# A NOVEL HYBRID MODEL FOR CLINICAL DECISION-MAKING

# CORBIN STRAUSS MODEL AND RESILIENCE ENGINEERING

by

Hisham Mohamed Fathi Sherif

A dissertation submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Biomedical Engineering

Summer 2018

**A NOVEL HYBRID MODEL FOR CLINICAL DECISION-MAKING**

**CORBIN STRAUSS MODEL AND RESILIENCE ENGINEERING**

by

Hisham Mohamed Fathi Sherif

Approved: _____
Dawn M. Elliott, Ph.D.
Chair of the Department of Biomedical Engineering

Approved: _____
Babatunde A. Ogunnaike, Ph.D.
Dean of the College of Engineering

Approved: _____
Douglas J. Doren, Ph.D.
Interim Vice Provost for Graduate and Professional Education

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Nii Attoh-Okine, Ph.D.
Professor in charge of dissertation

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Mark Mirotznik, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Ryan Zurakowski, Ph.D.
Member of dissertation committee

I certify that I have read this dissertation and that in my opinion it meets the academic and professional standard required by the University as a dissertation for the degree of Doctor of Philosophy.

Signed: _____

Hagit Shatkay, Ph.D.
Member of dissertation committee

## ACKNOWLEDGMENTS

Prof. Nii Attoh-Okine, for always believing in me, for the advice and guidance, for the introduction to the world of resilience engineering, and for his strong support for this innovative idea.

Prof. Ryan Zurakowski, for his cordial teaching, for his emphasis on excellence, for support of my academic career, and for helping me rediscover some of my abilities.

Prof. Mark Mirotznik, for his continuous, unwavering support, for being a true friend and colleague, and for the introduction to the biomedical engineering program at the University of Delaware.

Prof. Hagit Shatkay, for her support and valuable insights on improving this work.

Prof. Dawn Elliott, for being instrumental in this opportunity to join the biomedical engineering program at the University of Delaware.

Ms. Erin Huston, for her outstanding, expert, and timely professional assistance in formatting and editing this work.

Mr. Daniel S., for the unwavering support and encouragement and the valuable help and insight into mathematical equations and functions

Dr. Leslie P., for believing in me, and for the caring, support and cheerfulness from my brilliant “special person”

## DEDICATION

To my parents and my late grandfather. Highly accomplished professionals and loving mentors who instilled in me the love of knowledge, learning and teaching; and the strive for excellence.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

## ABSTRACT

This work has been motivated by real-life experience regarding the challenging decision-making of high-impact interventions in complex, high-risk clinical situations, when recommendations from existing practice guidelines are either ambiguous or based on low-level scientific evidence.

The central research question is as follows: Can we develop a new model that integrates the expected, time-related course of the disease to estimate the benefit from intervention in improving survival and/or quality of life against the cost of this intervention in terms of risk to the patient, financial cost and healthcare system resources?

A literature review was conducted, with review of the existing methodologies for data analysis, the basis for optimal approach to data analysis, the Corbin-Strauss disease trajectory model and principles of resilience engineering.

The objective of this research is to introduce a novel methodology for data analysis that can help clinicians make time-related, patient-specific and disease-specific recommendations for diagnostic and therapeutic interventions.

To achieve this objective, this work introduces a novel, hybrid model for clinical decision-making through the utilization of the Corbin-Strauss disease trajectory, which describes the expected/historical pattern of change in functional status and/or survival over time in chronic conditions and integrates resilience engineering tools to quantify the change in system function.

Based on this, our research strategy included the development of a new resilience model, integrating the Corbin-Strauss trajectory.

To test this model, data from a local cardiac surgery database was utilized in an index case of aortic valve replacement for aortic stenosis. Several equations were tested to quantify the survival benefit in this model. Our findings support a resilience model incorporating the Corbin-Strauss disease trajectory as a tool to help quantify the benefit of interventions in terms of improved survival and/or functional status.

In conclusion, we introduce a novel, hybrid model based on the Corbin-Strauss trajectory and rooted in resilience engineering as a tool to assist in clinical decision-making, especially in complex, high-risk situations.

# Chapter 1

# INTRODUCTION

In medical practice in general and in surgery in particular, recommendations regarding diagnostic and therapeutic decisions have a serious, life-altering impact on patients and the people around them. This is especially true in the area of cardiovascular surgery, which deals with diseases of the heart and the major blood vessels (namely the aorta), from infants to the elderly. Such surgical procedures carry a high risk of death or serious disability. Their results impact the entire life span of the patient, in cases of children and infants. Therefore, decisions regarding operating on the thoracic aorta, for instance, often present a significant challenge.

Clinical practice guidelines were developed to provide evidence-based recommendations for safe, appropriate and effective diagnostic and therapeutic interventions for such high-risk clinical situations. A methodology for the hierarchy of the strength and reliance of scientific evidence supporting these recommendations has been developed by professional organizations.

However, these guidelines frequently offer little or no support for the clinician, since their recommendations are often vague and—more importantly—based on low-level scientific evidence. Examples of such situations include:

1. Recommendations for management of the aorta in females with Turner syndrome are based on the guidelines for a significantly different disease (Marfan syndrome)

2. Recommendations for replacement of the ascending aorta in Turner syndrome patients are based on low-level evidence (Consensus of Expert Opinion or Level C)

3. Recommendations for replacement of the ascending aorta in patients with bicuspid aortic valve disease are not well defined.

