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A Chemical Engineer's Perspective on Health and Disease

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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, 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 modeling; and describe how these mirror onto the physiological counterparts of engineered systems.

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 the purpose of maintaining proper plant

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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: ὁμοιος, *hómoios*, similar, and στάσις, *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 extracellular 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 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 hypothesised 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 analysed 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 & 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 αλλος, 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 & 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 & Westerhoff, 2005; Cassman et al, 2007; Palsson, 2011; Rigoutsos & 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.

Industriepalast and the chemical plant

The use of mathematical models is definitely nothing new in physiology (Keener & 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 & Buchman, 2012). Since the aim of any medical intervention is to rationally improve diagnosis and patient care, clinicians are already appreciating the advantages of *model-based* approaches delineating the active role of specific components within a biological system. Such approaches are now common place in (chemical) engineering and serve a critical role in developing novel process, improve efficiency and understand, and explore, trade-offs. The point of this review is precisely to indicate that the concepts and ideas explored and mapped onto physiology are in fact among the defining elements of PSE.

In this context we focus on four fundamental principles associated with the design, analysis and operation of complex supply chains and attempt to demonstrate how these emerge also in our quest to better understand the dynamic principles characterizing health and disease, as

manifestation of emerging process of complex networks interacting with their environment. It should be noted that we have purposely chosen to cite primarily what would appear to be *old(er)* process systems engineering publications.

Flexibility, trade-offs and design through evolution

Evolution has endowed living organisms with adaptive mechanisms to maintain constancy of the *milieu intérieur* in the face of a changing external environment. Therefore physiological parameters are expected to remain within “reasonable limits” and deviation from these limits would imply either a response compensating from a deviation from the normal range of values, or a need to activate a compensatory response (Buchman, 1996). Thus the implication of Cannon's view of homeostasis was that if conditioning the *milieu intérieur* within its reasonable limits corresponds to the normal operation, deviations from that (steady) state would reveal a disease. The interpretation of these concepts was rather qualitative in nature as not exact measures of the concept of stability were available. However, much like scientific advances, whether algorithmic, technological or computational, enabled the more accurate characterization (spatial and temporal) of chemical processes and plants, similar developments enabled physicians to improve their quantification of “deviation from normal” (Rixen et al., 1995).

In an interesting parallel, Grossmann and Morari in their 1983 classic monograph (I.E. Grossmann & Morari, 1983) use the general term *operability* to describe “*the ability of the (chemical) plant to perform satisfactorily under conditions different from the nominal design conditions*”. Implied in this definition, much like when discussing homeostasis, is the fact the internal and external environments are expected to undergo variations which should not lead to significant deviations. When, further, discussing the objectives of a chemical plant, the following operability objectives are identified:

- i. Feasibility of *steady states* for a range of different feed conditions (i.e., external disturbances) and plant parameter variations (i.e., *milieu interne*)
- ii. Fast and smooth changeover and *recovery* from process disturbances
- iii. Safe and reliable operation despite equipment failures, and
- iv. Easy start-up and shut-down

Grossmann and Morari, proceed to further clarify the characteristics of the objectives but noting that the first two are associated with “normal” operation and the ability of the plant (or the host) to gracefully accommodate “reasonable” deviations from normal (homeostatic) operation. The last two, really concern however, what one could term “abnormal” operation resulting from equipment (organ) failure and the activation of compensatory mechanisms. The homeostatic (normal or steady state) operability characteristics are also described by terms such as *flexibility* and *resiliency*, indicating the ability to recover following a disturbance (stress). A straightforward way to increase flexibility and resiliency, in engineering parlance, is through *overdesign*. This approach could represent a viable solution in general, had it not been accompanied with a number of drawbacks (such as lost efficiency and/or increased cost to name a few) which highlight the need to balancing appropriate *trade-offs* when designing an operable plant. The dynamic adjustment of operating

procedures, in the chemical process industries, led to the integration of design and control architectures (Fisher et al., 1988a) which aim at increasing process operability (Fisher et al., 1988b) at the minimum cost penalty, in other words trying to strike a balance, i.e., *trade-off*, between flexibility and resource utilization. Over-design is clearly a poor man's solution to this dilemma and early on chemical engineers realized the need for rational overdesign (I. E. Grossmann & Sargent, 1978). As such, approaches were proposed to determine the design that maximizes an expected revenue or profit while simultaneously accounting for (design) feasibility and (economic) optimality (Pistikopoulos & Ierapetritou, 1995).

