall objective of maintaining physiological function (equivalent to keeping physiological variables within specification limits), the mammalian system must rely on specialized "control systems" in order to meet this overarching objective because of persistent perturbations that threaten to displace the physiological systems away from homeostatic conditions. Table 1 below shows a sample of typical "specification limits" for constituents of the extracellular fluid in humans.

TABLE 1: *Important Constituents and "Specification Limits" of the Human Extracellular Fluid: The specs for blood glucose are highlighted*



A short term but significant departure of physiological variables from normal limits is referred to as an "illness" where recovery occurs when the perturbed variables are returned to within normal limits. "Chronic illnesses" are characterized by long term (or systemic) departures from normal limits, but with the affected variables still within non-lethal limits. Death occurs when critical physiological variables fall outside non-lethal limits and are not restored within a reasonable period of time.

Physiological Control Systems

The mammalian system maintains homeostasis and desired physiological function in the face of constant perturbations with the aid of a collection of physiological systems, each with its dedicated function and objectives, and organized as follows:

The MASTER REGULATORS

1. *The Nervous System* (for overall control and regulation, among other functions such as memory, behavior, etc.)

2. *The Endocrine System* (for chemical regulation, among other functions such as growth and development, etc.)

The DEFENDERS, PROTECTORS & SUPPORTERS

3. *The Immune/Lymphatic System* (for defense and internal protection, among other functions including fluid balance and fat absorption, etc.)
4. *The Integumentary System* (for protection and heat transfer, among other functions such as Vitamin D production etc.)
5. *The Musculoskeletal System* (for movement and mechanical support, among other functions such as minerals warehousing and blood cell production, etc.)

The UTILITIES

6. *The Cardiovascular System* (for transport and supplies distribution)
7. *The Respiratory System* (for oxygen supply and CO_2 elimination, among other functions such as vice production and olfaction, etc.)
8. *The Digestive System* (for nutrient processing and supply)
9. *The Urinary System* (for waste extraction and elimination, among other functions such as Vitamin D synthesis, etc.)

The SPECIES PROPAGATOR

10. *The Reproductive System* (for species propagation from one generation to the next)

Biological Control Systems Configurations

Each of the ten physiological systems noted above consists of exquisitely calibrated control systems that enable it carry out its functions efficiently. These control systems consist of the same functional components as the engineering control system: *sensors, controllers, actuators, and the controlled process* itself. And, as with engineering control systems, depending on how these components are organized relative to one another, one finds a variety of control configurations: Feedback, Feedforward, Cascade, and unconventional multi-loop configurations that do net exist in tradition engineering control systems. The most common configuration is feedback control, an example of which is the blood pressure control system whose block diagram is shown in Figure 1.

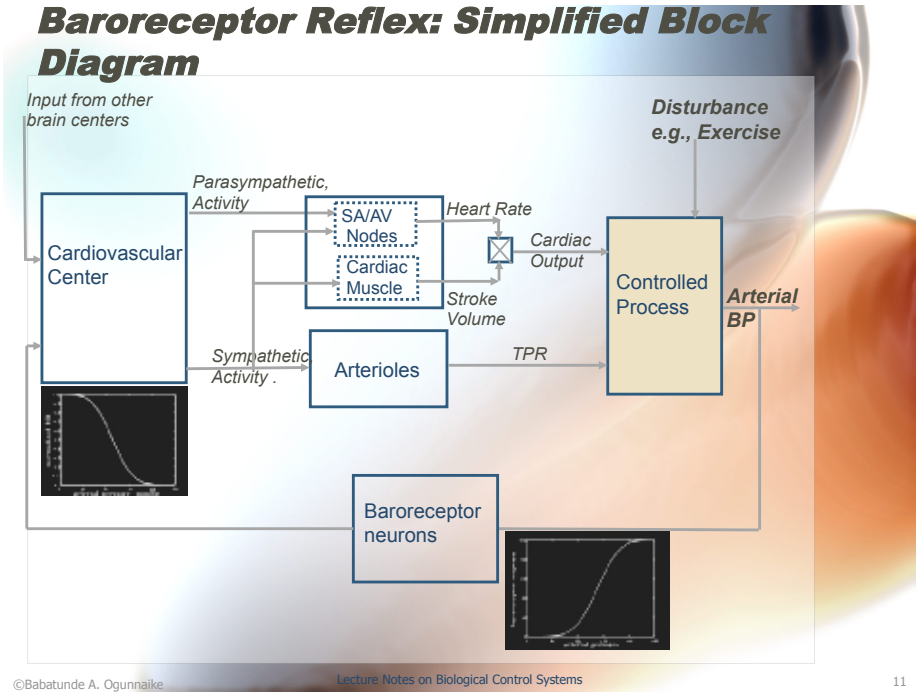


Fig 1. *Block Diagrammatic Representation of the Baroreceptor Reflex: The Blood Pressure Control Systems*

