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Editorial

System dynamics and bio-medical modeling

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Introduction

The capacity of organisms to maintain their constancy despite being challenged by changing internal and external environments has been of great interest to biologists for a long time, and the idea that higher animals possess complex regulatory mechanisms to maintain a stable internal environment for their living units, the cells, is one of the fundamental concepts in physiology (Strand, 1978). Hippocrates (460–377 B.C.) held the idea that disease is cured by natural powers, by a *vis medicatrix naturae*, which implies the existence of agencies which are ready to operate correctively when the normal state of the organism is disturbed. This idea is further developed by modern physiologists and reformulated by German physiologist Pflüger (1877), who noted that "each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance, p 20." Along the same lines, the Belgian physiologist, Leon Fredericq, in 1885, declared that "the living being is an agency of such sort that each disturbing influence induces by itself the calling forth of compensatory activity to neutralize or repair the disturbance. The higher in the scale of living beings, the more numerous, the more perfect and the more complicated do these regulatory agencies become, p 21" (Cannon, 1932).

In the late 19th century, the French physiologist Claude Bernard coined the term *milieu intérieur* which has since been incorporated into modern physiology as a unifying concept. He wrote, "the fixity (stability) of the internal environment [the *milieu intérieur*] is the condition for the free and independent life, p 21" (Bernard, 1878). The term is translated to English as the "internal environment." These are the underlying principles of what would later be termed *homeostasis*, a term coined and used by Walter Bradley Cannon, a professor of physiology, in his book *The Wisdom of the Body (*Cannon, 1932*)*. In this book, Cannon described the working principles of many physiological systems, such as the control of blood pressure, blood sugar, water intake, and salinity. While these systems appeared to be very different in their design and composition, Cannon observed that they obey the same principles when viewed in terms of homeostasis and suggested that physiological systems are mainly dominated by negative feedback loops.

Although Cannon made use of the concepts recognizable by system dynamicists, he only used qualitative descriptions in his writings. Another pioneer of systems thinking, Arthur Guyton, was the first to introduce the concept of systems analysis to physicians, which applied principles of engineering and systems analysis, before digital computers were available. His *Textbook of Medical Physiology* is the world's best-selling physiology text and has been translated into at least 15 languages with many consequent editions (Guyton, 1976). He had a unique quantitative approach to cardiovascular regulation which was initially met with skepticism, disbelief, and even ridicule, when he first presented his models. From 1950s on to the end of the 20th century, he built mathematical physiology models combining the results of extensive experimentation with the tools of mathematics, physics, engineering, and physiology, providing

the first comprehensive systems analysis of blood pressure regulation (Guyton, 1991). He constructed models of circulatory body-fluid dynamics mainly to examine the reasons of hypertension; but perhaps the most important message of his works was that complex system behaviors can be examined quantitatively. This approach led to the emergence of biomedical engineering, a discipline which changed physiology into a much more quantitative science.

In recent years, there has been a considerable increase in the application of mathematical methods, both in physiology and clinical decision-making. There is now a consensus that mathematical models of physiological systems can make a significant contribution to clinical diagnosis and to the teaching of many aspects of physiology (Hargrove, 1998; McDonnell *et al.*, 2013; Northrop, 2020; Rideout, 1991). Mathematical models also provide a means for evaluating hypotheses relating to the underlying pathology of a critical clinical disorder or used to explore differences between the learning experiences of different types of users, for example, between laypersons and healthcare professionals/students (Abdel-Hamid *et al.*, 2014; Ford, 2010). These views have culminated in the growth of simulation models, including interactive simulation games or (management) flight simulators that are gaining popularity as an interdisciplinary bridge between physicians, students, and other disciplines that attempt to formalize physiological relations through the process of modeling. These allow the user to test the possible effects of a set of treatment options on a virtual patient (Izzo and Camminatiello, 2020; Sokolowski *et al.*, 2014).

The application of the SD approach to physiology can support a greater understanding of the nature and behavior of complex physiological processes and systemic medical problems largely defined by coupled feedback systems. It is known that the constancy of the body's internal environment is maintained by various physiological control systems which employ negative feedback, and many disease states can be viewed as abnormalities of a particular control system. However, the time delays and the interplay of various factors (physical, hormonal, etc.) which regulate the function of the body's systems, renders it difficult or impossible to make quantitative predictions without a mathematical model or computer simulation, and therefore the SD approach turns out to be highly appropriate for the quantitative analysis of problems concerning medical disturbances and therapy (Gallaher, 1996).

System dynamics contributions to biomedical modeling

While the system dynamics (SD) approach has been mostly applied to industrial and environmental problems, it has also contributed to biomedical modeling since the early years of its introduction. Examples for applicable systemic medical problems include blood pressure management for hypertension, blood sugar management for diabetes, antibiotic resistance, drug addictions, obesity, and body weight management. In 1973, an SD model of glucose homeostasis was developed, and a clinical experiment suggested and implemented based on the simulation results. Later, the model was modified after examining the experiment's results (Foster *et al.*, 1973). In the opening issue of the *System Dynamics Review*, a physiological model of plasma water loss and control for patients with acute burns was included (Bush *et al.*, 1985), indicating the early attention to biomedical modeling in the field.