A trade-off is broadly defined as the situation when some property, or characteristic, is lost in favour of another. Trade-offs are abundant in physiology, likely driven by evolutionary principles dictating that changes in physiology that would improve a certain response will likely lead to decreased fitness due to subsequent effects. Often, much like in PSE systems, this loss in overall fitness is the result of limited resources and/or capacity constraints. Prominent among these types of trade-off is the so-called *reproduction-survival* trade-off expensing the fact that increased reproduction comes at the expense of reduced life span (Wingfield & Sapolsky, 2003). Another classic example of trade-offs associated with the inflammatory response balancing the costs and benefits of the defence (Okin & Medzhitov, 2012). To a great extent these trade-offs defined the essential principles of evolutionary medicine which attempts to elucidate how such trade-off balances evolved during the course of time and how the loss of this balance leads to disease susceptibility (Stearns, 2012). The idea of *trade-offs* is a pervasive characteristic defining biological systems (Kitano, 2010). In an elegant analysis John Doyle and co-workers (Chandra et al., 2011) demonstrate how glycolytic oscillations express an equivalent to the chemical plant's trade-off, expressing the interplay between *robustness* and *efficiency*, effectively expressing resource utilization and fragility. Earlier, and in the context of adaptive immunity, Segel and co-workers (L. A. Segel & R. L. Bar-Or, 1999) had expressed the need for balancing the trade-offs between the beneficial and detrimental effects of noxious chemicals produced to eliminate an invading pathogen. Although not apparent, this trade-off also expressed a balance between robustness and efficiency in terms of resource utilization. Irrespective of the exact nature of the host response to stress, these trade-offs effectively express the relationship between long-term cost and short-term benefits and “*was not designed by an engineer but shaped by a process of tiny tinkering changes* (i.e., evolution)” (Nesse et al., 2007). However, both are concepts pervasive in the way chemical engineers have approached process synthesis systematically reviewed in (Nishida et al., 1981) but really put forth but the pioneering work of Rudd dating back to the classic text book on “Strategy of Process Engineering” (Rudd & Watson, 1968). At these early stages of formalizing the problem of process synthesis, chemical engineers quickly realized two important aspects: (i) trade-offs (often termed “multiple objectives”) needed to be reconciled and accounted thus necessitating the integration of (process) control during the early design stages; and (ii) even though chemical plants are not evolved by nature, the procedural idea of invoking “evolution” as a means of generating “permissible structural changes” progressing the engineering construct towards its “optimum” were early on realized and eventually pursued via various computational means (Androulakis & Venkatasubramanian, 1991; Nishida et al., 1981).

Operational trade-offs are often manifestations of feedback control mechanisms which sense deviations from homeostasis and activate appropriate functions. This notional picture, which characterizes control architectures in a chemical plant (Fisher et al., 1988c) was equivalent the mental picture Cannon had created in describing his homeostatic control mechanisms which expressed *disease* as a deviation from steady state, during external perturbations, which need to be recognized and compensated for by restoring forces. Interestingly enough, surgical textbooks describe regulation of homeostasis through mechanisms which require: a signal detector, a processor and an effector organ controlled through “*negative feedback servo-mechanisms*”(Buchman, 1996).

Disease as abnormal event – Diagnosis as abnormal event detection

Timely detection, diagnosis, and correction of abnormal deviations from the steady state operation of a chemical plant is a critical task, particularly, if catastrophic deviations can be foreseen while the plant is still normally operating. The overall process of *Abnormal Event Management* (AEM) has been the focal point of active research in the chemical engineering community. It involves a number of critical steps (Venkatasubramanian, Rengaswamy, Yin, et al., 2003), namely:

- i. Detection on an abnormal event,
- ii. Identification of its causal origins,
- iii. Selection of appropriate control decision, and
- iv. Implementation of said decision.

Notionally, two major approaches have been proposed for addressing this fundamentally ill-posed inverse problem: *Model based* (quantitative and/or qualitative) which presume the existence of logical links between state, observable and control variables, and *knowledge based* methods, which do presume causal relations, but rather attempt to infer them based on prior historical process data (Rich & Venkatasubramanian, 1987; Venkatasubramanian, Rengaswamy, & Kavuri, 2003; Venkatasubramanian, Rengaswamy, Kavuri, et al., 2003; Venkatasubramanian, Rengaswamy, Yin, et al., 2003).