We showed in the presentation that feedback control allows for robustness and performance without the need for detailed process knowledge. The cascade structure is the stereotypical structure of choice for endocrine control systems, an example of which is shown in Fig 2. Many more structures, far more complex than commonly seen in engineered systems, exist in biological control systems (for example, Fig 3 shows a simplified representation of the immune system block diagram).

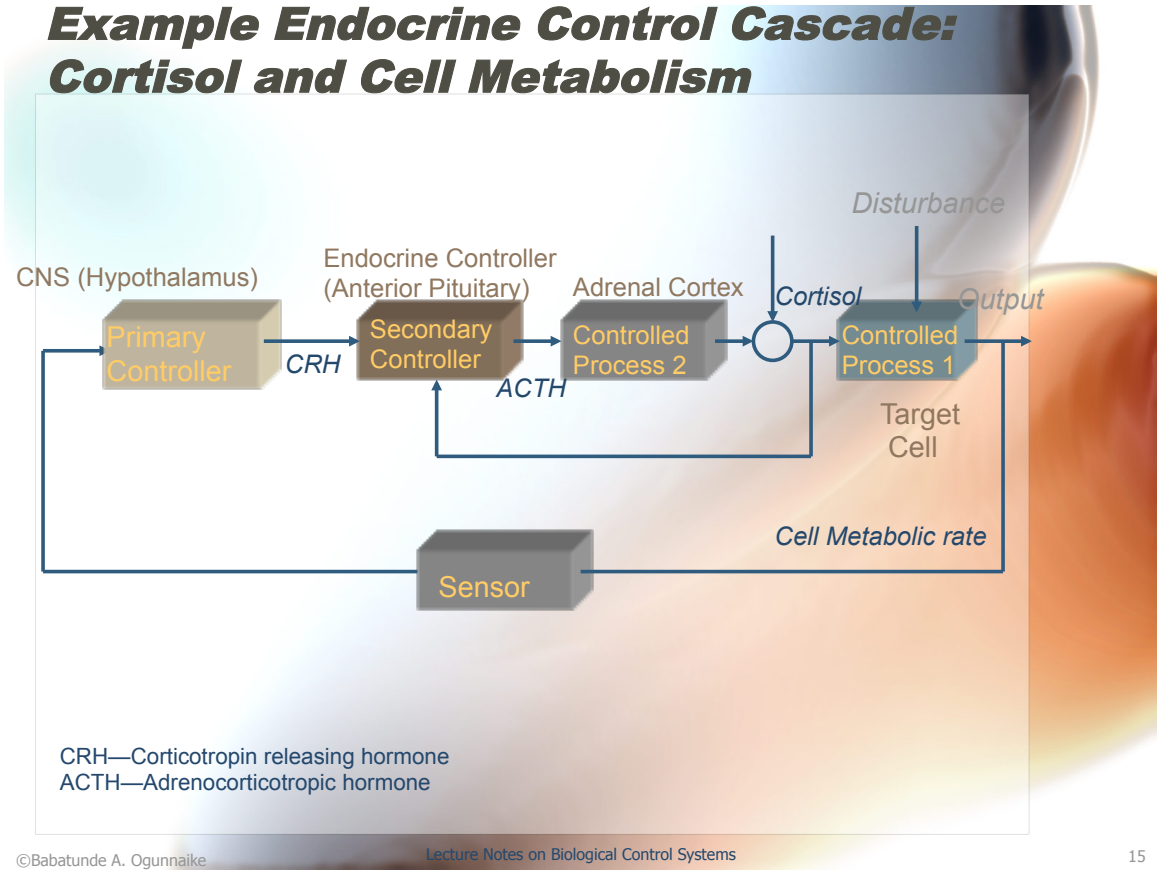


Fig 2. *Block Diagrammatic Representation of a typical endocrine control cascade*

2. PATHOLOGIES & CONTROL ENGINEERING PERSPECTIVES

Many diseases arise from the failure or malfunction of one or more control system components. For example, diabetes arises as a result of the failure in the control system responsible for blood glucose regulation. However, the type of diabetes depends on which component of this control system failed. Type I diabetes arises from an *actuator failure* because, in this case, the pancreas is incapable of producing insulin. On the other hand, Type II diabetes arises from impaired insulin sensitivity by the "process" to be controlled. Diagnosis and the prescription of appropriate treatments often involve clinical observations which are tantamount to the collection and analysis of "input-output" data, in the sense that the physician "perturbs" the system in question and observes the patient's response through various assays of samples taken from the patient, for example, blood sample analysis following fasting to determine "fasting blood glucose" levels in a potentially diabetic patient.