4. Indications for replacement of the ascending aorta in cases of bicuspid aortic valve disease are based on Level C (Consensus of Expert Opinion)

5. Recommendations for implantation of a left ventricular assist device (LVAD) in moderately advanced heart failure patients (New York Heart Association Functional Class IIIb) are unclear.

These examples of real life, everyday situations that clinicians face clearly demonstrate the inadequacy of recommendations from current clinical practice guidelines, thereby causing decision-making to be more challenging for both the patient and clinician. There remain several shortcomings of the current methodology for data analysis that supports the recommendations in these guidelines. Because such clinical situations impart a significant impact on the patient's survival, growth and quality of life, an improved and more effective approach to data analysis is imperative.

## 1.1 Motivation

The main motivation for this work stems from the following illustrative cases, which are all real situations encountered during the author's clinical career:

- A 37-year-old mother posing a question to the scientific panel of six distinguished experts during the annual Turner Syndrome Society meeting, regarding her 9-year-old daughter who had just been diagnosed with the condition. She wanted to know if she should agree to the highly invasive and high-risk aortic replacement surgery for the young girl, since the current guidelines consider her to be at an increased risk for aortic dissection. The response from the panel was that "We do not have enough data."

- A 46-year-old male, who was changing jobs. During the routine employment physical examination, he was noted to have a bicuspid aortic valve with an ascending aortic diameter of 4.7 cm. Patient was informed of the possibility of a major surgery to replace his ascending aorta because of a perceived increased risk for dissection. The cardiac surgeon presented the case in a major national conference dedicated to aortic surgery. However, the issue was not resolved due to conflicting data.

- A 32-year-old male with slowly declining functional status due to congestive heart failure, though he was still able to perform most of daily activities on medical therapy. He was not a candidate for transplantation because of social issues. The optimal time for implantation of an LVAD—based on "how sick" the patient is and the expected worsening of his functional status—could not be decided during a discussion in a major national meeting.

- A 25-year-old, morbidly obese female with rapidly deteriorating shock state due to end-stage heart failure, currently maintained on a short-term mechanical circulatory support pump and experiencing kidney failure. Body size and kidney failure preclude transplantation, and the shock state severely increased the risk for LVAD implantation. No reliable data exist about the probability of meaningful recovery of heart function in such situations.

## 1.2 Knowledge Gap

Changes in modern healthcare systems and practice have highlighted the following challenges:

- Quantification of the benefit of implementing high-risk, high-cost interventions in complex clinical cases is inadequate and is often left to "clinical judgment."

- In many clinical situations, the scientific evidence is insufficient or of low level and thus unreliable as a basis for life-changing interventions.

- Current guidelines do not support long-term projections about the results of interventions in terms of changing the course of the disease towards improved survival and quality of life, especially in younger patients.

- Current and emerging approaches for data analysis are not yet able to provide quantifiable predictions about the outcome of interventions to guide clinical decision-making.

In light of the paucity of data relating to this specific situation—with anecdotal and "expert opinion" evidence being the only options available—and the inadequacy of standard statistical approaches in determining risk (Sherif 2017, Rizzo 2014, Bertrand 2004, Dimik 2014), clinical decision-making regarding the implementation and outcomes of high-risk and high-cost interventions continues to be formidable challenges on a daily basis. Examples of such situations are the replacement of the ascending aorta in a young, asymptomatic female patient with Turner syndrome (Sherif 2016, Sherif 2015, Mauriera 2012) or the decision to perform mitral valve repair in mild-to-moderate valve insufficiency in the context of coronary artery bypass grafting (Chan 2012, Di Donato 2003). Such decisions are often called for in emergent, life-threatening situations, an example of which is the implementation of an extra-corporeal membrane oxygenator (ECMO) in cardiogenic shock, severe trauma or severe respiratory failure (Schmidt 2015, Schmidt 2013).

### 1.3 Scope and Objectives

The Corbin-Strauss model of disease trajectory (Corbin 1991) has been established in the medical and nursing literature as a graphical representation of the change in survival status, functional status, disability/dependence and/or quality of life over time in each specific disease.

This trajectory provides a better understanding of the temporal aspects of disease progression and their impact on survival, functional status and overall well-being; it is also a framework for correlating the scientific findings relevant to the disease process. This trajectory also depicts the results of various diagnostic and

therapeutic interventions, as well as “disruptive events”; i.e., disease genesis and trauma. The trajectory model comprises several “nodes” on the trajectory line, each corresponding to a “critical event” that shifts the course of the trajectory “up” towards improved survival/recovery or “down” towards deterioration/death.

As such, the Corbin-Strauss trajectory is a dynamic, graphical model of the performance of the system over time, through phases of stability, injury and recovery leading to the return to stability. Thus, the change in the trajectory line relative to disruptive events reflects the “hardiness” or “resilience” (Attoh-Okine 2016) of the system (on various levels from the cellular, organ or system to the entire organism).