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A recent systematic literature review of SD modeling in health and medicines categorizes disease-related SD models into two groups of infectious and noninfectious diseases and subcategorized them into individual- and population-level models (Darabi and Hosseinichimeh, 2020). In a population-level model, the dynamics of an illness is studied for a selected population while an individual-level model captures a particular physiological structure of an individual or mechanisms underlying a disease for an individual patient. An individual model can be simulated for diverse patients. Several SD population-level models have contributed to a better understanding of infectious diseases including polio (Thompson and Tebbens, 2007; Thompson *et al.*, 2015), HIV/AIDs (Dangerfield *et al.*, 2001), tuberculosis (Atun *et al.*, 2007), chlamydia (Townshend and Turner, 2000; Viana *et al.*, 2014), Ebola (Pruyt *et al.*, 2015), middle east respiratory syndrome coronavirus (Shin *et al.*, 2017), and COVID-19 (Ghaffarzadegan and Rahmandad, 2020) and provided decision supports for national and global decision-makers. The underlying structure of these models is the foundational susceptible-infected-recovered (SIR) model.

The majority of the SD work in health areas have focused on population-level modeling of noninfectious diseases including cardiovascular disease (Homer *et al.*, 2010; Hirsch *et al.*, 2014), diabetes (Homer *et al.*, 2004; Jones *et al.*, 2006), cancer (Karanfil and Sterman, 2020), PTSD (Ghaffarzadegan *et al.*, 2016), chronic kidney disease (Kang *et al.*, 2018) and dental cavities among children (Hirsch *et al.*, 2012). Models of cardiovascular disease and diabetes often examine effect of diverse interventions on prevalence, mortality, and costs. In cancer research, the SD approach has been mostly used to replicate clinical trials or to identify the best screening regime to avoid overscreening or underscreening of cancer patients.

Individual-level models of weight gain and subsequent diseases (Abdel-Hamid, 2002; Lounsbury *et al.*, 2014), as well as models of major depressive disorder (Wittenborn *et al.*, 2016; Hosseinichimeh *et al.*, 2018) contributed to a better understanding of noninfectious diseases. This category includes physiological models of water and sodium regulation (Karanfil and Barlas, 2008), cholesterol metabolism (Demirezen and Barlas, 2009), hypothalamus-pituitary–adrenal axis (Hosseinichimeh *et al.*, 2015) as well as thyroid hormone dynamics (Seker *et al.*, 2011). An exemplary application in this category is the SD model developed for anemia management for patients with end-stage renal disease. The model provides individualized erythropoietin dose which has improved patient outcomes and reduced costs (Rogers *et al.*, 2018).

Articles in the special issue

In extending the SD literature on biomedical applications, the articles that follow in this special issue of the *System Dynamics Review* demonstrate that many significant medical challenges can be supported using a systems perspective, through the design, in an interdisciplinary manner, of quantitative models that provide valuable insights. Acknowledging the different perspectives of biomedical modeling, the issue commences with three *microscale* biomedical articles and then continues with two articles that are at an increasing level of aggregation, with longer time horizons, as the focus moves from physiological modeling to population-level health modeling. A brief summary of each contribution is now provided.

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Blood production is a highly regulated physiological process, and disturbances can pose a severe risk to human health. The related blood disorder Polycythemia vera (PV) is characterized by an excessive production of red blood cells (erythrocytes). In "System dynamics of cancer in erythropoiesis with multiple EPO feedbacks", Sajid, Andersen and Ottesen introduce a biomedical model of blood production, where the aim is to explore the growth factors that contribute to red blood-cell production. As context, the authors present a valuable schematic of the different stages involved in the development of erythrocytes and reference related SD articles that capture the behavior of the nonlinear dynamic structures present in the human body. Their modeling method results in a five-stock dynamic model with an interesting set of parameters from the literature and estimated via experimentation. They also generate a dimensionless PV model which is investigated numerically, with results encompassing steady state and sensitivity analysis. They combine this model with data from PV patients, and from this they demonstrate the utility of the model in helping to determine the likely course of a medical condition. The results indicate that efficient treatment needs to target stem-cell properties such as the bone-marrow microenvironment and stem-cell death rates.