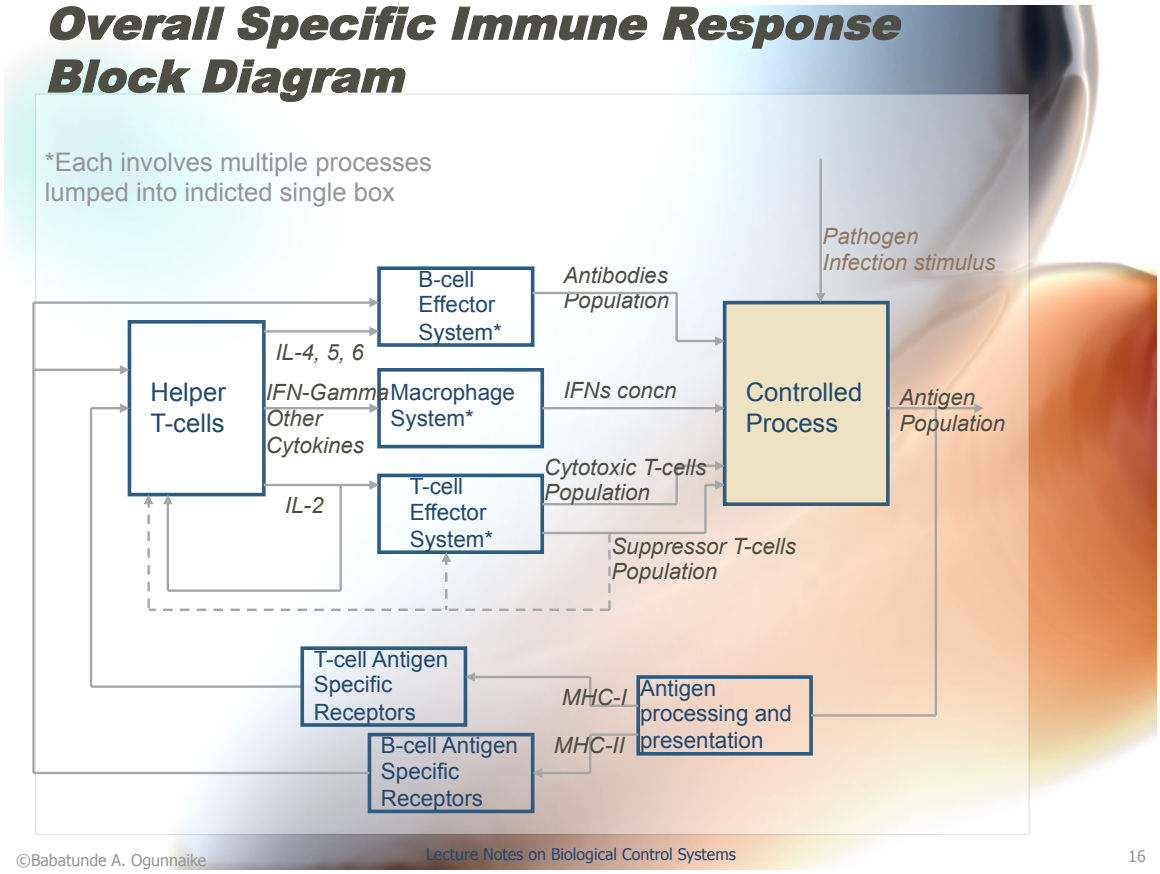


Fig 3. *Simplified Block Diagrammatic Representation of the Immune Response*

The two thematic concepts central to this part of the presentation may be stated as follows:

1. If the involvement of feedback control in a biological system is unrecognized, naïve input-output data analysis will likely lead to erroneous conclusions;
2. A control engineering perspective of diseases decreases the possibility of "faulty" diagnosis caused by confounding and conflating "component malfunctions"