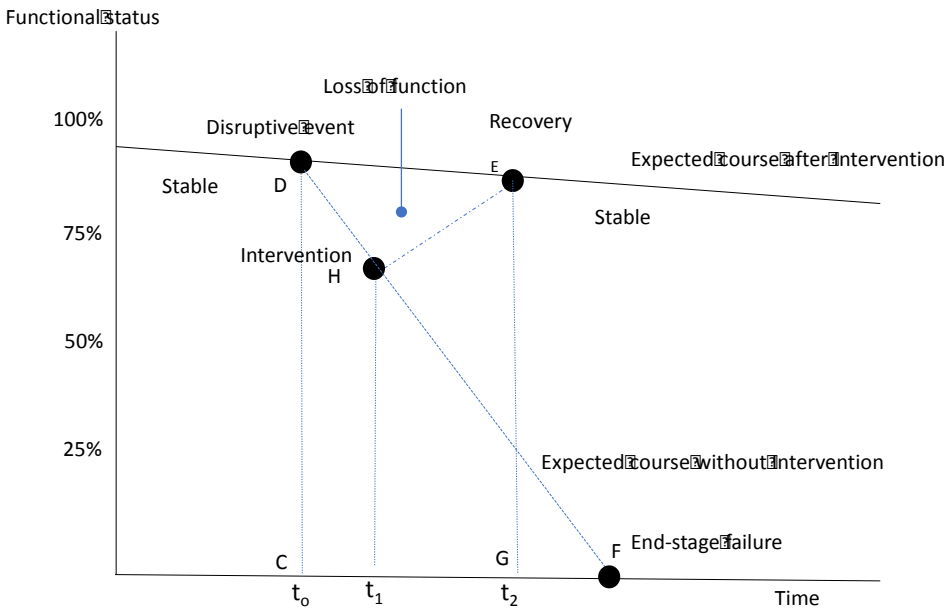



Figure 1 A simplified diagram of the resilience response

As Figure 1 details, the “normal” or expected functional status and/or probability of survival is represented by the point D on the actuarial curve (line A-D-E). Assuming D to be the point when the disruptive event occurs, the progressive change in functional status and/or survival follows the Corbin-Strauss trajectory (line D-H-F), with point F being the ultimate failure point (e.g., death) if the effects of the disruptive event are unaddressed. Thus, an intervention at point H should be expected to produce a shift in the functional status and/or survival towards an improvement in probability of survival and/or an improvement in the quality of life, i.e., recovery. This shift in the trajectory represents the goal of interventions: to recover or improve system function (at different levels from the molecular or cellular levels to the entire human body or populations).

Resilience is defined as the system’s capacity to recover its function to its baseline level after an event with a significant adverse impact on its performance. Mathematical relationships and formulae already in place (Attoh-Okine 2016, Bruneau 2003, McDaniels 2008) can be adapted to quantify the effect of introduced events (i.e., interventions) on the trajectory course within a specific period of time for a specific disease process in a specific patient.

### 1.3.1 Research Objectives

#### 1.3.1.1 Main objective

The formulation of a novel hybrid model for decision making combining the Corbin-Strauss disease trajectory model and resilience engineering.

#### 1.3.1.2 Sub-objectives

1. To formulate a novel model based on the Corbin-Strauss disease trajectory model and resilience engineering,

2. To utilize this hybrid model to quantify the probability of survival and/or functional status in an index case of aortic stenosis, using real-world data from the medical records of a local cardiac surgery group, and

3. To apply resilience engineering principles to quantify the probability of change in system performance (i.e., probability of survival) relative to the intervention.

4. To evaluate the performance of the proposed model in an index case of surgical aortic valve replacement.

## 1.4 Research Approach

### 1.4.1 Conceptualization:

An analysis of the principles and process for clinical decision-making by clinicians (especially physicians and surgeons) is discussed. The goal of clinical practice is to halt the course of the disease (i.e., effect a "cure") or slow its progression, thus improving survival, quality of life, independence and freedom from interventions. (Porter 2010, Buck 1992, Donabedian 1990). This expectation of outcomes is fundamental for safe, effective, equitable and affordable utilization of diagnostic and therapeutic resources to address the disease process.

Clinicians' approach to data is discussed: The focus is the established process for obtaining, identification and categorization of scientific data (Lomas 1989, Sherif 2009, Soley-Bori 2013, Denaxas 2015) in hierarchical levels of evidence that support different tiers of recommendations for practitioners, based on the perceived

importance or risk of the disease or condition and the known or expected benefit from the proposed intervention.

A trans-disciplinary approach is introduced: Instead of using the traditional approach to data and procedures limited to the medical disciplines, the analytical approaches (Hollangel 2015, Attoh-Okine 2016, Cimellaro 2017) used by different engineering disciplines, such as civil engineering, mathematical biology, etc., are examined. Their principles are utilized to introduce a novel model for data analysis.

