

The Need for Systems Tools in the Practice of Clinical Medicine

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ABSTRACT

Humanity is currently facing an unprecedented chronic disease burden. Healthcare needs have significantly shifted from treating acute to treating chronic conditions. Chronic diseases tend to involve multiple factors with complex interactions between them evidenced by the continually growing medical knowledge base. The health profession requires the ability to manage this rapidly deepening knowledge base to assimilate the lessons from research and clinical care experience by systematically capturing, assessing, and translating it into the highest level of reliable care. A more systems approach to practicing medicine exists and is referred to as functional medicine. It takes into account the many subsystems in the human body and their many interactions. Although the science behind treating the patient as a system exists, the application of systems tools and techniques have not been utilized. It is only natural to begin to formalize the systems thinking using the established tools from the systems engineering field. Specifically, this paper presents the need for systems tools in the practice of clinical medicine and includes an example application of model-based systems engineering to clinical medicine. © 2017 The Authors Systems Engineering Published by Wiley Periodicals, Inc. Syst Eng 00: 1–18, 2017

Key words: engineering systems; model-based systems engineering; managing knowledge complexity; improving health outcomes

1. INTRODUCTION

Humanity is currently facing an unprecedented disease burden. In the first time in history, our children's generations are expected to lead shorter life spans than our own [Olshansky et al., 2005]. Although science and technology have allowed for significant advancements in health treatments, these treatments tend to be either (1) curing, in many cases, of acute conditions or (2) managing, at best, in cases of chronic conditions.

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Healthcare needs have significantly shifted from treating acute conditions to treating chronic conditions. Given that 78% of total healthcare costs in the United States are due to chronic disease [Anderson and Horvath, 2004], clinical medicine needs to evolve and shift to specifically address the growing chronic disease epidemic. This is a significant cost given that the U.S. healthcare expenditure reached \$2.9 trillion in 2013 [Service, 2013]. Noncommunicable diseases (NCDs) are the leading causes of death globally, killing more people each year than all other causes combined [Alwan, 2010]. In 2000, approximately 125 million Americans (45% of the population) had chronic conditions and 61 million (21% of the population) had multiple chronic conditions [Anderson and Horvath, 2004]. In 2005, chronic diseases were estimated to cause more than 35 million (60% of all deaths) and more than 80% of these deaths occurred in low-income and middle-income countries [Abegunde et al., 2007]. In 2005, the WHO reemphasized the importance of NCDs as a neglected global health issue [World Health Organization, 2005]. As an example, in 2007, about 72% of all deaths in Brazil were attributable to NCDs [Schmidt et al., 2011]. In 2010, 34.5 million deaths (65% of the population) could be attributed to NCDs [Lozano, Naghavi, and Foreman, 2012]. The global burden of disease also revealed the importance of taking disability from chronic diseases a great deal more seriously than we do today: 54% of disability-adjusted life years worldwide were caused by NCDs in 2010, compared with only 43% in 1990 [Murray, Vos, and Lozano, 2012]. To achieve the World Health Assembly target of 25% reduction in preventable deaths from NCDs by 2025 [WH, 2012], a concerted effort needs to be applied to tackle chronic diseases and not merely the reworking and reapplying of acute care methods to chronic care.

Chronic conditions, unlike acute conditions, are particularly complex in that they tend to involve multiple factors with multiple interactions between them [Ahn et al., 2006b]. It is now established that combating chronic disease requires treating the patient more holistically [Kitano, 2002; Inquiry, Epstein, and Legacy, 2004; Ahn et al., 2006a,b; Snyderman and Langheier, 2006; Galland and Lafferty, 2009; Bland, 2010a,b; Jones and Quinn, 2010; Bousquet et al., 2011; Hyman, 2014]. This is currently a challenge given that the science of clinical medicine is fundamentally reductionist [Ahn et al., 2006b]. Many domains within the health field believe that the limit of reductionist thinking has been achieved and to understand the whole system, one must start to apply systems thinking [Kitano, 2002; Ahn et al., 2006a,b; Snyderman and Langheier, 2006; Bousquet et al., 2011]. The paradigm shift to a more whole patient focus where the patient is treated as a system exists and is called functional medicine [Jones and Quinn, 2010].

Functional medicine is a systems approach to practicing medicine. It takes into account the many subsystems in the human body and their many interactions. Although the science behind treating the patient as a system exists, the application of systems tools and techniques have not been utilized. It is only natural to begin to formalize the systems thinking using the established tools from the systems engineering field.

This paper first describes in Section 2 the background concepts of systems engineering, systems thinking in the health field, and functional medicine. Section 3 discusses the po-

tential application of systems tools in clinical medicine and Section 4 shows an example application of model-based systems engineering tools to clinical medicine.

2. BACKGROUND CONCEPTS

This section serves to introduce the working vocabulary and concepts discussed in this paper. Section 2.1 describes the basic concepts of systems engineering related to complexity management in this work. Section 2.2 discusses the two health areas that have incorporated systems thinking and Section 2.3 includes a brief description of a systems approach to the practice of medicine: functional medicine.

2.1. Systems Engineering as Complexity Management

Systems engineering, based on general systems theory, emerged out of the need to combine, utilize, and understand complex interconnected and interdependent information. The foundations of general systems theory are credited to the biologist Ludwig von Bertalanffy. His book describes the common features of systems from different fields of knowledge, which apply to both natural and built systems [Von Bertalanffy, 1968]. Since then, systems engineering has emerged as an approach to *synthesize* and design large complex systems [Buade, 2011; Wiley, 2015]. That said, the process is also highly *analytical* in that it encourages the development of multiple complementary models to view, describe, and communicate the system at varying levels of detail, abstraction, and complexity.

The pertinent background concepts needed to understand systems engineering application to clinical medicine include:

- Concept 1: system function, form, and their allocation.
- Concept 2: scale and scope.
- Concept 3: system properties (e.g., emergence, robustness, modularity, etc.).

These concepts can be applied to clinical medicine by utilizing the latest tools and techniques such as SysML.

2.1.1. Concept 1: System Function, Form, and Their Allocation

One of the most fundamental ideas in systems engineering is that a system has (1) one or more functions, (2) a physical form or structure, and (3) their allocation as the mapping between the former to the latter. In the human body, there exists high-level functions (e.g., Assimilation [digestion & absorption], Defense and Repair, Energy Regulation, Elimination, Transport, and Communication). As these functions occur they evolve an individual's health "state." These functions may be performed by specific primary high-level structures of multiple-organ systems (e.g., Digestive System, Immune System, and Cardiovascular System). Their mutual allocation or mapping is typically found in the knowledge base of medicine describing the functions of different organs and specific cells within them. This knowledge base is continually growing in

size, detail, and complexity based on the continued research of scientists and experience of clinicians, ultimately giving you a new big data application.

The complexity of systems, be they engineered (e.g., power and transportation systems) or natural (e.g., environmental or human systems) arises from several factors that stem from the limitations of human short term memory. In 1956, Miller 1994 noted that human short-term memory is limited to 7 ± 2 elements. Consequently, in systems engineering, complexity is often discussed in terms of the number of system elements written in power of sevens. Systems with more than 7^n where $n \geq 3$ are considered fundamentally complex de Weck, Roos, and Magee 2011. These elements can be parts of the system form or the system function. The human body is therefore complex not just by virtue of its trillions of cells but also by virtue of its many functions. Second, systems may also be classified as complex because these elements of function and form may interact. Naturally, the more interactions there exist between two form elements or two function elements, the more complex the system is. Finally, complexity arises when there is not a one-to-one exclusive mapping between elements of function and form. For example, in the human body, the pancreas organ is typically included in the *form* Endocrine System performing the *function* secrete insulin and glucagon hormones. This serves the high-level *function* controlling blood sugar throughout the day. Nevertheless, the pancreas is also essential to the *form* Digestive System performing the *function* excreting enzymes to break down proteins, lipids, carbohydrates, and nucleic acids in food. Therefore, a disruption to the pancreas organ may not only disrupt the function of the primary endocrine system, but it may also have disruptive effects on the digestive system. This is a problem because while the medical field draws its clinical lines and divisions at the organ system level and therefore requires multiple specialists; their combination of individual specialty knowledge does not address the body connectedness and therefore the complexity of healthy human function.