While diagnosis of a disease may not have been described using terms such as *abnormal event* and the corresponding treatment may not be considered an *event management*, the reality is that physicians recognize illness by observing changes, or lack of changes, in vital sign patterns (Buchman, 2010). However, the problem with *bedside monitoring* is that observing the current state of the patient is equivalent to recording of points a high-dimensional space attainable from a myriad of initial conditions (past history). Furthermore, the critical concerns from an intervention point of view are (a) where will the patient end up in the future; and (b) what kind of interventions would restore the patient's condition or avoid undesirable excursions. In an interesting analogue to AEM, not only the problem definition is equivalent, but also the approaches taken are similar. Emerging methodologies in the clinical setting involve either an attempt to define, and solve, the inverse problem using *model based* approaches (Zenker et al., 2007) or attempt to reconcile the patient's prior history and identify trends on historical data, i.e. *knowledge based* (Cohen et al., 2010). The importance of steps (ii) and (iii) just described really define the essence of a physician's

dilemma, which aims at distinguishing processes (causal origin) from outcomes (event manifestation) (Buchman, 2009). Most recently, we demonstrated how combining the concepts of stability with network reconstruction would likely point towards the direction of predicting imminent events, i.e, health deterioration, in a model of systemic inflammation (Scheff et al., 2013).

Distributed/decentralized control systems and physiological control mechanisms

Driven by increased complexity, tighter operational constraints and technological advances; the control structures of modern chemical plants, deployed to ensure flexibility and operability, are becoming more and more elaborate and adopt plant-wide distributed characteristics. These have presented both opportunities and challenges (Jillson & Erik Ydstie, 2007). At an even higher level, the process community realized the need for integration beyond the plant, thus introducing the concept of the “*smart plant*” (Christofides et al., 2007), where the process, the plant and the corporation all participate in establishing operating procedures which properly balance the required trade-offs. Therefore, disturbances (of any kind including supply and demand, machine breakdown, policy decisions etc) in an integrated supply chain are detected, and handled in a, both local as well as integrated manner which involves processes, plants and corporate offices (Christofides et al., 2007). The inherently distributed nature of the observations introduced new requirements necessitating handling of asynchronous information flow (Androulakis & Reklaitis, 1999; Xu & Bao, 2011) which, in complex supply chains, implies the lack of central (master) controller, and by extension lack of a unique guiding goal (or objective).

In a very analogous manner, a living organism deals with threats to its homeostasis via means of a prototypical autonomous decentralized system (Segel, 1997; L. Segel & R. L. Bar-Or, 1999). A number of interesting questions emerge related to how the host senses a local deviation from homeostasis, how the host measures performance towards restoring homeostasis, what objective is used, how the virulence of response is controlled, which of the various effectors are activated to name a few. When an attack on the host is encountered, a complex inflammatory response is initiated with localized (humoral) responses aiming at modulating the inflammatory response, most notably through anti-inflammatory cytokines and hormones (Nathan, 2002) as well as fast acting, centrally controlled neural-based mechanisms (Tracey, 2002). The latter, it has been argued, exhibit a formidable example of evolutionary engineering since humoral responses are slow, distributed, non-integrated and depend on local gradients. However, neural mechanisms (so-called cholinergic anti-inflammatory pathways) are fast, integrated and localized (Tracey, 2007). The possibility of a variety of levels of control have led us to hypothesize that loss of stability across any of these distributed levels (so-called “tipping points”) lead to failure of containment failure and through the multiple feedback loops propagate the response through the periphery and centrally, thus host deterioration becomes a diffusible ailment (Dick et al., 2012).

Variability: Undesired perturbations or optimal strategies?

We now realize that the deeper meaning of *constancy* of the internal environment is not one which implies invariability, as one may have considered it to be in the context of Kahn's equivalent chemical plant, but rather implies specific dynamic characteristics, manifesting