### 1.4.2 Methodology

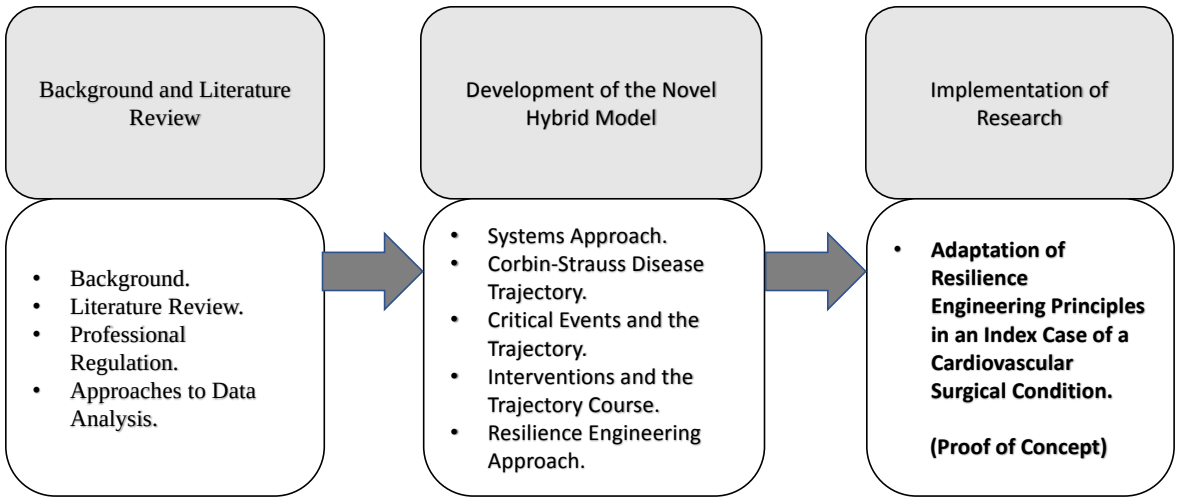



Figure 2 Details of research methodology

#### 1.4.2.1 Background and Literature Review

A historical background about medical decision making is presented. An extensive review of the scientific literature was performed. This review encompasses the following: A discussion of the basis, process and implementations for establishing guidance and accountability for clinical decision-making (Digby 1994, Kish 2001, Steinberg 2011). Professional regulations and the evolution of clinical guidelines as best evidence-based standards of practices to improve outcomes and protect the citizenry from the harmful effects of unregulated practice (Grimshaw 1993, Pronovost 2013, Sherif 2014).

Approaches to data analysis: A discussion of the current approaches to data in evaluating and stratifying scientific evidence from observational and experimental studies (Rizzo 2015, Denaxas 2015, Sherif 2015) including discussion of their limitations.

Wisdom in data analysis: A discussion of the incorporating wisdom as the basis for an approach to data analysis towards supporting a decision which is most likely to benefit the patient(s) in terms of maintained status of health, improved functional status and improved probability of survival.

#### 1.4.2.2 Development of the Novel Hybrid Model

A systems approach discussing the process line which details the sequence of events (Vincent 2004, Graves et al 2010, Sherif 2015) leading to the expected or observed outcome in clinical situations as the basis for understanding clinical decision-making and planning interventions designed to improve the outcome.

Corbin-Strauss disease trajectory: An introduction to the Corbin-Strauss disease trajectory model (Glaser 1975, Corbin 1975, Corbin 1991, Corbin 1998) as the

graphical representation of the time-related change in survival and/or functional status as a result of the progression of disease in specific clinical conditions.

Critical events and the disease trajectory: The sequence of specific events responsible for changes in the survival probability and/or functional status is emphasized as the basis for the progression of the disease (Robinson 1993, Conrad 1997, Bury 2010) and for planning points of interventions aimed at changing its course.

Impact of interventions on the trajectory: Using an illustrative example of a published analysis (Camboni 2011, Zangrillo 2012) of using extracorporeal membrane oxygenator (ECMO) in respiratory failure, the parameters of dysfunction and failure as predictors of outcome at the time of intervention are discussed.

Resilience engineering approach: An introduction to resilience engineering (Woods 2004, Attoh-Okine 2009, Attoh-Okine 2016, Hollangel 2006, Hollangel 2015) with focus on resilience in biology, is discussed. The basis for choosing a resilience engineering approach (Sherif 2017) to clinical decision making is discussed.

### 1.4.3 Implementation of Research:

Introduction of a new model: The resilience pathway, its phases, the resilience triangle, recovery patterns and trajectories are discussed. The graphical mathematical modeling of the resilience pathway and its variables are discussed.

Formulation: Through a review of the literature, different approaches to develop metrics for the resilience response were identified and relevant equations listed. The Corbin-Strauss trajectory model for aortic stenosis is discussed. A resilience model for aortic stenosis is constructed.

Proof of concept: Retrospective data were obtained from the medical records of a local cardiac surgery group. Exploratory data analysis was conducted and its results discussed. The probability of survival 30 days after aortic valve replacement was estimated. A model of the Corbin-Strauss disease trajectory was constructed to quantify the probability of survival without valve replacement surgery. Predicted values for the probability of survival according to the Corbin-Strauss model and the exploratory data analysis were compared. A resilience engineering model was constructed, incorporating the Corbin-Strauss model, to examine the probability of survival 30 days after aortic valve replacement. Different equations were implemented to quantify the resilience response in this index case.