2.1.2. Concept 2: Scale and Scope

Given the complexity of the human body, it is important to discuss the concepts of system scale and scope in the context of complexity management. The *structure* of the human body is organized into several (length) scales. In anatomy and physiology, this is typically referred to as “levels of organizations.” In systems engineering terminology, there is the scale of the human body as a whole, followed by the second highest level consisting of organ systems (e.g., nervous system), followed by individual organs (e.g., the brain), followed by organ structures (e.g., the cerebellum). The *function* of the human body is organized into several temporal scales ranging from long-term effects (e.g., aging) to fleeting transients (e.g., neuron firing). Naturally, the complexity of a system grows with the number of scales under consideration. Therefore, it is often important to restrict the scope of study to a certain length or temporal scale in form or function; potentially leading to reductionist approaches. In contrast, systems tools facilitate the integration of multiple length or temporal scales so as to give both broad holistic views with lower resolution as well as detailed views at higher resolution. Consequently, an

individual’s health state can also viewed at varying levels of granularity associated with scale and scope.

2.1.3. Concept 3: System Properties

Complex interconnected systems exhibit system properties that would not necessarily have appeared from understanding the individual parts alone. For systems engineering, these are often called “life-cycle properties” and often take a grammatical form ending in “ility” (e.g., flexibility, reconfigurability) [de Weck et al., 2011; Wiley, 2015]. The functional medicine literature (to be discussed in the next section) has paid particular attention to three such system properties, namely, emergence, robustness, and modularity [Jones and Quinn, 2010]. Emergence refers to the properties such as larger entities, patterns, and/or regularities that arise through interactions of smaller entities that themselves do not exhibit such properties and cannot be predicted from an understanding of the individual parts. This is primarily why medicine has started to recognize that a reductionist approach is not providing a realistic picture of some of the manifestations that can arise in people’s overall health [Ahn et al., 2006b; Hyman, 2006a]. Robustness is the ability of a systems to maintain itself in the face of changing environmental conditions. Modularity refers to a system that is composed of functional units working together to produce an outcome that cannot be produced by any of the units working independently [Oliver, Kelliher, and Keegan Jr, 1997; Buede, 2011]. The more complex a system is, the more these properties manifest themselves in seemingly unpredictable ways.

2.1.4. SysML as a Complexity Management Tool

The systems engineering field has developed many tools and techniques to build and manage complex systems in defense, aerospace, and infrastructure. These are specifically intended to manage systems with many form and function elements, their interactions, and their mapping. In recent years, the Systems Modeling Language (SysML) [Weilkiens, 2011], [Friedenthal, Moore, and Steiner, 2014] has emerged as a highly popular tool embedded within the systems engineering process [Wiley, 2015]. It is a graphical modeling language that facilitates the description of system function, form, and their allocation. It also supports parametric descriptions that may be used to develop quantitative models in coherent and well-organized ways. Therefore, SysML is chosen as an appropriate analytical tool in this work to model the complex, interconnected, and heterofunctional nature of human health with the ability to handle this big data application.

2.2. Systems Thinking in the Health Field

Similar to most of the sciences, the health field is based on reductionist thinking. Systems thinking tools and techniques have only recently gained strides within the biological and health fields. Figure 1 shows the classical decomposition of subfields along the reductionist scale (negative y-axis) with increasing smaller physical detail, while the systems scale (positive y-axis) shows the domains where systems tools have

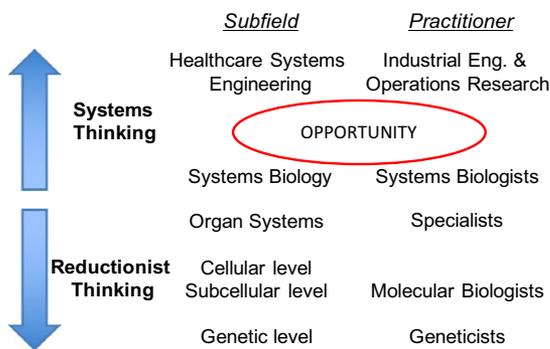


Figure 1. Systems thinking map in medicine: map of the subfields and corresponding practitioner showing two areas where systems thinking has been applied: (1) Healthcare Systems Engineering and 2.) Systems Biology. This also shows an opportunity for systems thinking at the patient level.

been applied with increasing larger physical scope, including (1) Healthcare Systems Engineering and (2) Systems Biology. The right most column describes the typical practitioner of the associated subfield. The figure also identifies an opportunity for systems tools to be applied at the patient level.

One of the domains applying systems thinking is Healthcare Systems Engineering. It is a relatively new field that applies systems theory and systems engineering tools to healthcare delivery. This field can be viewed as a health application of industrial engineering and operations research. Although there were traces of the interactions between systems thinking and healthcare back in the 1950s, it is only recently that the field has started to discuss these possibilities [Anderson and McDaniel, 2000; Murray and Berwick, 2003; Proctor et al., 2005; Ben-Tzion Karsh and Alper, 2005; Wu et al., 2006; Omachonu and Einspruch, 2007; Kopach-Konrad et al., 2007; Wickramasinghe et al., 2007; Rouse, 2008; Rouse and Cortese, 2010; Ross and Bidanda, 2014]. A new journal has been recently started [Fowler et al., 2011] in 2011 with applications ranging from scheduling [Mobasher et al., 2011; Herring and Herrmann, 2011; Pérez et al., 2011; Turkcan et al., 2012; Koeleman and Koole, 2012; Huang, Hancock, and Herrin, 2012; Lin et al., 2013; Mancilla and Storer, 2013; Claudio et al., 2014; Ewen and Mönch, 2014; Alaeddini et al., 2015], to reducing errors [Alvarado et al., 2012], improving hospital outpatient flow [Marmor et al., 2012; Peck et al., 2014], improving emergency room operations [Kaner et al., 2014], and improving patient safety [Rivera and Karsh, 2008].

The other primary domain applying systems thinking is Systems Biology. Systems Biology can be broadly viewed as a convergence of molecular biology and systems theory where the focus shifts to understanding the system structure and dynamics rather than the static connections of the components [Ideker, Galitski, and Hood, 2001; Kitano, 2002; Hood, 2003; Westerhoff and Palsson, 2004; O'Malley and Dupré, 2005; Boogerd et al., 2007; Bruggeman and Westerhoff, 2007; de Backer, de Waele, and van Speybroeck, 2010; Gatherer, 2010; Bizzarri, Cucina, and Palombo, 2014; Palsson, 2015]. One of the goals of systems biology is to understand a complex biological process in sufficient detail to allow for the building of a computational model. This model would then allow for

the simulation of system behavior thus elucidating system function [Dekkers, 2015]. This can be viewed as applying systems theory at the cellular and subcellular level, one of the smaller physical scales. One of the first numerical model simulations in cell biology was in 1952 by Nobel prize winners Alan Lloyd Hodgkin and Andrew Fielding Huxley [Hodgkin and Hodgkin, 1952]. At the subcellular level, another system engineering modeling language, OPM, has been applied [Dori and Choder, 2007; Somekh et al., 2012, 2014]. With the advancements in technology and the birth of functional genomics, the Systems Biology field took off with the National Science Foundation's grand challenge in 2006 to build a mathematical model of the whole cell [Omenn, 2006]. This field has exploded with tens of *Systems Biology Journals* and many thousands of publications.

There have been suggestions of extending systems biology theory to a higher physical scale, sometimes referred to as Systems Medicine [Hyman, 2006b; Federoff and Gostin, 2009; Majumder and Mukherjee, 2011; Bousquet et al., 2011; West, 2012; Wolkenhauer et al., 2013; Vogt et al., 2014]. The term has been used in a few articles, but the meaning it represents varies significantly. The idea though is trying to apply systems thinking to a higher physical scale than cells. However, this has generally been in theory rather than with practical methods.

