Computers and Chemical Engineering 71 (2014) 665–671

Contents lists available at ScienceDirect

Computers and Chemical Engineering

journal homepage: www.elsevier.com/locate/compchemeng

A chemical engineer's perspective on health and disease

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ARTICLE INFO

Article history:
Received 12 July 2014
Received in revised form 2 September 2014
Accepted 9 September 2014
Available online 19 September 2014

Keywords:
Health
Disease
Homeostasis
Systems engineering

ABSTRACT

Chemical process systems engineering considers complex supply chains which are coupled networks of dynamically interacting systems. The quest to optimize the supply chain while meeting robustness and flexibility constraints in the face of ever changing environments necessitated the development of theoretical and computational tools for the analysis, synthesis and design of such complex engineered architectures. However, it was realized early on that optimality is a complex characteristic required to achieve proper balance between multiple, often competing, and objectives. As we begin to unravel life's intricate complexities, we realize that that living systems share similar structural and dynamic characteristics; hence much can be learned about biological complexity from engineered systems. In this article, we draw analogies between concepts in process systems engineering and conceptual models of health and disease; establish connections between these concepts and physiologic modelling; and describe how these mirror onto the physiological counterparts of engineered systems.

1. Man, the industrial palace and the concept of homeostasis

Early in the 19th century German gynaecologist and world-renowned popular science writer *Fritz Kahn* presented his rendition of a human, and its fundamental physiological functions, in the form of an *industriepalast* (*industrial palace*), something chemical engineers, would like to think of as a chemical plant (Debschitz et al., 2009). Such renditions, apart from being artistically enticing, conveyed a simple, yet powerful message: the human body is a collection of networked processing units (reactors), assembled in the form of a (chemical) plant, which exchange mass and energy, among themselves and with the environment, so as to maintain proper function by appropriate physico-chemical transformations of mass while producing/consuming energy. We could envision a variety, and nested hierarchy, of mass and energy balances as material is transformed for be purpose of maintaining proper plant function, i.e., survival. One could easily expand, and elaborate more on, this analogy but for the sake of simplicity we will skip this discussion, as it is most probably evident. The idea of "mapping" a physiological system onto a "connected network" is, to a great extent what eventually drove the development of the basic principles of *physiologically-based pharmacokinetic models* (PBPK) (Sung et al., 2014).

Around the same time period, a pioneer in human physiology, *Walter B. Cannon*, was beginning to lay the foundations, based on the earlier work of French physiologist *Claude Bernard*, of the concept of *homeostasis* (Cannon, 1929; Gross, 1998), a word of Greek origin: ὅμοιος *hómoios*, similar, and στασις, *stásis*, standing still, nowadays defined as the "*relatively stable condition of extracellular fluids that results from regulatory systems actions* (Windmaier et al., 2004)". The argument was that humans are composed of an intricate web of living parts which exist in an internal environment which surrounds them. The fixity, or constancy, of this *milieu intérieur* (internal environment referring to the extra-cellular fluids which provide stability to the organs) becomes therefore the condition of free an independent life, and therefore physiological functions, in the face of the ever changing environment in which living organisms exist, aim at preserving the constancy of conditions of life and the constancy of the internal environment.

Thus, as early as 1929 Walter Cannon was establishing the concept of homeostasis in relation to the surrounding environment by stating that "*The highly developed living being is an open system having many relations to its surroundings – in the respiratory and alimentary tracts and through surface receptors, neuromuscular organs and bony levers. Changes in the surroundings excite reactions in this*

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http://dx.doi.org/10.1016/j.compchemeng.2014.09.007
0098-1354/

system, or affect it directly, so that internal disturbances of the system are produced. Such disturbances are normally kept within narrow limits, because automatic adjustments within the system are brought into action, and thereby oscillations are prevented and the internal conditions are held fairly constant." Therefore the building blocks of Kahn's rendition now become active, living, modules of a network of interacting elements, linked through feed-forward and feed-back loops, which act in tandem to maintain the "constancy" of the *milieu intérieur* and do not simply process information in a forward and linear manner. Cannon therefore postulated that it is the regulation of homeostasis which endows living organisms with the ability to evolve, adapt and survive.

It is rather intriguing to realize that almost 100 years ago, physiologists were using terms which are quite common in chemical engineering parlance, such as: open system, disturbance, automatic adjustment (reflecting of course control mechanisms) and constancy (reflecting steady state) to imply the existence of control architectures which dissipate disturbances so as to maintain normal "plant" operation. In a very insightful manner Cannon proceeded to postulate six hypotheses dictating how physiological factors interact so as to maintain homeostasis, what Chemical Engineers may refer to as the stability of the steady state, in a way which brings in mind interesting analogies:

(i) *Existence of internal anticipatory control mechanisms*: Cannon hypothesized that living organisms, being in essence open systems, are continuously subjected to ever changing environmental conditions. Therefore, maintenance of homeostasis is most likely the evidence of the existence "agencies" either acting or ready to act. In other words he hypothesized the existence of physiological model predictive controllers which evaluate state variables and act upon their (expected) deviations.