Findings and limitations: Results of the equations and their interpretations were discussed. Comparison of the documented results from the local data set and results of the new model was performed. A commentary on the limitations of the study is included.

Concluding remarks: A discussion of the research conducted and their implications on future applications of this novel approach in different clinical situations. Examples are given to illustrate the potential benefit of this approach and future directions of its application.

## 1.5 Dissertation Organization

Chapter 1: Introduction

A brief discussion of the background and area of study is included. Discussion of the motivation to embark on this research is listed. The major objective and sub-objectives of this research work are detailed. Specific details of the research approach are described.

## Chapter 2: Background

This is an overview of clinical decision-making, including a background of the evolution and adoption of professional regulation of medical practice through clinical guidelines towards a safe and effective practice; the basis for identification and selection of scientific evidence to support recommendations for medical interventions is also discussed.

Chapter 3: Basic Medical Decision-Making

This chapter presents a discussion of the basic principles in approaching data selection, organization and categorization as the foundation for making "wise" clinical decisions; *i.e.*, responsible, safe and effective clinical management strategies designed to have the optimal benefit for the patients in terms of improved survival and/or quality of life.

Chapter 4: The Corbin-Strauss Disease Trajectory Model

The Corbin-Strauss disease trajectory model as a descriptive model of time-related changes in disease course relative to critical events and interventions is discussed. This model is introduced as the basis for incorporating resilience engineering to develop a novel, hybrid model for data analysis.

Chapter 5: Formulation

This chapter includes a discussion of resilience of complex systems in engineering and in biology. Details of the resilience pathway and equations to quantify the change in system performance are discussed. As proof-of-concept, a resilience model for aortic stenosis is constructed. Exploratory data analysis using a local data set was conducted. The model was then tested using the same data set, and results of the conventional approach and the new approach were compared. A commentary about the results and limitations of the study is included.

Chapter 6: Concluding Remarks

A discussion of the results of this research work in incorporating resilience engineering in medical and healthcare decision making. A discussion and examples of possible future directions for applications of this approach are included.

## Chapter 2

## BACKGROUND

For millennia, the practice of medicine has been limited to an elite group, often the priests of gods, who were capable of producing dramatic results in terms of survival and cure. Ancient documents (Ghallioungui 1987, Feldman 1999) demonstrate the first instances of recommendations for medical decision making: "*…say: This is a condition I shall treat".*

Until recently, medical practice had a high level of variation between different practitioners. Moreover, the limited amount of medical information (Sherif 2014, Ackerknecht 2016) available at the time was scarce and only available to this elite group. These practitioners were considered infallible holy men or even gods (Risse 1986). Their decisions and recommendations unquestionable and above reproach. An adverse outcome was never seen as the result of inappropriate diagnosis or treatment.

The Enlightenment in medical education (Smith 1980, Hajar 2013) changed medical practice to be based on rigorous scientific knowledge rather than social status.

Guilds were the first organization attempting to set of standards of medical practice (Robinson 1984, Pelling 1997, Briggs 2005) for the practice of surgery. These standards were based on the best available scientific evidence. Later, the Royal College of Surgeons emerged as the sole authority for regulating the practice of surgery. Its mission statement affirms this: "committed to promoting and advancing the highest standards of surgical care for patients, and regulating the practice of surgery."

Thanks to advances in the 20th century, the medical professional is no longer regarded as an infallible holy man, whose words, directions and decisions are never contested but rather as the true human professional he/she really is: A knowledgeable, highly educated, trained and skilled practitioner making decisions based on the best available and accessible information and held accountable for the outcomes of such decisions. Fortunately, the basic underpinnings of medical practice aiming to "do no harm" (Smith 2005) and striving to offer the most possible benefit to the patient—in terms of improving survival, reducing or eliminating pain, suffering and disability—remain as steadfast today as in Hippocrates' time.

## 2.1 Field of Study

### 2.1.1 Professional Regulation and Clinical Practice Guidelines

The area of exchange of services involving the health and well-being of people has been known as the Medical Marketplace Interactions between the demand side (i.e., patients or the "consumers") and the supply side (i.e., medical practitioners) have changed drastically over the centuries (Digby 1994, Bodenheimer 1999, Hall 2007). Fierce competition (Posner 1975) among the "providers" existed, each vying for their own "market share" and the opportunity to make quick profits without consideration for the risks to the unsuspecting public.

The first serious efforts to regulate (Browne 1935, Maks 2002, Garoupa 2004) the practice of medicine, with an objective of protecting the citizenry and promoting the safety of the public, were the formation of professional organizations (i.e., colleges, societies, boards and associations) dedicated to:

1. Define the requirements in education, training and skills to practice a specific area of medicine.

2. Develop clear, scientific, evidence-based guidelines for the safe practice of the profession.

3. Determine the competency of candidates to safely practice medicine.

4. Provide a mechanism to hold practitioners accountable for their decisions as compared to the standards-of-care.

This evolution of these bodies (Ackerknecht 2016) has dramatically influenced the practice of medicine, restoring its main objective of preventing harm and improving survival and quality of life. This fundamental principle of safety (Knebel 2003, Leape 2009) remains the sine qua non foundation of quality of medical practice for all medical professionals and the major incentive to join this prestigious profession.