2.3. Functional Medicine: A Systems Approach to the Practice of Medicine

Functional medicine is a systems approach to medicine that is not a separate discipline or specialty; rather, it is an approach to clinical care that is patient-centered, personalized, and grounded in the science of clinical medicine [Jones and Quinn, 2010], utilizing diagnostic tools and analytical evaluating mechanisms of disease [Lord and Bralley, 2008; Jones and Quinn, 2010]. It addresses chronic conditions by treating the individual as a system of complex interactions of multiple organ systems and multiple physiological and biochemical pathways with internal genetic predispositions and external environmental influences [Jones and Quinn, 2010].

From a clinical perspective, functional medicine is a dynamic approach to assessing, preventing, and treating complex chronic disease. It helps clinicians identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health [Jones and Quinn, 2010]. Specifically, functional medicine practitioners have published on chronic diseases discussing them in an interconnected and systemic fashion. Specifically, cancer has been described as a systemic functional disorder associated with malignant cellular proliferation [Bland, 2010a,b]; irritable bowel disease has multiple antecedents, triggers, and mediators that interact to produce dysfunction [Galland and Lafferty, 2009]; and obesity and diabetes (diabesity) are driven by a pandemic of insulin resistance mediated by many internal and external factors [Hyman, 2014].

The foundation of functional medicine stands on the identification of the primary functions/processes of the body, which through the systemic interconnectedness in the body manifest

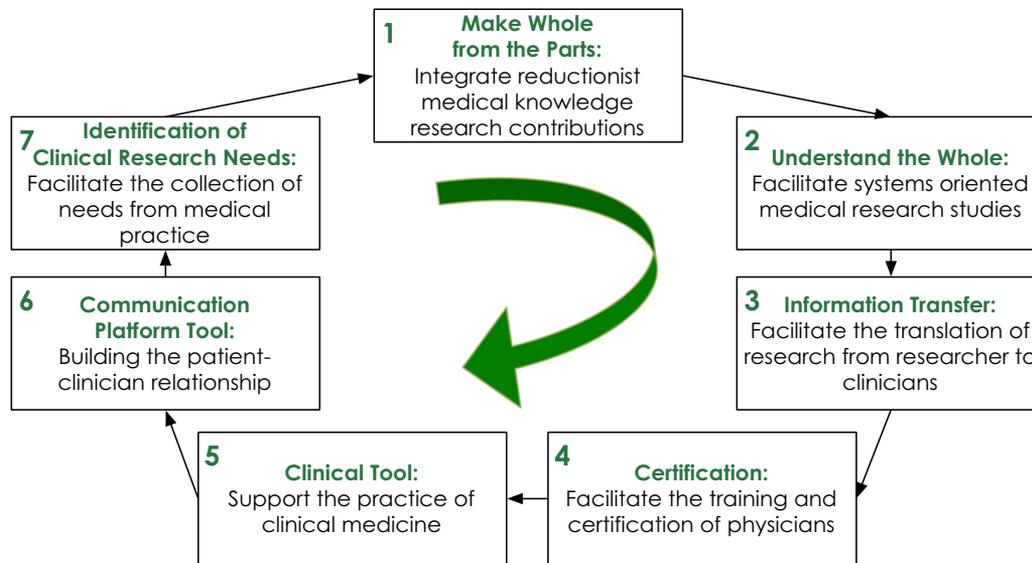


Figure 2. Multiple stages involved with clinical medicine.

as dysfunction. The fundamental physiological processes that ultimately determine health or disease include: (1) communication, both outside and inside the cell; (2) bioenergetics, or the transformation of food, air, and water into energy; (3) replication, repair, and maintenance of structural integrity, from the cellular to the whole body level; (4) elimination of waste; (5) protection and defense; and (6) transport and circulation [Jones and Quinn, 2010]. To assist clinicians in the process of linking ideas about multifactorial causation with the perceptible effects called disease or dysfunction, functional medicine has adapted and organized a set of core clinical imbalances that function as the intellectual bridge between the rich basic science literature delineating physiological mechanisms of disease (first two years of medical training and mentioned above) and the clinical studies, clinical experience, and clinical diagnoses of the second 2 years of medical training [Jones and Quinn, 2010]. These clinical imbalances include: (1) hormonal and neurotransmitter imbalances; (2) oxidation–reduction imbalances and mitochondriopathy; (3) detoxification and biotransformational imbalances; (4) immune and inflammatory imbalances; (5) digestive, absorptive, and microbiological imbalances; and (6) structural imbalances from cellular membrane function to the musculoskeletal system [Jones and Quinn, 2010].

From a systems perspective, functional medicine was developed with the understanding of the system properties of emergence, robustness, and modularity, as mentioned in Section 2.1. Pages iii–iv of the functional medicine textbook [Jones and Quinn, 2010] state:

“Emergence represents the specific characteristics that are displayed in a complex system that are not demonstrated by its individual parts and cannot be predicted from an understanding of the individual parts alone. In the functional medicine model, this has been termed the *web-like interconnections* of physiological processes and biochemical pathways. Robustness is termed *homeo-dynamics*. The greater the degrees of physiological freedom individuals have, the more

robust their health. For example, very simple EKG patterns are indicative of cardiac disease, whereas the more chaotic fine structure of heart rhythm (i.e., a homeodynamic pattern) is associated with cardiovascular fitness. Modularity refers to a system that is comprised of functional units working together to produce an outcome that cannot be produced by any of the units working independently. An example of this concept in functional medicine is the view of the immune, endocrine, and nervous systems as parts of one super-system, the neuroendocrine immune system. Only by looking at that system as a whole, and not at each of its units in isolation, can the practitioner fully understand the complex presentation of multiple signs and symptoms that patients so often exhibit.”

It is clear that functional medicine already exhibits systems thinking. It is only natural to begin to formalize that systems thinking using the established tools from the systems engineering field. This is especially advantageous for the reasons discussed in the following section.

3. POTENTIAL APPLICATIONS OF SYSTEMS TOOLS IN CLINICAL MEDICINE

The goal of applying systems tools to clinical medicine is to manage the complexity of medical knowledge to effectively improve patient care and health outcomes at lower costs. The Institute of Medicine’s 2010 report [Institute of Medicine (U.S.), 2012] states that “Pervasive inefficiencies, *an inability to manage a rapidly deepening clinical knowledge base*, and a reward system poorly focused on key patient needs, all hinder improvements in the safety and quality of care... Achieving higher quality care at lower cost will require fundamental commitments to the incentives, culture, and leadership that foster continuous learning, *as the lessons from research and each care experience are systematically captured, assessed, and translated into reliable care.*” This medical knowledge base is generated, translated, and practiced along a

Bench-to-Bedside-and-Back circular chain that spans from research (basic, translational, and clinical) to clinical practice and back.

The management of the complexity of medical knowledge to effectively improve patient care and health outcomes can be described with seven critical steps along the Bench-to-Bedside-and-Back chain. The seven steps shown in Figure 2 include: (1) integrate reductionist medical knowledge research contributions [Integrate Reductionist Research], (2) facilitate systems oriented medical research studies [Facilitate Systems Research], (3) facilitate the translation of research from researcher to clinician [Facilitate Translational Research], (4) facilitate the training and certification of physicians [Facilitate Practitioner Certification], (5) support the practice of clinical medicine [Support Clinical Tool], (6) building the patient–clinician relationship [Communication Platform Tool], and (7) facilitate the collection of needs from medical practice [Facilitate Needs Identification]. Each of these steps will be described in further detail under the corresponding subsection.