(ii) *Negative feedback control mechanisms*: Cannon hypothesized that any variation which would results in deviation from homeostasis is counter balanced by "increased effectiveness" (sic) of the factors that would counter the change. In essence, Cannon hypothesized the existence of prototypical, and optimized, negative feedback control structures. It is noteworthy that Norbert Wiener was significantly influenced by Cannon's work on homeostasis, and the search for the reasons for it, while formalizing his cybernetics theories, and more specifically the origins and implications of negative feedback (Cooper, 2008).

(iii) *Specialized action of control mechanisms*: Cannon argued the directionality in a factor's action is uniquely defined and the same factor cannot, simultaneously, increase and decrease a response. One, however, in light of non-linear responses could possibly question this assertion.

(iv) *Distributed control*: Cannon hypothesized that homeostatic agents may be antagonistic in one part of the body while cooperating in another. His assertion implies the existence of a distributed network of sensors with a set of actuators characterized by spatially distributed interactions.

(v) *Network structure*: Cannon hypothesized the existence of a regulating system which is composed of a number of proximal and distal factors which can be either sequentially or simultaneously activated. In essence, Canon hypothesized the existence of a *supe-structure* which responds and adapts to dynamics changes. Finally,

(vi) *For any action there is a reaction*: Cannon hypothesized that for every factor which is expected to move away from the homeostatic state a control mechanisms for that, or some other, factor exists which will impose an opposite effect. It is important to realize the use of the term *control mechanism* by Cannon himself (Cannon, 1929).

The importance of Bernard's original hypothesis, later refined by Cannon, was the realization that "*(. . .) the fixity of the milieu supposes a perfection of the organism such that the external variations are at each instant compensated for and equilibrated. . .. All of the vital mechanisms however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment. . . The stability of the internal environment is the condition for the free and independent life*". More than eighty years later these fundamental concepts are still being studied and analyzed as we are now endowed with the ability to better assess what the "factors" and "controls" might be at a cellular and molecular level. Interestingly enough the language that is now used has evolved and we talk about the fact that the "mechanisms for maintaining this stability [of the milieu intérieur] require sensors to recognize discrepancies between the sensed and set of acceptable values and require effectors that reduce those discrepancies – i.e., negative feedback systems (Goldstein and Kopin, 2007)". If health expresses a harmonious integration of molecules, cell, tissues and organs; disease (and stress in general) corresponds to a displacement compensated for and corrected by activation and combination of compensatory feedback mechanisms.

This "control theoretic discussion" would not be complete without a recognition of the emerging model of *allostasis* (from the Greek word αλλοζ, meaning different) as an alternative to *homeostasis*. Allostasis (Sterling, 2004) takes a broader view which combines the feedback responses with adaptability thus constraining regulation to be efficient in the context of minimizing cost to the body (Brame and Singer, 2010). Therefore, the central hypothesis of allostasis is that responses promote adaptation to a changing environment, thus further elaborating on the concept of trade-offs in the context of multiple biological objectives.

The purpose of this paper is not to provide a summary of the seminal contributions the Process Systems Engineering (PSE) in particular and the Chemical Engineering communities in general have made. These are too many and powerful, including but not limited of course to great books by Stephanopoulos, Palsson, Westerhoff (Alberhina and Westerhoff, 2005; Cassman et al., 2007; Palsson, 2011; Rigoutsos and Stephanopoulos, 2007) to name just a few. This review, is rather focused on exploring how fundamental concepts of Process Systems Engineering can be invoked and explored so as to establish bridges between Chemical Engineering and Physiology. Therefore, this review is not about the process of building mathematical models and/or executing complex calculations per se, but rather about mapping physiology concepts onto PSE principles and the likely opportunities that exist for mutually benefiting interactions between clinicians and process systems engineers.

2. *Industriepalast* and the chemical plant

The use of mathematical models is definitely nothing new in physiology (Keener and Sneyd, 2009). However, it is only recently that we begin to realize that the theoretical underpinnings of the principle of with the analysis, design, and control of complex engineered systems (complex supply chains) can serve as a general foundation for the analysis of physiological systems at the organism level ("Systems Engineering to Improve Traumatic Brain Injury Care in the Military Health System Workshop Summary," 2009). As a result, physicians are increasingly becoming more appreciative of the emerging opportunities (Jopling and Buchman, 2012). Since the aim of any medical intervention is to rationally improve diagnosis and patient care, clinicians are already appreciating the advantages