The 20th century has witnessed a dramatic and explosive growth in biomedical knowledge, connecting with other fields such as data storage, material science, biomedical engineering, mathematical modeling, simulation and bioinformatics. This multidisciplinary overlap continues provide us with a vast volume of rapidly expanding data.

For instance, the Human Genome Project (Sawicki 1993, Kelavkar 2006) has enabled practitioners to offer treatment of conditions previously deemed untreatable. Advances in the development of devices have had a tremendous impact in improving survival and the quality of life for numerous patients. Partly because of increased public awareness of such advances this has created an ethical dilemma when a patient is “kept alive” for an extended period of time (Bramstedt 2008) and at an exorbitant cost simply because the technology is readily available.

These heightened expectations of ‘miraculous outcomes’ even in dismal clinical situations and rising demand from the public for the most advanced, and expensive therapeutic modalities has strained the available resources of the healthcare

system. In addition, there has been a dramatic increase in the number and cost of litigation against medical practitioners at all levels, increasing the cost of malpractice insurance. This led to a shift towards defensive medicine, including unnecessary interventions to defend their decisions; further increasing the cost of healthcare.

Besides, the increasingly active role of industry in influencing medical practice has contributed to an increase in the number of sponsored clinical trials examining "products" ranging from food substances and additives to artificial organs. The established industry marketing, cost versus profit, "customers" versus "patients"—has dramatically changed the landscape (Hall 2007, Angell 2008) for medical practice.

Practitioners are hardly keeping abreast of the latest findings from basic sciences and other areas of research, let alone incorporating them in their practice.

Recently (Bloche 2002), the influence of non-medical administrators dictating specific practices has grown. This is driven by insurers and their own assessment of risk in terms of reimbursement—not outcomes. In the well-publicized "sugar window" (Fullerton 2014) report of regulation for the cardiothoracic surgical community, the entire hospital was held accountable and sustained punitive financial measures based on an arbitrary, single measurement that was inappropriately used as a "metric" despite being unrelated to the outcomes, safety or quality of the clinical process.

Therefore, over the past decades, more and more practice guidelines have been developed –and are being promoted by such authorities as the Institute of Medicine (Field 1990, Audet 1990)—with the following goals in mind:

- To clearly define therapeutic goals—in terms of irreversibly halting the disease process ("cure"), altering or delaying its course, thereby improving survival and quality of life.

- To improve healthcare quality through: standardization of safe, effective and appropriate interventions.
- To promote the highest yield at the lowest cost to the patients, payers and the healthcare system.
- As the basis for metrics of success or failure of therapy.

Though imperfect, clinical practice guidelines remain a foundation for healthcare practice. These recommendations for safe and high-quality healthcare practice have been credited with improving survival and quality of life for millions as they are being adopted by more healthcare authorities and practitioners around the world. Additionally, these guidelines provide a sustained momentum to scientific research in medical, biomedical and biotechnology fields. This constant feedback and interdependence between regulatory agencies, professional organizations, healthcare practitioners and the scientific community continues to prove beneficial for the health and welfare of patients everywhere.

## 2.2 Current State of the Art

### 2.2.1 Derivation of Clinical Guidelines

Most of the clinical practice guidelines in force today are based on a consensus of a group of experts (Hiratzka et al 2010, Epstein et al 2002) in the field through writing groups and task forces assembled by professional organizations; to provide safe, evidence-based recommendations for specific clinical problems deemed of high importance, risk or population impact. Such groups review the scientific literature and establish a hierarchy of the level of evidence depending on the type of research addressing the field that has produced this evidence.

The standards for developing and stratifying scientific evidence supporting the recommendations for diagnostic and therapeutic interventions is illustrated in the following excerpt from the 2010 guidelines (Hiratzaka et al 2010) for management of thoracic aortic disease, issued by a combined task force from several professional organizations.

Table 1 Classification of recommendations as based on the level of evidence

| Level of Evidence |
|---|
| Level A:<br>Multiple randomized-controlled trials or meta-analysis of multiple large populations |
| Level B:<br>Single randomized or non-randomized studies of limited populations |
| Level C:<br>Consensus of experts' opinions, case reports. very limited populations |
| Classes of Recommendation |
| Class I:<br>Benefit is MUCH > risk. SHOULD perform intervention |
| Class IIa:<br>Benefit > risk. REASONABLE to perform intervention |
| Class IIb:<br>Benefit ≥ risk. May CONSIDER intervention |
| Class III:<br>No benefit/ harmful. Should NOT perform intervention |

As outlined in the table, the level of evidence assessment for each recommendation is not indicative of the rigor of the scientific evidence supporting it.

The highest level (Level A) is data from multiple randomized, controlled studies, which offer the optimal opportunity to evaluate the causative effect of factors contributing to the disease process. However, such studies are often impractical, high-risk or unethical to conduct. Therefore, much reliance has been given to lower-level evidence (Level C) or Consensus of Expert Opinion, which is essentially the common conclusion of personal experiences and viewpoints of such senior figures. It is estimated that only 11% of these recommendations are based on evidence from the "gold standard" (Sullivan 2011, Bothwell 2016) of controlled randomized trials. Reasons for this are multiple and include ethical considerations, difficulties in recruiting subjects, funding issues and disappointing results from some trials—at a considerable cost.