3.1. Integrate Reductionist Research—Make Whole from the Parts

Systems tools provide an effective method to organize the results of decades of reductionist medical research and science. As previously described, current scientific research models and practices are intrinsically reductionist. Various fields are set up and work independently within their own silos, although they may be tackling the same problem. A good example is the variety of research on obesity. Obesity has been tackled by many fields taking into account social [Christakis and Fowler, 2007; Kestila et al., 2009], environmental [Yousefian et al., 2011; Miller, 2011], and biological/genetic [Bell, Walley, and Froguel, 2005; Herrera, Keildson, and Lindgren, 2011; Hasstedt et al., 2011; Gorkin and Ren, 2014; Burgio, Lopomo, and Migliore, 2015] factors. Surprisingly, in many cases, each of the fields believe that their primary area of research holds the *secret* to solving the disease as suggested by comments such as: “The results emphasize the lasting effect of childhood socioeconomic position on adult obesity.” [Kestila et al., 2009] and “Only a comprehensive understanding of the underlying genetic and epigenetic mechanisms, and the metabolic processes they govern, will allow us to manage, and eventually prevent, obesity” [Herrera et al., 2011]. Fortunately, researchers are starting to recognize the complex and interconnected nature of chronic diseases. Continuing with the obesity example, a recent Institute of Medicine (IOM) Panel on evidence and obesity decision-making outlined the need for consideration of a broad range of evidence and for utilization of a systems perspective [Sim et al., 2010]. This utilization of a systems approach is also evidenced in published work on obesity [Gortmaker et al., 2011; Nader et al., 2012; Black and Hager, 2013; Huang et al., 2013; Hummel et al., 2013; Perez-Escamilla and Kac, 2013; Gortmaker and Taveras, 2014; Sabounchi et al., 2014].

In applying systems tools, reductionist research can be integrated at the appropriate human body level of organization

at which it impacts the individual. In system form, graph theory can be applied to determine the most centrally important elements. In system function, chains of multi-input multioutput relations can be strung together to provide insights into seemingly unrelated factors. In such a way, disparate bodies of knowledge can be integrated into systems-wide views of the body functions and malfunctions.

And yet, the results of decades of reductionist research is not well organized and presented into a single scale. Systems tools help manage our human understanding of form, function, scale, and resolution. Furthermore, by nature, the human body is unique in that a change in the microscopic scale can quickly lead to a macroscopic behavioral change. For example, the expression of mutated genes may lead to the systemic dysfunction of cancer. Understanding such system-wide phenomena in ultimate detail is beyond the capabilities of the human brain and modern computers. Therefore, system tools provide structured ways to bring in the well-known complexity-management constructs of abstraction, decomposition, specialization, and scale. In such a way, detail is added only when required, opening up possibilities in understanding human health broadly when only depth was possible before. Such a process need not be done all at once, rather it can be approached incrementally and can be supported by databases for information management. As system tools come to embody the knowledge of clinical medicine, they have the potential to integrate with systems approaches to healthcare human resources management [Farid and Khayal, 2013; Khayal and Farid, 2013, 2015]. System tools also have the potential to aid in the process of developing integrated models of clinical care [Khayal et al., 2017].

3.2. Facilitate Systems Research—Understand the Whole

Once a body of reduction research results have been integrated in SysML, systems tools can serve to facilitate systems research in two respects: (1) the models developed as a result of the integration, described in the previous subsection, can now be tested and validated experimentally or clinically and (2) system tools also provide an approach to predict and explain emergent behaviors.

The first aspect of facilitating systems research is in testing and validating experimentally or clinically the models developed from the integration of research described in the previous section. In system form, graph theory can be applied to determine the most centrally important elements. In system function, chains of multi-input multioutput relations can be strung together to provide insights into seemingly unrelated factors. As an example, functional medicine was an integration of medical knowledge into a system-wide view of the human body. “It was born out of collaborations among clinicians of many different disciplines and specialties, clinical laboratory specialists, health sciences researchers, health educators, health policy professionals, and healthcare administrators to address the rising incidence and cost of chronic disease” [Jones and Quinn, 2010]. The functional medicine model has evolved clinically over the past 20 years [Jones and Quinn, 2010] and in 2015, the Cleveland Clinic established a Center

for Functional Medicine, which is expected to further test this model and contribute to the medical research knowledge base.

Systems tools also provide an approach to predict and explain emergent behaviors. Once built, these SysML models may be translated into stochastic discrete event and/or Markov chain simulations to show how the health of individuals in a population probabilistically evolves for better or worse. By putting the many pieces of an individual's health state evolution together, there is a greater ability to assess the overall effectiveness of treatment pathways. Consequently, this would allow for the quantification of the benefits of integrative and holistic treatment approaches like functional medicine over more specialized approaches. This work is also expected to highlight where new biomedical and bioengineering technological interventions are most likely to make a difference in health outcomes. These tools also allow for the assessment of treatment pathways and their associated technologies. Predicting and explaining these emergent behaviors may (1) enable hospitals, clinics, and engineers to be truly progressive and shift to addressing today's most pressing conditions, (2) enable health insurance providers to develop value-driven services, and (3) inform government health policies and funding.

3.3. Facilitate Translational Research—Information Transfer

In managing system complexity, systems tools also support the transfer of information in more simple and easy to understand ways. The Institute of Medicine, "in its landmark indictment of the quality of healthcare in the United States, lamented that many proven effective treatments are not incorporated into everyday care" [Institute of Medicine, 2001]. Balas and Boren 2000 showed that only 14% of research findings filter down to everyday practice, and those that do take an average of 17 years [Morris, Wooding, and Grant, 2011]. The director of the National Institutes of Health (NIH) responded by increasing the NIH's emphasis on translation of research into practice [Zerhouni, 2005]. The current practice is to integrate this knowledge into review papers that combine primary research results. Morris [Morris et al., 2011] argues that a process is needed to gather and organize these data and results. Systems tools like SysML can serve to facilitate such a process within a single framework and would ultimately link the community of health practitioners to that of systems engineering. This would fulfill the need for systems engineering in medicine recognized by the National Academy of Engineering and the Institute of Medicine [Proctor et al., 2005].

3.4. Facilitate Practitioner Certification

In the United States, many states require continued medical education (CME) for medical professionals to maintain their licenses. Unfortunately, research has shown that many activities routinely used for continuing education and quality improvement in general practice, such as written information and lectures, have little or no effect on practice [Stephenson

and Imrie, 1998; Mazmanian, Davis, and Galbraith, 2009; Jones and Quinn, 2010; Price et al., 2010; Van Hoof and Meehan, 2011]. There is a need to enhance the way that physicians are taught and to make continuing medical education more effective, especially as the medical knowledge base continues to grow. Several studies have shown that a bottom up approach of individuals learning what they need based on their goals may be more useful and effective [Stephenson and Imrie, 1998; Rodriguez et al., 2010; Cervero and Gaines, 2015; Kapur et al., 2015]. Therefore, the continuing education and certification of medical practitioners is most effective when the conveyed medical knowledge has been organized into ways that systematically manage complexity. This allows practitioners to target areas of interest from the knowledge base showing the evolving clinical information and easily showing the changes along with the systems implication of this information.

3.5. Clinical Support Tool

In managing the complexity of human health, system tools also have a direct application in the clinic during care. As medical knowledge continues to grow in depth and complexity, the system tools serve to organize information into constructs that may be readily used by the clinician.

As previously stated in Section 2.1.1, Miller 1994 noted that human short-term memory is limited to 7 ± 2 elements. For that reason along with a continuously growing medical knowledge base, healthcare has devised clinical pathways and protocols to direct physician care. This has been implemented using basic (paper) and more advanced (computerized) clinical support tools. Unfortunately, their application and usefulness have not been validated or demonstrated as having fulfilled their promised expectations across several health conditions [Ali, Shah, and Tandon, 2011; Jaspers et al., 2011; Roshanov et al., 2011; Welch and Kawamoto, 2013; Jeffery, Iserman, and Haynes, 2013; Blum et al., 2014]. Furthermore, research and clinical experience argue that blindly following clinical pathways and clinical protocols may be viewed by some as a panacea for providing quality care, but in the absence of critical thinking, this may not be so [Staib, 2003; Fesler-birch, 2005; Groopman and Prichard, 2007; Pizzorno, 2012; Croskerry, 2013]. The organization and presentation of information into constructs based on function may provide the platform for expanding clinical protocols while using more personalized patient information to allow for critical thinking by the physician in tailoring personalized treatment.