themselves in the form of “homeostatic rhythms” rather than a “homeostatic flat line” (Achoff, 1981). Most likely the rhythmicity which is best recognized refers to circadian, or diurnal, changes (biological processes which exhibit inherent oscillations of approximately 24 periods) whose role has been repeatedly recognized as a key contributing factor to, as well as manifestation of, disease (Chan et al., 2012). Stress and disease are characterized by significant loss of internal variability which could act as a major predisposing factor as well as a sign of a compromised host (Lowry, 2009). Among the most catastrophic failures of a living organism, and often end stage condition, is likely represented by the what is known as Multiple Organs Dysfunction Syndrome (MODS) defined as “*the development of potentially reversible physiologic derangement involving two or more organ systems not involved in the disorder that resulted in ICU admission, and arising in the wake of a potentially life-threatening physiologic insult* (Marshall, 2001)”. Thus the presence of altered organ function in the patient is such that homeostasis cannot be maintained without external support. Interestingly, organ dysfunction, characterized through associated biological impairment, need not necessarily reflect histology abnormalities and damage, posing an intriguing question as to its cause (Brealey et al., 2004). As such, the *milieu intérieur*, is hypothesized to play a more subtle role than simply being the environment within which the building blocks (organs) reside. In a series of theoretical papers, Chauvet and co-workers (Chauvet, 1993a, 1993b, 1993c) argue that the increased association among function biological groups, thought communication via the fluids in the extra cellular internal environment, enables increases in the *domain of stability* of a biological system. Expanding further on this idea, it was subsequently hypothesized that MODS is likely the result of the disruption of inter-organ communication which results in uncoupling and isolation, further progressing in ultimately irreversible damage (Godin & Buchman, 1996). Further, theoretical analyses demonstrated that in fact such long range connectivity would improve recovery (Hubler & Buchman, 2008). It is hypothesized that the changes in the dynamic characteristics of the signals, reflective of the internal environment and which establish communication among organs that either induce host dysfunction, or are themselves manifestations of host dysfunction. Thus, illness, either organ-specific or systemic, might result in loss of signal variability which in turn may further compromise adaptability (Lowry & Calvano, 2008). This is a profound result in that it demonstrated theoretically, that the dynamic characteristics of the communication channels, that is the characteristics of the *milieu intérieur*, play a central role in maintaining overall network stability. Thus it has been argued that the physiologic and biochemical homeostatic rhythmicity induces a temporal predictability of endogenous controls which is “*presumed to confer acute adaptive advantages that likely extend to modulating systemic illness and solid organ function*” (Lowry, 2009).

Much is known about the origins and role of biological rhythms as the “*time-keeping*” machinery maintaining coordination between living organisms and their geophysical time (Kramer & Mellow, 2013). These rhythmic characteristics (phase and amplitude) play a central role enabling the host to respond to “*predictable*” changes (light to dark for example) by maintaining coordination among physiological processes (Edery, 2000; Sterling, 2012). In mammalian organisms the circadian machinery is organized as a hierarchical, interconnected, network of clocks, with the brain and liver playing preeminent roles

(Albrecht, 2012). The clocks are distributed across all cells and need to be synchronized within and across tissues and organs. The master, or central, clock in the suprachiasmatic nuclei (SCN) is mainly linked to light/dark cycle, and synchronizes the network of clocks by controlling timing of feeding and activity cycles (Cardone et al., 2005; Cassone, 1990). Rhythmic hormonal and metabolic signaling between organs establishes proper phase relations among the various clocks and these rhythmic signals play a major role in immune (Lee & Edery, 2008; Paladino et al., 2010; Silver et al., 2012) and metabolic functions (Feillet et al., 2006) conferring adaptive advantages by means of anticipatory control mechanisms (Edery, 2000). Although suppression of biological rhythms is an energy preserving mechanism beneficial under stress (Clark et al., 2008; Logan & Sarkar, 2012), the effects of a long term suppression of rhythms are pathologic (Chan et al., 2012; O'Callaghan et al., 2012; Preuss et al., 2008), correlate with severity of outcome (Gazendam et al., 2013) and hamper recovery (Bornstein et al., 1998; Cao et al., 2001; Drew E. Carlson & William C. Chiu, 2008; D. E. Carlson & W. C. Chiu, 2008; Filipinski & Levi, 2009; Fu et al., 2002). We recently demonstrated that internal rhythmic does manifest itself at the systemic level, while its loss is an indication of stress moving the host away from homeostasis while further emphasizing the coordinating and entraining role of rhythmic oscillations (Mavroudis et al., 2012; Scheff et al., 2011).