With the first concept, the central issue is that a control system response to an external disturbance is drastically different under *open loop* conditions as opposed to *closed loop* feedback control. To illustrate, consider a seminar room with a single door that opens directly to the outside. Further consider that it is winter, with a temperature 0 degree Celsius outside, but the temperature inside the room is maintained at a comfortable 25 degrees Celsius by a "perfect" thermostat. Under these circumstances, frequent and periodic opening of the door, which exposes the room to the outside temperature, will be countered by the action of the perfect controller with the net effect that the room temperature will remain unchanged. Without recognizing the presence of the thermostat in the room, observers analyzing the response of the room temperature to the perturbations caused by exposure to the outside elements will come to the erroneous conclusion that the room temperature is fundamentally unaffected by exposure to the outside temperature.

The second concept is predicated on the fact that a control system consists of an interconnection of four functional modules/components: the sensor, the controller, the actuator, and the controlled process itself. Thus, a control system can fail or malfunction when one or more of these components fails or malfunctions, in which case, a rational approach to rectifying the problem must begin with the determination of which specific component malfunction is responsible for the observed system failure. But, a sensor failure, for example, is not the same as an actuator failure, in precisely the same sense in which Type I diabetes (an actuator failure) is fundamentally different from Type II (a process malfunction). However, because the components are connected, an indiscriminate analysis of the overall system response to any arbitrary perturbation, conflates the responses of the components making it difficult, if not impossible, to identifying the malfunctioning component.

TGF-β regulation of cell population

The first concept is illustrated by the role of TGf-β in late stage cancer where, because *the amount of TGF-β, a known tumor suppressor, was clinically observed to be unusually high in the worst cases, it was proposed that TGF-β somehow switches function from a tumor suppressor to a tumor promoter.* The premise was that since an observed increase in tumor size corresponded with increasing amounts of TGf-β, then this growth inhibitor must have transformed into a growth promoter in late stage cancers. This paradox was resolved in Chung et al., (2012)[1] by taking a control engineering approach and showing that the observation and misleading conclusion is due to the presence a control system that employs TGF-β to regulate cell proliferation, with the following conclusions arising from an analysis of the mathematical model of the control system:

- **Under Normal Conditions** the controller regulates growth, inhibits proliferation effectively using the tumor suppressor ligand, TGF-β; however,
- **Under Cancerous Conditions** (characterized by TGF-β resistance, in a manner reminiscent of Type II diabetes), the role of TGF-β is unchanged; the control system still intact; but it must now secrete more of TGF-β *in a futile attempt to achieve the level of tumor suppression attainable with normal, responsive cells.*

Thus, the increased level of TGF-β is consistent with its unchanged role as a tumor suppressor; the observed correlation was confused with causality because the presence of a control system went unnoticed.

Calcium Regulation

The second concept is illustrated with differential diagnosis of three different manifestations of Hypercalcemia (a condition where the calcium level is higher than normal) using a quantitative model of the Ca^{2+} regulation system in the human body[2] based on the control engineering block diagram in Fig. 4.

The three different manifestations of hypercalcemia, are:

- Primary Hyperparathyroidism (PHPT), responsible for ~70% of all cases
- Familial Benign Hypercalcemia (FBH) and
- Humoral Hypercalcemia of Malignancy (HHM)

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[1] S.W. Chung, C. R. Cooper, M. C. Farach-Carson, and B. A. Ogunnaike, "A control engineering approach to understanding the *TGF-β* paradox in cancer", J. *R. Soc. Interface* (2012), 9, 1380-1397

[2] C. Christie, L. E. K. Achenie and B. A. Ogunnaike, 2014, "A control engineering model of calcium regulation", *J Clin Endocrinol Metab,* 99(8): 2844–2853