3.6. Communication Platform Tool

The complexity management benefit of system tools is not just restricted to researchers, educators, and clinicians. Rather, system tools can help patients in several ways, including: (1) helping patients to be actively engaged participants in their healthcare and recovery, (2) helping patients from having myopic views to potential conditions, (3) helping foster patient-physician partnerships based on outcomes, and (4) helping patients understand how their behavior outside

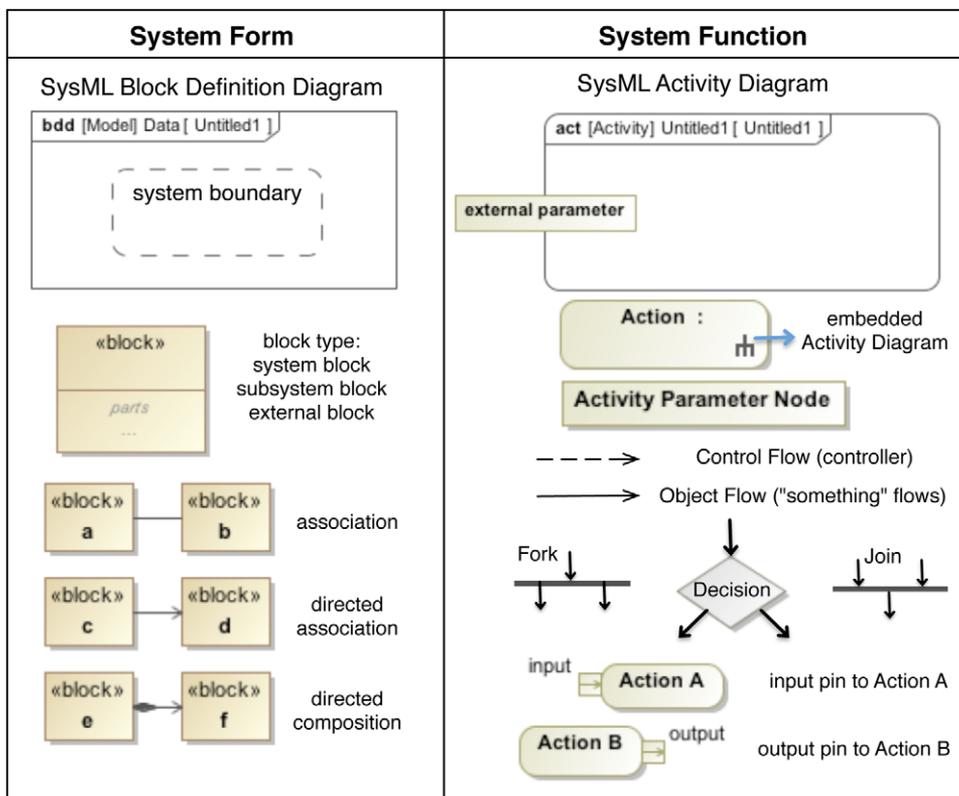


Figure 3. SysML semantics for the SysML block definition diagram (system form) and the SysML activity diagram (system function).

of the clinic can have positive outcomes. While the SysML language may be too formal for a general audience, simplified diagrams can serve as the basis for open communication.

Patient engagement in their own health is becoming exceedingly needed as chronic conditions force patients to assimilate, digest, and follow treatments from multiple specialists. “Perceived self-efficacy is an important mediator of health and healing. Enhancement of patients’ self-efficacy through information, education, and the development of a collaborative relationship between patient and healer is a critical goal in each encounter” [Galland, 2010]. This is evidenced by empowered patients being more satisfied in their medical encounters [Sepucha et al., 2000]. The IOM’s 2010 Best Care at Lower Cost report [Institute of Medicine (U.S.), 2012] states “A learning health care system is anchored on patient needs and perspectives and promotes the inclusion of patients, families, and other caregivers as vital members of the continuously learning care team.”

The IOM report also includes patient–clinician partnerships as one of the four characteristics of a learning health care system [Institute of Medicine (U.S.), 2012]. Communication and collaboration between patients and practitioners is critical and has been known for some time and continues to be demonstrated [Simpson et al., 1991; Thompson and McCabe, 2012].

Current patient decision tools are typically focused on helping patients make a decision between two or more treatment options [Elwyn et al., 2013], whereas system tools serve as a platform for providing such information while more clearly

demonstrating the connections and effects of various choices. This is critically important since patients make changes to their decisions and behavior when they truly understand and see the impact [Funnell, 2000].

3.7. Facilitate Needs Identification—Identification of Clinical Research Needs

Finally, system tools can help clinicians manage the information gained from their clinical practice. For a single clinician, years of clinical cases can develop into a repository that embodies the experience of their career. Furthermore, if patients have consented to share their medical information, multiple clinicians can share this case study data. In today’s medical practice, this would likely result in unorganized text. However, if systems tools were an integral part of clinical practice, the sharing of organized graphical information can lead to a valuable repository of current medical needs. Such sharing of data has the potential to inform areas where new research is needed.

4. APPLICATION OF SYSML TO FUNCTIONAL MEDICINE: AN EXAMPLE

In this section, the Model-Based Systems Engineering tool SysML is utilized to translate aspects of the functional