In assessing the results from all such clinical trials, the standard methodology for statistical analysis is always employed. Assumed distribution with measures of central tendency, deviation, mean, median and p values provide the bedrock foundation for examining and interpreting all scientific evidence. As expected, case reports and anecdotal evidence ("expert opinion") do not lend themselves to such mathematical analysis. Yet, such unquantifiable, low-level evidence still provides the 'foundation' for high-level recommendations that have a significant impact on patient's lives and welfare.

### 2.2.2 Inadequate Adoption of Guidelines

Despite their important role in improving survival and quality of life for patients, clinical practice guidelines remain under-utilized (Cabana 1999, Pronovost

2003) by the healthcare community, but may be over-utilized by the regulatory agencies and healthcare payers, such as insurance companies.

A balanced, rational approach to understanding and implementing these guidelines remains elusive. Several factors contribute to the under-utilizations of clinical practice guidelines:

Awareness:

The majority of practitioners are struggling to keep abreast (Balk 1997, Cruse 2002, Holland-Barkis 2006) of the recent results from scientific studies and the subsequent recommendations through conferences and journals; especially research emerges from a different discipline or specialty.

Applicability:

Since current practice guidelines are developed to address the most common (therefore most studied), most risky or most famous conditions, their application to (Mansfield 1995, Olesen 1997) less frequently encountered or rare conditions is less than optimal.

Relevance:

Most scientific studies emerge from industrialized countries in Europe, North America and Asia. Though well-designed, rigorously executed and analyzed, practitioners in other parts of the world may consider the results not relevant (Klein 2002, Ahmed 2003) or inapplicable to their own population.

Reproducibility:

A recent article in *Nature* (Baker 2016) reports that researchers have not been able to duplicate the published results of over 70% of scientific studies, including the

original researchers in many cases. This lack of reproducibility casts a shadow of doubt over the results of such studies as the basis of clinical decision-making.

Precision:

Clinical guidelines are often based on intermediate and low-level scientific evidence, derived largely from small-sized studies and even anecdotal evidence. Thus, they do not have the statistical power to make well-supported recommendations. (Alston 1997, Hutchinson 1996, Sherif 2016)

Credibility:

Since many of the guidelines are based on expert opinion, there is an inherent suspicion among practitioners that these are not necessarily scientifically valid or that they are even outdated. (Steinberg 2011, Rosenfeld 2013, Sherif 2016). This continues to be a major barrier to developing and adopting guidelines.

Trust:

Guidelines are developed by small groups of 'experts', with little or no input from other stakeholders, such as allied medical personnel or patients. This disconnect between these experts as professional regulators (Salem-Schatz 1997, Christianson 2005, Tiler 2008) and actual users results in a mistrust of recommendations seen as "top-down". Importantly, the increasing influence of non-medical administrators drafting institutional or national guidelines has led to increasing resentment from practitioners who consider these administrators to be "telling professionals how to do their job".

Adaptability:

Based on their unique knowledge, medical professionals have always developed their own self-regulatory mechanisms. (Weiss 1982, Light 1986, Cutler

2009, Sherif 2016) Hence, they are usually averse to regulations perceived to force them to practice “standardized” or “cookbook medicine”. This is especially relevant in the current era of “industrialized or corporate medicine.

Liability:

Existing guidelines are seen as the “gold standard” for practice, and any perceived deviation from these recommendations is considered malpractice. Therefore, many practitioners are shifting their decisions (Kessler 1996, Studdert 2005, Banja 2010, Sherif 2014, Bishop 2010) towards adhering to the letter of the recommendations at all costs.

These barriers to adoption are due to the paucity of a rational, common sense, easily understandable and adaptable set of clinical practice guidelines. A discussion of the characteristics (Nathan 1998, Seligman 1996, Grol 2003, Pronovost 2009, Lugtenberg 2009) of such guidelines follows.

## 2.3 The Ideal Practice Guidelines

By definition, clinical practice guidelines serve a dual role:

On one hand, they function as triage models, aiding the clinician in establishing a quick and accurate diagnosis of the condition or the problem at hand, as well as the level of severity and/or urgency associated with it, based on the predicted risk of this specific condition at this specific juncture in the course of the natural history of the disease.

On the other hand, they are meant to be powerful decision support systems, providing the rationale, scientific foundation and predictive property to the course of action decided upon, whether diagnostic or therapeutic. The body of evidence and supporting the guidelines should help the clinician choose the decision most likely to

beneficially impact the natural history of the disease for this specific patient at this specific time, given the other factors influencing this natural history.

As such, an ideal set of practice guidelines should be:

1. Relevant: Guidelines should aim (Davis 1997, Lohr 1992, Laine 2011) to address the most common, most serious or most significant complication(s) of a specific disease process or a group of diseases sharing common pathophysiologic or clinical features.

2. Encompassing: Guidelines should provide recommendations for all possible effects or complications of a disease process or a treatment modality. (Hutchinson 2003, Burgers 2003) This offers an opportunity for the utilization of the increasingly large volume of data.