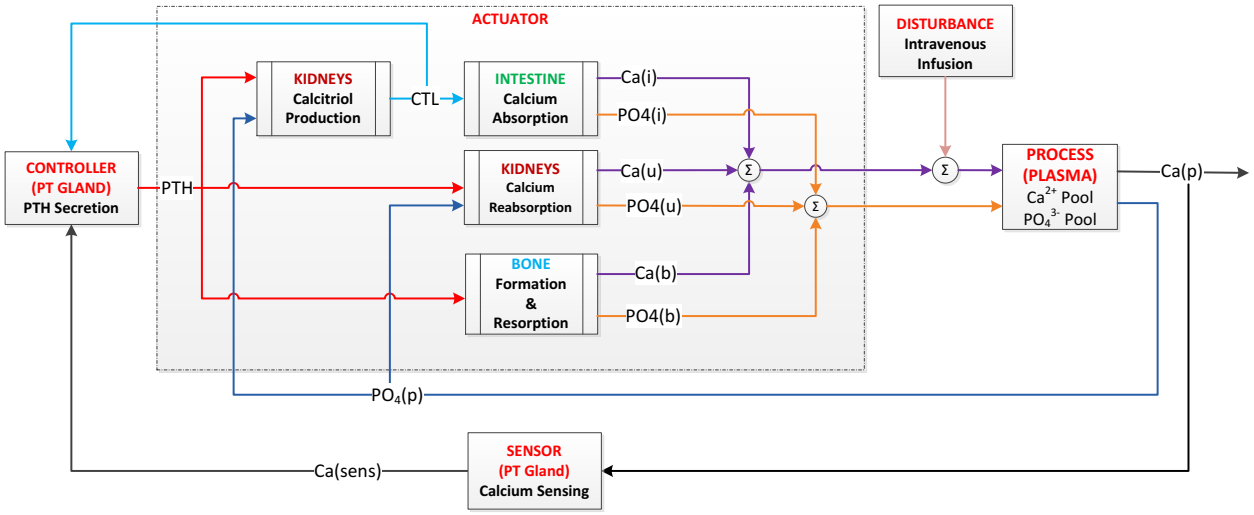

Fig 4: *The Calcium Regulation Control System.*

The primary challenge is that they are all classified as "Hypercalcemia" and show similar clinical presentations (High Ca and High Parathyroid Hormone-like effects), making differential diagnosis difficult. However, PHPT is caused by abnormal enlargement of the parathyroid glands, in which case this is equivalent to a "controller defect". On the other hand, FBH is a hereditary genetic disorder involving a missense mutation of the Ca-sensing receptors—clearly a "sensor defect". Finally, HHM arises from complications of some cancers (Breast; Lung; Hematologic), where tumor cells produce PTH-related protein (PTHrP), which acts like PTH. When PTH receptors detect/respond to PTHrP, the result is "high PTH"-like response, characteristic of other hypercalcemic responses. While it is not as obvious, we showed in the presentation that this is an "actuator disturbance".

Having thus identified the component malfunction responsible for each manifestation of hypercalcemia, we used the (validated) mathematical model to investigate input stimuli design to generate theoretical differentiated responses. We showed that even with standard induced hypercalcemia pulses, the post infusion dynamic response profiles of the parathyroid hormone and calcitriol are sufficiently distinguishable for each of the three different cases of hypercalcemia.

3. ENGINEERING CONTROL SYSTEMS & DISEASE TREATMENT

When natural biological control systems fail, engineered control systems can provide effective substitutes. With proper recognition of the intrinsic complexity of biological system dynamics, control engineering principles can be (and have been) applied successfully to compensate. The most well known example is the "Artificial Pancreas", an engineered device designed for Type I Diabetes patients. Based on engineering control principles, a glucose sensor is combined with an embedded controller and an insulin pump, in a single device that delivers precise amounts of insulin for patients suffering from Type I diabetes.

Here we present a case study of a control system designed to achieve platelet count control for an Immune Thrombocytopenic Purpura (ITP) patient.[3]

[3] C.-H. Tsai, J. B. Bussel, A. A. I mahiyerobo, S. I. Sandler, and B. A. Ogunnaike, Platelet count control in immune thrombocyropenic purpura patient: Optimum romiplostim dose profile, *J. Process Control*, 45, (2016) 76-83.

Immune Thrombocytopenic Purpura (ITP)
The clinical definition of ITP is a platelet count lower than 150×10^9 cells/L, putting the patient at a high risk of excessive bleeding. (See table below.)

Platelet count, PLT ($\times10^9$ cells/L)	Description	Symptoms	Treatment suggestion [1, 2, 3]
150 < PLT < 400	normal	none	none
30 < PLT < 150	mild ITP	might be asymptomatic	no treatment required
PLT < 30	high risk of bleeding	subarachnoid bleeding, gastrointestinal bleeding, intracranial hemorrhage	treatment usually required;
PLT < 10	severe ITP		treatment definitely required

ITP is characterized by increased platelet destruction in patients, and/or reduced platelet production; its root cause is unknown. It is common to treat ITP with periodic injections of romiplostim, a thrombopoietin (TPO)-mimetic, which functions like endogenous TPO. Natural TPO, which is synthesized in the liver, is central to the production of platelets according to the following mechanism:

- TPO binds to its receptor, c-Mpl, on the plasma membrane of the platelet precursor (e.g., megakaryocyte)
- This leads to megakaryocyte differentiation and eventually to platelet production
- However, platelets also have TPO receptors, c-Mpl; so that binding TPO lowers its concentration in circulation, providing a natural feedback regulation of the amount of TPO.