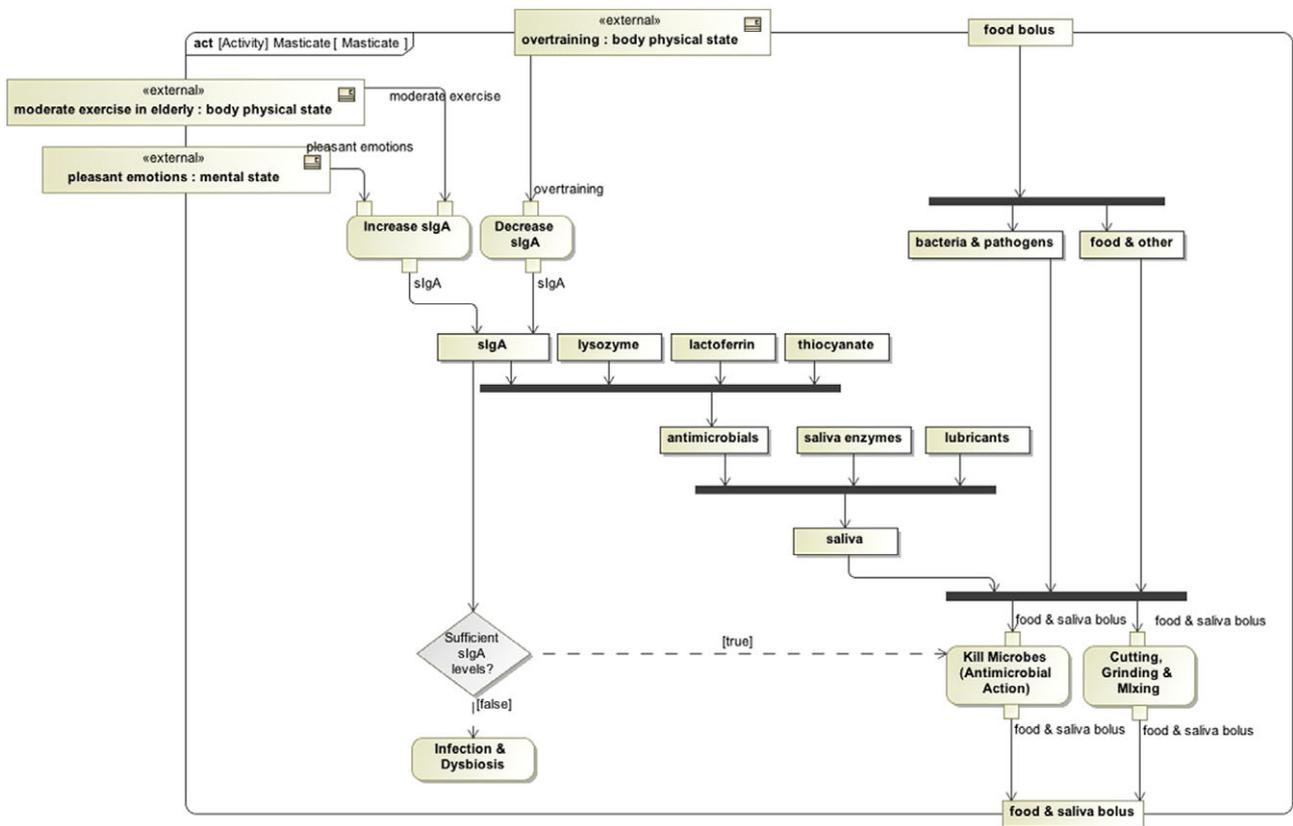


Figure 4. The block definition diagram consists of the defined system: digestive system (defined in this example as the mouth to the stomach), the subsystems (mouth, esophagus, and stomach), and the external components that interact with the system (lower GI tract/intestines, CNS, body physical state, mental state, enteric nervous system, and the normal system).

medicine text to produce graphical models. A small yet interconnected example of the beginning stages of digestion is chosen. This will keep the example manageable yet enlightening as a first example of translating medical knowledge into graphical models. Section 4.1 states the medical text translated for this example, while Section 4.2 describes the semantics of SysML, and finally Section 4.3 describes the SysML model.

4.1. Medical Text

The text translated for the SysML example is from chapter 24 (Digestive, Absorptive and Microbiological Imbalances) of the *Textbook of Functional Medicine* pages 327–328 [Jones and Quinn, 2010]. An example of digestion was chosen since it is critical to understand imbalances of the gastrointestinal (GI) system given that visits for GI distress of one kind or another account for significant healthcare visits [Sandler et al., 2002; Lacy and De Lee, 2005; Peery et al., 2012]. There is also a growing research knowledge base of the functional importance of digestion and the growing symptoms of its dysfunction can cause to our overall health [Hyman, 2007; Galland and Lafferty, 2009; Bland, 2010a; Jones and Quinn, 2010; Bischoff, 2011; Hyman, 2014]. The text from the fol-

lowing two sections was translated in the development of the SysML Model example.

The Mouth

“Mastication, or chewing, is the process of cutting, grinding, and mixing the food bolus with saliva. Saliva is a complex mix of lubricants, enzymes, and antimicrobials. An underrecognized and very important function of the saliva is the antimicrobial component. Saliva contains several anti-infective agents including thiocyanate, lactoferrin, secretory IgA (sIgA), and lysozyme. These agents help prevent infective agents from hitchhiking with the food bolus into the lower GI tract, thus preventing infection and dysbiosis. Salivary sIgA is the primary immunoglobulin of the mucosal immune system; its levels are improved by pleasant emotions [Watanuki and Kim, 2005]. Interestingly, overtraining in athletes will lower sIgA, resulting in upper respiratory infection (URI) [Mackinnon and Hooper, 1994]. It appears that this effect can be muted with the use of acupuncture [Akimoto et al., 2003b]. In the elderly, moderate exercise has been shown to improve sIgA, possibly reducing the age-associated lowered resistance to URI [Akimoto et al., 2003a]. Pathogen-specific sIgA has been reported in response to bacterial and fungal species [El Hamshary and Arafa, 2004; Vojdani et al., 2003]. Connecting the mouth to the stomach is the esophagus. Dysmotility disorders of the esophagus are common. The origin of these phenomena is not known, but evidence exists to suggest that ENS

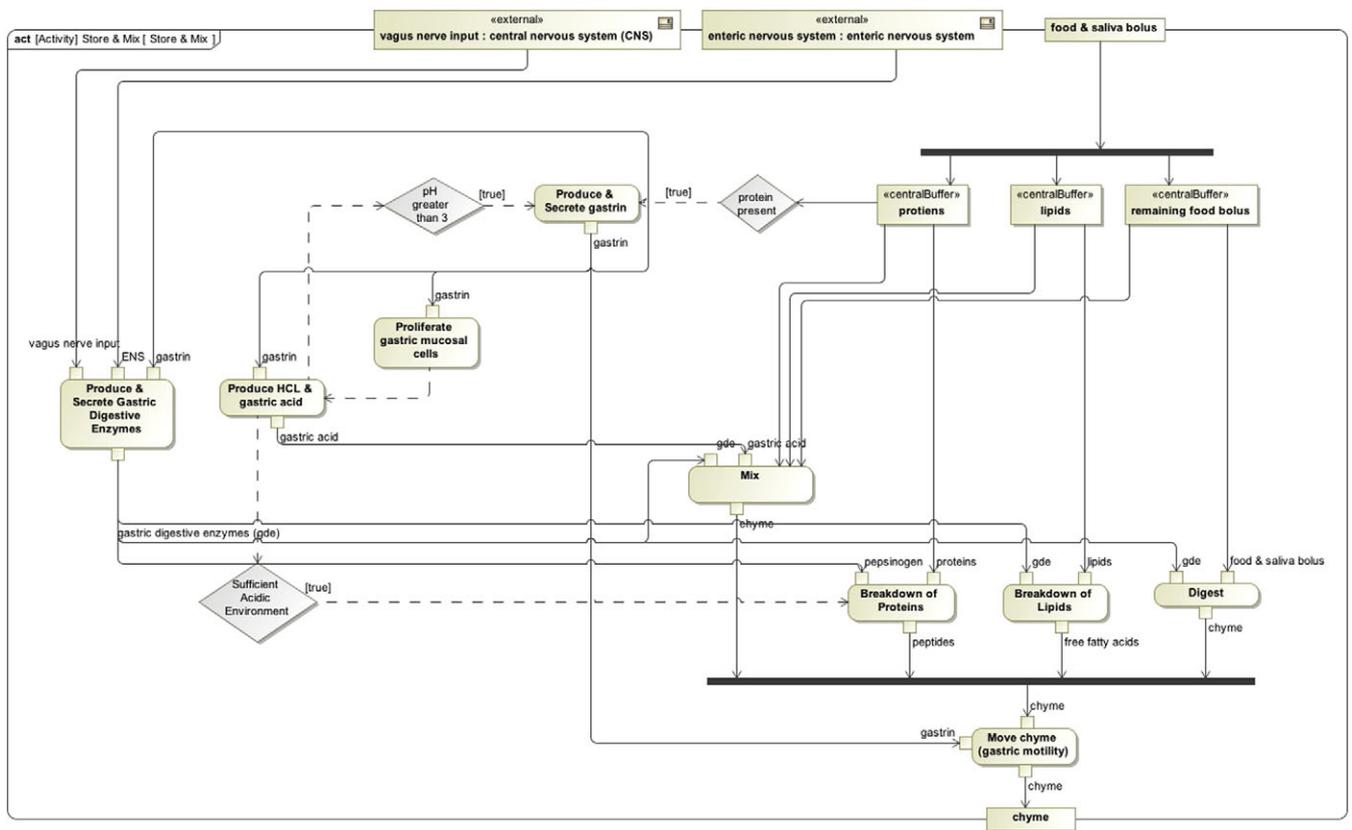


Figure 5. The primary activity diagram describes the function or action of digestion. This includes three primary actions: masticate, transport, and Store & Mix with several external parameters, inputs, and an output to this activity.

autoimmunity is partly responsible; however, controversy still exists [Moses et al., 2003].”