Unlike physiological systems, it would appear that most of our efforts in operating chemical plants have focused on making certain that *external variability* is minimized. It would seem natural to assume that control structures and mechanisms are in place to ascertain that fluctuations are absorbed. However, is it indeed so? If the *industriepalast* is now considered to be an integrated system which operates under the influences of a periodically varying external environment in order to improve the stability and operability of its homeostasis, it is worth noting that the idea of operating chemical reactors under time varying conditions, in order to explore intrinsic nonlinearities, has been argued for a long time. As early as 1966 Douglas and Rippin had realized that the “[...] *usual chemical engineering assumption of designing to operate at a steady does not always give the best results*” (Douglas & Rippin, 1966). Ray (Ray, 1968) recognized the implications of periodically varying monomer concentration in produce less disperse molecular weight distributions for the same average polymer chain length, whereas Renken (Renken, 1972) discussed theoretical models of increased selectivity in chemical reactors through periodic operation. Bailey (Bailey, 1974) nicely summarized these early theoretical results exploring the hypothesis that (cyclic) fluctuations could in fact be considered desirable operating policy and not necessarily disturbances which ought to be eliminated through appropriate control actions. At the heart of all this early work was the fact that nonlinearities induce responses which may be benefited by the presence of internal dynamics. In catalytic reactor system, changing operating conditions is hardly something new in the chemical engineering community (Silveston et al., 1995). By and large in these situations the periodicity in the operations is a means to recover from naturally occurring events which damage the catalyst's activity. Interestingly, an optimization-based study by chemical engineers recently indicated that the intrinsic dynamic of enzyme catalysed reactions can be manipulated by means of imposing optimal, oscillatory, profiles in enzyme activity likely balancing growth *trade-offs* (Sowa et al., 2014).

It is therefore rather clear that the design and analysis principles and tools that the systems (and reaction) engineering communities can provide substantial insights towards the understanding of the design principle underlying biologically observed oscillatory dynamics.

Concluding Remarks

Tim Buchman prefaced his 2002 insightful *Nature* review (Buchman, 2002) by pointing out two things: (1) if good health reflects a dynamically stable and harmonic integration of molecules, cell, tissues and organs then (2) disease indicates stability displacement which is compensated for and corrected by appropriate activation and combination of feedback mechanisms through interconnected networks. He then predicts that while now physicians “diagnose” disease by evaluating whether the networks are correct, in the future physicians will intervene to make sure that the networks are correct. Both questions are driven, to a great extent, by physicians’ quest for “... *encouraging* [physicians] *to make the subtle but important distinction between* [clinical] *outcomes and* [biological] *processes*” (Buchman, 2009), thus moving biological information to the bed-side in order to understand and predict systemic behaviours seen in clinical settings (McDunn et al., 2008).

Physicians and engineers share much in common (Heller et al., 2008). Both are attempting to propose technical solutions to problems. In a physician's case, the problems are clinical. A critical goal of translational research is to convert novel insights from basic science into clinically relevant actions related to disease prevention and diagnosis, eventually enabling physicians to identify and evaluate treatment strategies. Integrated initiatives are identified as valuable in uncovering the mechanisms underpinning the progression of human diseases. The advent of high-throughput technologies has enabled the generation of massive amounts of biological data at an unprecedented rate, facilitating a dramatic increase in the degree of quantification applied to modern biological research (Beard et al., 2005). Despite the explosion of such high-dimensional datasets, the complex, nonlinear organization and regulation of biological systems too often defy intuitive predictions, and require the development of computational models in order to gain an understanding of the systems' functions. Central to this integrative systems biology approach is the identification of the critical components and interactions that give rise to the emergent host response. Such computational models are not, however, intrinsically useful in a clinical context, and therefore they must be structured in a manner that allows them to both leverage clinically obtainable data and ultimately produce clinically useful predictions (Vodovotz, 2010; Vodovotz et al., 2007). Systems-based translational research considers physiological conditions as dynamically evolving, networked systems with clearly identified boundaries and rules that define their response, providing a systematic framework for translating biological information into organism-level insights (An et al., 2008; Foteinou et al., 2009; McGuire et al., 2011; Parker & Clermont, 2010; Vodovotz, 2010).

What was therefore attempted in this perspective article was to draw analogies between fundamental concepts pervasive in chemical engineering theory and practice and equivalent concepts in physiology, as they have evolved, for addressing those problems. We opted to establish interesting, and possibly intriguing, connections between fundamental concepts in the analysis, synthesis, design, control and operation of complex chemical plants (and

supply chains) and their physiological counterpart and have identified how these concepts mirror themselves onto critical aspects characterizing Dr. Kahn's *industriepalast*.

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- we draw analogies between concepts in process systems engineering and conceptual models of health and disease
- establish connections between these concepts and physiologic modeling; and
- describe how these mirror onto the physiological counterparts of engineered systems
- focus is on: Flexibility and trade-offs, decentralized decision making; fault detection; and variability