Romiplostim thus increases platelet count by stimulating platelet production in the same manner as endogenous TPO. However, with romiplostim therapy, the platelet count response is often oscillatory for many patients, with very dangerous lows and highs, making it difficult to maintain steady platelet count. In addition, romiplostim is expensive and its administration is accompanied by long delays before its effect (which depends nonlinearly on platelet count) can be observed.

Platelet Count Control
The specific objective of this study may be stated as follows: For an actual clinical patient, determine "optimum" dose profile required to maintain the ITP patient's platelet count at 70×10^9 cells/L, subject to the following constraints:

- Treatment is limited to pulses (injections) of fixed magnitudes at discrete points in time;
- Current practice is limited to weekly or biweekly treatments

The approach is to develop and validate a custom pharmacokinetic-pharmacodynamic (PK-PD) model for the patient in question, analyze the model for insight, and use it to develop/evaluate control schemes. See Ref 3 for details, which show that:

1. This particular patient has platelets with average lifespans less than half those of healthy subjects; and
2. A model predicted dose response curve shown in Fig 5 below:

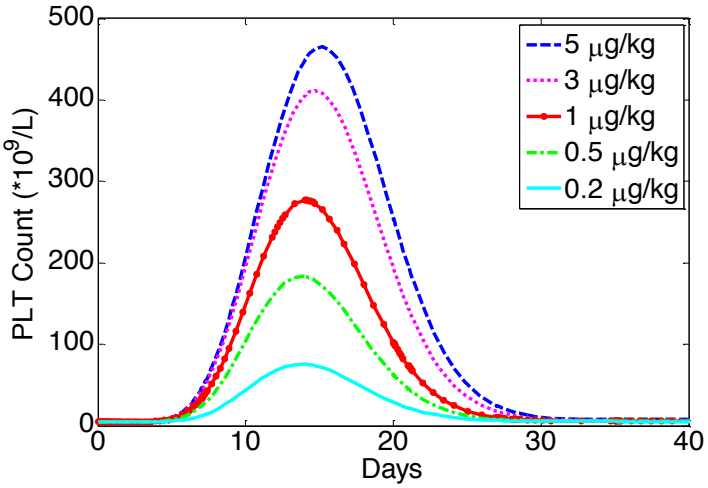

Fig 5: *Predicted dose response curve from an initial low platelet count, for the patient in question: Legend indicates various doses of Romiplostim.*

The following control schemes were studied in simulation using the PK/PD model to represent the patient dynamics:

- Fixed dose, Open-Loop (current practice)
- Optimally-Tuned PI Control
- "Variable Dose" Optimal Open-Loop Control

with the following results. Fig 6 shows the results of fixed doses (2 μg/kg; 1 μg/kg, and 0.5 μg/kg) applied weekly or bi-weekly. The platelet count is oscillatory and the objective of a steady count of 70×10^9 cells/L (the red line) has not been attained.

Fig 7 shows the results for an optimally tuned PI controller strategy. In this case, the controller parameters K_p and K_I are determined, along with u(k=0), using *fminsearch* in Matlab to minimize:

$$\sum_{k=0}^{n_k}(y_k - y^*)^2$$

where y* is the desired set-point. We observe that the bi-weekly measurements are not representative of true dynamics as a result of aliasing due to sampling.

Rather than use a PI controller, if the implemented dose, *u(k)*, is determined instead by optimal control, where the decision variable determined by minimizing the same sum-of-squared deviations shown above is *u(k)*, directly, and not the controller parameters, the results are shown in Fig 8. Not surprisingly, the responses are similar to those in Fig 7.

As a result of these simulations, we are able to make the following observations:

- With carefully designed controllers, it is possible to stabilize platelet count, but only with weekly injections;
- Bi-weekly injections still produced oscillations, regardless of the controller type.

The latter observation prompted a closer look at the intrinsic characteristics of the patient's response to romiplostim as indicated in Fig 9.