The Stomach

“The stomach holds food in storage and further mixes the food bolus with HCl and gastric digestive enzymes. These enzymes continue the process of digestion that was begun in the mouth. Proteins are broken down into peptides. Lipids are broken down into free fatty acids. This prepares the food bolus, or chyme, for delivery to the small intestine. The stomach produces HCl in the parietal cells via an ATP-dependent process. (This is the site of action of the proton pump inhibitors [PPIs].) This acid environment favors the unfolding, or denaturation, of proteins to facilitate enzymatic breakdown. Pepsinogen is converted to pepsin and many microorganisms are destroyed by the low pH. These processes are under both neural and hormonal control. The primary central nervous system (CNS) influence on gastric secretion and motility is the vagus nerve. The primary hormonal influence is gastrin. The vagus nerve is the dominant CNS input, but is still a minority influence on the GI system. The ENS has inputs to the GI system that are orders of magnitude larger [Gershon, 1998]. Gastrin is produced in the antrum of the stomach in G cells. Its secretion is stimulated by the presence of protein in the gastric lumen. It is inhibited by a pH lower than 3. Gastrin stimulates gastric motility and the release of gastric acid and pepsinogen. It also plays a role in the proliferation of gastric mucosal cells, especially the acid-secreting cells. One is left

to wonder what the long-term implications of chronic acid suppression might be on the total number of acid-secreting cells and gastric motility.”

4.2. SysML Semantics

Figure 3 describes the semantics needed to describe SysML for the model developed in Section 4.3 but not detailed enough as to serve as a complete reference for SysML. Other sources generally referred to are referenced here [Weilkiens, 2011; Friedenthal et al., 2014].

4.3. SysML Model

The SysML model developed includes five figures: one block diagram (structure), one primary activity diagram (function) with two subactivity diagrams, and one allocation diagram. Figure 4 shows the structure with the block diagrams consisting of the defined system: digestive system (defined in this example as the mouth to the stomach), the subsystems (mouth, esophagus, and stomach), the external components that interact with the system (lower GI/intestines, CNS, body physical state, mental state, enteric nervous system, and the normal system), and the human body block they all belong to. Figure 5 shows the functions within the primary activity

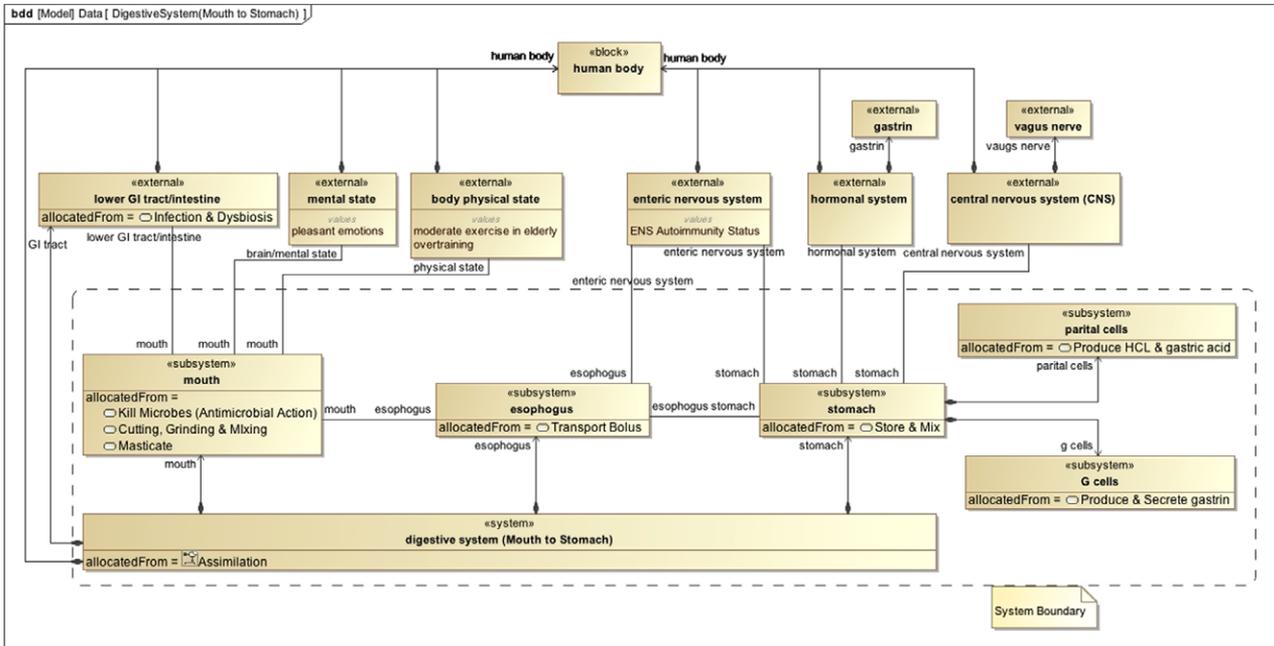


Figure 6. The secondary activity diagram describes more specifically the function masticate. This involves several inputs and several activity parameters with an output to the function masticate.

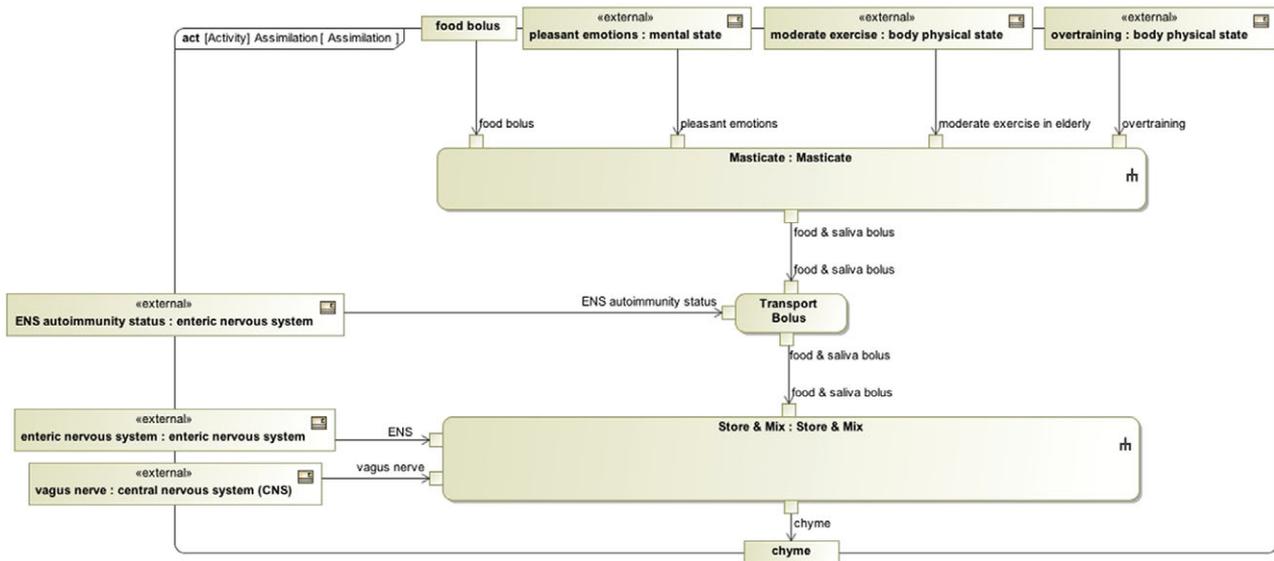


Figure 7. The secondary activity diagram describing in more detail the function Store & Mix. This involves several inputs, several activity parameters, and an output to Store & Mix.

diagram. Figure 6 shows a deeper level activity diagram of the action *Masticate* from within the primary activity diagram, while Figure 7 shows the deeper level activity diagram of the action *Store & Mix* from within the primary activity diagram. Additionally, Figure 8 shows the allocation of function (the activities) to the form (the structures). The allocation clearly shows functions, within the form system, occurring and/or affecting far reaching external structure blocks.