Chemotherapies are nonselective drugs and target any cell that is going through rapid growth including healthy cells. As a result, one of the common side effects of chemotherapy is neutropenia—abnormally low number of neutrophils, a type of white blood cells. To keep neutrophils level above the neutropenic threshold, exogenous granulocyte colony-stimulating factor (G-CSF) is administered. Administration of G-CSF to minimize the damages of chemotherapy is a complex dynamic management task because G-CSF increases production of neutrophils and puts them at risk of being targeted by chemo agents. Thus, the timing of exogenous administration of G-CSF is critical. In "Dynamic trade-offs in Granulocyte Colony-Stimulating Factor (G-CSF) administration during chemotherapy," İrsoy, Güz, Akan, and Yücel, develop a system dynamics model of neutrophils production and processes related to the dynamics of G-CSF and a chemotherapy agent. They validate the model using clinical data and simulate G-CSF administration protocols showing that overuse of exogenous G-CSF may have unintended consequences and increases loss of neutrophils and stem cells. Although the numerical values generated by the model are sensitive to parameters related to the chemotherapy agents and patients' characteristics, the same behavior patterns are observed across different simulations. This study provides insights about contributions of mechanisms that drive the observed neutrophils behaviors during chemotherapy and G-CSF administration protocols, and it is a stepping stone toward personalized treatment of patients with cancer.

High-performance sports involve the human body and its associated dynamic complexities, as the performance of athletes depends on many factors, including their physiology. Unfortunately, some athletes look for methods and drugs to gain advantages in competition. In "Modeling the pharmacodynamics of nandrolone doping drug and implications for antidoping testing", Sahin, Senturk, Yasarcan, and Barlas address a new application of system dynamics to biomedical systems, which is a study of performance-enhancing drugs (PED) and the dynamic pathways of nandrolene, an anabolic steroid, which is primarily used to enhance muscle building for bodybuilding competitions. The use of nadrolene generates metabolites known as 19-NA, which are a target of PED detection tests. However, in order to mask the use of nadrolene, an inhibitor known as finasteride is taken by athletes, which leads to the inhibition of enzymes

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that turn nandrolone into its metabolite 19-NA. The authors present a dynamic model with key feedback structures and three interacting sectors, including: nandrolone's pathway, finasteride's pathway, and a reductase enzyme sector that connects the finasteride and nandrolone sectors. The dynamic model is tested using structural validity tests, and its outputs align well to data synthesized from the literature. A number of scenarios are explored showing the possible mechanisms where drug users can avoid detection before competing, and, based on these results, suggestions are presented that could improve testing processes for antidoping agencies.

Aging populations become increasingly susceptible to chronic diseases including chronic kidney diseases (CKD), which has become staggeringly more prevalent in the past 20 years and may lead to end-stage renal disease (ESRD). In "An evaluation of the impact of aggressive diabetes and hypertension management on chronic kidney diseases at the population level: A simulation analysis," Tan, Lui, and Ansah present a valuable modeling study on CKD, an emerging noncommunicable disease (NCD) globally with an ever-increasing burden on healthcare systems. The main objective of this study is to explore the impact of diabetes and hypertension management on CKD outcomes. The CKD outcomes of interest in this study include CKD events, CKD prevalence, and CKD-related deaths. To this end, they demonstrate the effect of several selected policy interventions on mitigating the incidence and prevalence of CKDs, based on a case study in Singapore. The article provides an informed overview of the disease area and is informed by evidence from randomized-controlled trials and Singapore Renal Registry and related literature. Results suggest that CKD outcomes can be improved, and CKD events can be reduced substantially if diabetes and hypertension patients are managed adequately, with focused interventions.

Over the past five decades, system dynamics modelers have addressed the global issue of growth and sustainability, and initial models – for example, those presented in book *The Limits to Growth* – highlighted that global population and economic growth might lead to food and resource shortages and also environmental degradation. In "Modeling global loss of life from climate change through 2060," Homer revisits the key feedback loop of *population-economy-environment*, and, as part of this new analysis, incorporates recent data on climate change and its impacts on loss of life. The model includes: a *population sector*, with age groups aligned with UN data and projections, where deaths are disaggregated by noncommunicable diseases, communicable diseases, and injuries; a climate sector, with greenhouse gas emissions (GHG) from fuel combustion, natural processes, and other GHGs; and a simplified economic sector based on a single stock of global GDP per capita. The model explores the extent to which feedbacks from climate change are likely to affect important population metrics such as life expectancy and years of potential life lost, and, as such, provides an exploratory step to assist global modelers to explore the impact of climate change on human welfare.

Conclusion

The application of system dynamics to health and medical issues has increased substantially over the past decades. Furthermore, recent advances in computing power, calibration methods, and data availability has created new opportunities for modelers to tackle a range of complex, and pressing, medical issues.

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In this special issue, we bring together new research that explores a fascinating array of biomedical problems, from the modeling of pharmacokinetics, hematologic disorders, and blood cell production to chronic disease progression at an aggregate level. This collection highlights the interdisciplinary strengths of system dynamics and its potential to facilitate genuine collaboration between teams of modelers and medical and health experts and thus explores important novel application areas for systems modeling.

Our closing message is an optimistic one focused on new opportunities, which is very much aligned with that from the recent systematic review of system dynamics modeling in health and medicine (Darabi and Hosseinichimeh, 2020), which is to invite SD health modelers to engage with interdisciplinary teams of medical and policy experts in order to explore exciting new biomedical research opportunities.


Özge Karanfil, Niyousha Hosseinichimeh and Jim Duggan
Email: james.duggan@nuigalway.ie

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