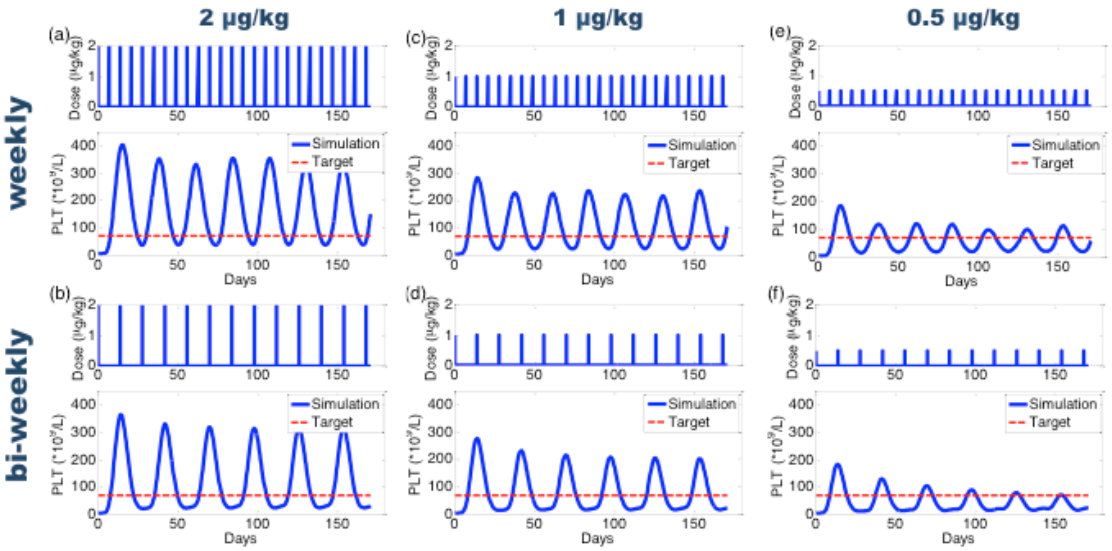

Fig 6: *Simulation results of platelet count response to a fixed-dose open loop control strategy for weekly and bi-weekly treatemtns of 2 µg/kg; 1 µg/kg, and 0.5 µg/kg*

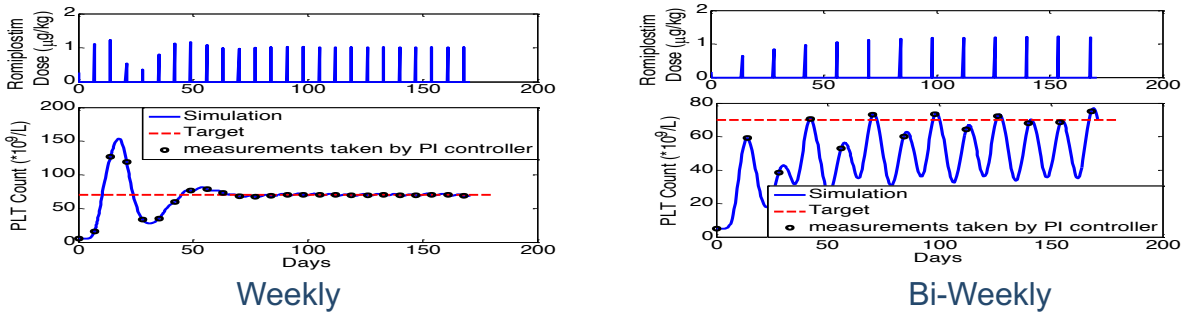

Fig 7: *Simulation results of platelet count response under an optimally-tuned PI control strategy*