5. DISCUSSION

This paper presents the need for system tools in the practice of clinical medicine with the goal of managing knowledge complexity to effectively improve patient care and health outcomes. An example of the model-based systems engineering tool SysML was utilized to translate functional medicine text to produce visual graphical models. To our knowledge, this is

	mouth	esophogus	stomach	parital cells	G cells	lower GI tract/intestine	enteric nervous system	central nervous system (CNS)	vagus nerve	hormonal system	gastrin	mental state	body physical state
Assimilation(food bolus, ENS autoimmunity status : enteric nervous system)													
food bolus													
chyme													
pleasant emotions : mental state												X	
moderate exercise : body physical state													X
overtraining : body physical state													X
ENS autoimmunity status : enteric nervous system							X						
enteric nervous system : enteric nervous system							X						
vagus nerve : vagus nerve									X				
Masticate:Masticate	X												
Transport Bolus		X											
Store & Mix:Store & Mix			X										
Masticate(food bolus, food & saliva bolus, pleasant emotions)													
food bolus													
food & saliva bolus													
Increase sIgA													
Decrease sIgA													
overtraining : body physical state													X
moderate exercise in elderly : body physical state													X
pleasant emotions : mental state											X		
Infection & Dysbiosis						X							
Cutting, Grinding & Mlxing	X												
Kill Microbes (Antimicrobial Action)	X												
Store & Mix(food & saliva bolus, vagus nerve input : central nervous system)													
food & saliva bolus													
chyme													
enteric nervous system input : enteric nervous system							X						
vagus nerve input : central nervous system (CNS)								X					
Produce & Secrete gastrin					X								
Proliferate gastric mucosal cells													
Produce HCL & gastric acid				X									
Produce & Secrete Gastric Digestive Enzymes													
Mix			X										
Breakdown of Lipids													
Breakdown of Proteins													
Digest													
Move chyme (gastric motility)													

Figure 8. The allocation matrix includes form on the vertical scale and function on the horizontal scale. The form includes the system components followed by the external components. The function include three primary activity figures with each separated to include the inputs/outputs, the external factors affecting the activities and the internal activities.

the first paper applying systems engineering tools to clinical medicine at the patient level. With this example in place, the discussion can return to the systems thinking concepts introduced in Section 2.

The first concept described the importance of both *form* and *function* of a system. A system, such as the human body, is “a set of interrelated components (physical form or structure) working together toward some common objective (function or functions)” [Kossiakoff et al., 2011]. In many cases, conventional medicine treats the human body with a focus toward structure rather than function. This is evidenced by the fact that medical practice is broken down into specialties generally based on organs and organ systems (e.g., Audiology, Ophthalmology, Neurology, Endocrinology, Cardiology, Gastroenterology, Nephrology, Dermatology, and Podiatry). Functional medicine, however, has an equal focus on both structure and function of the human body when assessing dysfunction or disease. A prominent physician states “Chronic illness is not a discrete phenomenon within an organ, but a long-standing dysfunction between many ‘systems’ or ‘orbs’ of the body, all interacting to create the manifestations we see as symptoms and suffering in our patients. Our current model of care and our orienting paradigm for modern illnesses do not allow the practitioner to navigate these functional orbs. This leads to misguided ‘anatomical’ solutions, whether it is gastric bypass surgery for obesity; angioplasty for atherosclerosis; or a smart drug targeting an anatomical receptor, enzyme, or biochemical pathway” [Hyman, 2006a]. Systems thinking allows for a practice of medicine that truly addresses chronic conditions, from both structure and function, rather than “reworking” or “reapplying” of acute care models.

The second concept of systems thinking described *scale* and *scope*. The ability to vary scale and scope is critical to understanding a system. This can be described as “seeing the forest from the trees.” One of the more recent advances in systems biology includes the understanding that the complexity, which is unarguably present in biological systems, is often not a complexity of function. It is rather a complexity of regulation that is necessary to ensure that a relatively simple function can be maintained robustly in spite of severe perturbations from the environment” [Dekkers, 2015]. Similarly, page 179 of the functional medicine textbook states: “The pathways utilized to maintain homeostasis may look bewildering, but in reality, control is achieved by the application of relatively few mechanisms, highly elaborated to be sure, but fairly simple at their core... If one steps back and tries to visualize the forest rather than the trees, the beauty and functional simplicity of the systems are remarkable” [Jones and Quinn, 2010].

This ability to vary scope and scale is also what clearly helps to demonstrate the interconnections of the system and how seemingly unrelated organs can have an effect on each other, especially in chronic disease. Specifically, from the example case, the activity Masticate, which uses the structure mouth can lead to the function Infection & Dysbiosis, occurring in the structure lower GI tract/intestines. System tools aid to easily show these types of interconnectedness, especially when keeping all this information in memory and accessible to a physician during a patient visit is not practical.

While some of these clinically applied systems thinking concepts are similar to those found in systems biology, there are two critical distinctions between the typical techniques used in systems biology and the model-based systems engineering approach proposed here. First, the model-based systems engineering method is fundamentally a top-down approach. It fixes the scope of the model and grows its size as one drills down further and adds greater detail. In contrast, the systems biology approach is intrinsically a bottom-up approach. It begins with one or more relatively detailed “building-block” models (e.g., translations, transcriptions of RNA and proteins) and then grows its size outward in scope to include interactions between these smaller models. Some would argue that Systems Biology is better categorized as a middle-out approach [Brenner et al., 2001]. Nevertheless, the approach “is based on conceptualizing insight at whichever level there is a good understanding of data and processes, and on then incorporating greater levels of structural and functional integration [Kohl and Noble, 2009]. Therefore, the two approaches have very different approaches to model development.

The second distinction has to do with the fundamental difference in data used to build and develop these models. In the clinically applied model-based systems engineering approach, the data come from mining patient histories, records, and case studies. The fidelity of this model is driven by the existing medical science as it is already published and hence the translation of medical text used as an example in this paper. Systems biology, in contrast, is biologically focused and uses data from wet lab experiments or first principles of the natural sciences. Typical approaches then require ‘system identification’ where the right coefficients are assigned to mathematical descriptors of each block and connecting links. These modeling techniques have left an incredibly large translational gap to clinical medicine. That said, there have been incredible advances in our medical understanding of certain systems such as the cardiovascular system through the use of control theory and systems analysis by Guyton, Coleman, and Granger 1972. However, the authors describe that this model works because of the extreme stability of the actual circulatory control system “where the function of any single block or any single control mechanism, can be in error as much as $\pm 50\%$ (sometimes even more than this) without significantly affecting the overall output of the systems.” Therefore, “If it were not for the extreme stability of the overall circulatory control system, we would have to know far more basic physiology to make such a systems analysis as this work” [Guyton et al., 1972]. The model-based systems engineering approach proposed here is much more applied in that it both draws from and contributes directly to clinical practice.

Finally, although the systems concept may appear novel relative to current conventional treatment, this is not new. It has already been stated that the viewpoint of systems biology is consistent with the holistic perspective of traditional medicine [Lee, 2015]. The notion of functional medicine is also not a new paradigm. It may be the case for conventional medicine, however, traditional medical practices (e.g., Traditional Chinese Medicine, Unani Tibb) treat the body as an interconnected system [Chishti, 1991; Abdelhamid, 2012c,

2012a,b]. “At the center of Chinese medicine is the notion of functional relationships within the body. Organs are of interest, not for their anatomical relationships, but for their functional patterns and distant effects with other “organs.” Organs in Chinese medicine are concepts organized around function, not discrete anatomical entities” [Hyman, 2006a]. This also explains the rise and use of alternative therapies in conjunction with conventional western medicine [Ernst, 2000; Ahn et al., 2010; Frass et al., 2012; Harris et al., 2012]. Although systems thinking at the patient level is not novel, this paper begins to formalize the systems thinking using the established tools from the systems engineering field.

6. CONCLUSION and FUTURE WORK

In conclusion, this paper presents the need for system tools in the practice of clinical medicine with the goal of managing knowledge complexity to effectively improve patient care and health outcomes. To our knowledge, this is the first paper presenting the utilization of system tools and providing an example at the patient level. Specifically, the example model demonstrated how model-based systems engineering tools can be utilized for clinical medicine, ultimately giving a new big data application. This presents opportunities for collaboration between clinical stakeholders, research stakeholders, systems engineers, and patients with the goal of developing these tools to be utilized within clinical medicine.

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