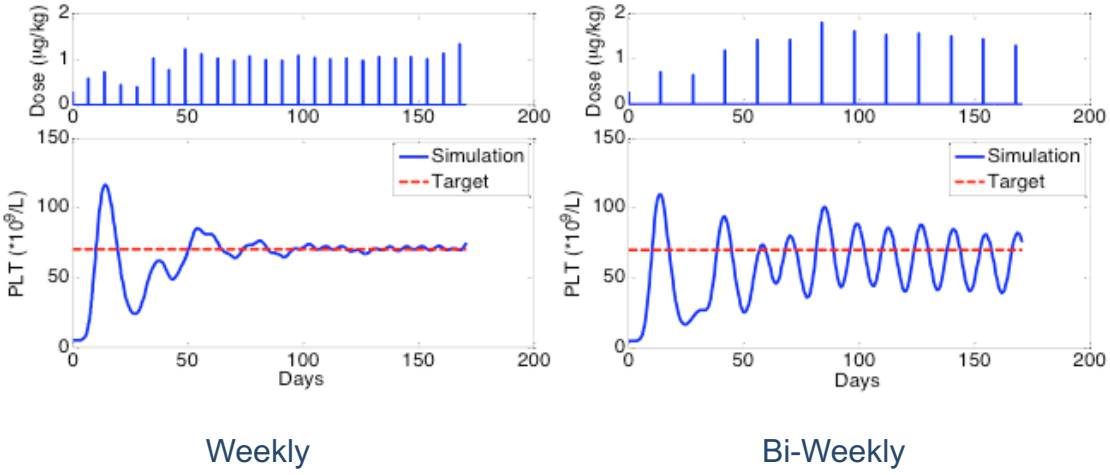

Fig 8: *Simulation results of platelet count response under variable-dose optimal control.*

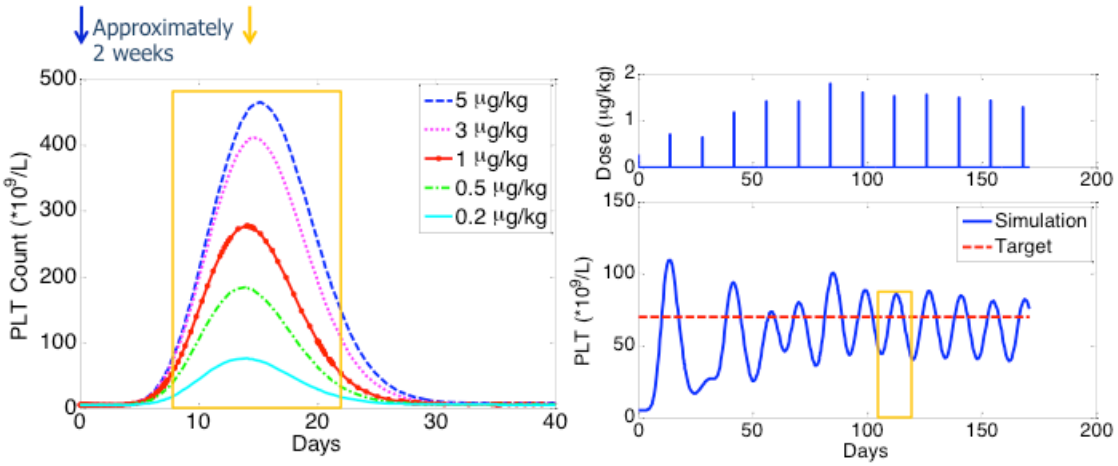

Fig 9: *Basic dose-response curves for Romiplostim and bi-weekly platelet count response under variable-dose optimal control of Fig 8).*

From this figure, we may now observe why it will be virtually impossible to eliminate oscillations in bi-weekly injections. The pharmacology of romiplostim is such that from the application of the injection to the peak platelet count is approximately 2 weeks, for this specific patient. And since the observed platelet response is nothing but a "nonlinear convolution" of this theoretical dose response "basis function", because the 2-week implementation period coincides almost precisely with the natural period of the dose response, the steady state response will be expected to be a repetition of the dose response curve on the left over and over again. Hence, the oscillations are not due to an overactive controller; rather, they are due to the natural period of the response to romiplotism coinciding with the treatment period. Any treatment period that is less than two seeks should produce better results, as Figs 7 and 8 have shown with weekly treatments. We are thus able to make the following recommendations:

- Current practice did not work well for the candidate in question because of the natural pharmacodynamics of romiplostim in this patient;
- Constant dose injections (regardless of actual platelet count), weekly or bi-weekly, can never produce stable platelet count
- However, stable platelet control possible with variable dose, measurement-based, weekly discrete treatment, even when determined via PI control.

4. CONCLUSIONS

Because control is a central and inevitable feature of biological systems, it is not surprising that "Control Engineering" has a lot to offer any systematic study of biological control systems, especially with regard to diseases and their treatment. In such an endeavor, a control engineering perspective offers the following advantages:

- It provides a means for efficient modeling, particularly making the resulting models analytically tractable while retaining high fidelity;
- It facilitates diagnosis and prevents the potential problem of confounding the root causes of diseases, especially those that are caused by the malfunction of a control system component.
- Finally, it provides a rational basis for engineered treatment.