3. Reproducible: Recommendations should be expected to have the same result when applied to the disease process with a fairly high degree of consistency. (Grimshaw 1993, Grimshaw 1995, Grilli 2000)

4. Individualized: Diagnostic and therapeutic modalities must have a tailored approach (Marshall 2000, Eddy 2011, Reach 2014) to accommodate for the high degree variations in phenotypes, biology and quality of life.

5. Engaging: The welcome trend of empowering patients (Toman 2001, van de Chiaramonte 2008, van de Bovenkamp 2009) in shared decision-making as the central members of the healthcare team requires that different but complementary versions of guidelines for different "users", e.g., patients, caregivers, nurses, etc.

6. Easily applicable: Guidelines are meant to be applied to the largest patient population possible. They must be formulated in clear language, using clear objectives, with clearly defined intervention criteria. (Terenziani 2004, Abidi 2006, Pérez 2010)

7. Expandable and adaptable: As the body of scientific literature rapidly expands, (Shekelle 2001, Boxwala 2001, Rosenfeld 2013) thanks to the increasing communication and collaboration between different scientific disciplines, guidelines must be designed to accommodate new data.

8. Logic-based (common-sense guidelines): Medical practice in general is a complex environment. Surgery, and particularly cardiovascular

surgery, deals with complex, high-risk, life-changing situations. Thus, guidelines should incorporate not only the clinical data but also personal, legal, financial and ethical considerations. (Dans 1994, Wang 2002, O'Connor 2005, Sherif 2016).

9. Incorporating predictive properties: The complex, dynamic, changing clinical environment offers a highly non-uniform and highly "unstable" data set that responds to factors, such as growth, physical activity lifestyle choice, pregnancy, etc. (Burgers 2004, Porter 2010) Therefore, guidelines should support decisions based on data sets predicted to happen in the future (e.g., career change or pregnancy).

10. Probabilistic: Instead of a 'snapshot' approach to data analysis, guidelines should adopt a dynamic approach based on addressing the clinical conditions most likely to be high risk, high impact or resource-intensive. (Borum 1996, Sherif 2009, Sherif 2015, Mitchell 2008, Peleg 2013)

11. Systems approach: Modern healthcare is shifting from the single practitioner model to multi-disciplinary teams, especially in high-risk areas. (Cretin 2001, Terenziani 2004, Brouwers 2010) Therefore, guidelines should incorporate recommendations from other disciplines involved in the management plan.

A report by the Institute of Medicine in 2011 lists over 3700 clinical practice guidelines in existence in 39 countries. At the same time, the number and cost of medical errors (Brennan 2000) have continued to rise, being responsible for an estimated 94,000 to 143,000 preventable deaths and over 1,000,000 injuries each year. Clearly, what is needed is not more regulations but rather more precise and effective regulations. One of the most formidable challenges towards this goal is the sheer volume of scientific evidence since the first guidelines were introduced over 25 years ago. However, this also offers a great opportunity to base modern guidelines on a robust, wide-ranging and constantly updated volume of data. The rapid growth and widespread implementation of bioinformatics and artificial intelligence tools holds

great promise towards more dynamic, better structured, more precise clinical practice guidelines.

## 2.4 Approaches to Data Analysis

Statistical analyses of clinical or healthcare data face several challenges: Errors in measurement decrease their precision (Soley-Bori 2013, Denaxa 2015), especially in smaller-sized populations. The correlation between the variable and its predictor significance is very important, thus making using too many predictor variable correlations undesirable. In addition, most statistical analytical approaches assume a normal or quasi-normal distribution. Standard approaches work best with a smaller number of variables, particularly those that are discrete or categorical in nature. This limits their efficacy in incorporating continuous variables or borderline states. Overfitting (Rizzo 2014, Hawkins 2004) the model by including too many variables can lead to imprecise measurements. In addition, current analyses are based on static past observations, limiting their predictive power.

## 2.5 Developing Improved Guidelines

Clinical practice guidelines are evidence-based recommendations in support of clinicians' decisions and actions towards the foundational goal of healthcare of improving survival and quality of life through safe, effective, reliable, appropriate care with the optimal utilization of resources. This holistic, altruistic principle remains the bedrock of healthcare at all times, regardless of the methodology or tools implemented in its practice.

Guidelines also aim to reduce errors and unjustifiable practices. In processing the relevant body of scientific data, the goal should always be to utilize analytical data

approaches that have (ideally) zero or negligible margin of error, to further promote the safety, reliability and usability of their recommendations.

Thus, the ideal set of guidelines (Woolf 2000, Miller 2000, Séroussi 2004, Grando 2011, Peleg 2013) must be goal-oriented, i.e., its objective must be to meet the goals of care defined by the specific patient or population, not just addressing an isolated factor in the clinical situation. It also should be process-based; i.e., based on a comprehensive understanding on the multiple factors involved in the causation and progression of disease and not focused on one or a few parameters.

Guidelines must support precision medicine, i.e., patient-specific, disease-specific, disease phase-specific assessments. This is through offering a dynamic, time-dependent assessment of the risks and benefits of interventions relative to specific points along the patient's lifetime and/or the course of the disease.

In order to increase their acceptance and compliance by practitioners, guidelines should strive to mimic the reasoning and decision methodology (Hunt 1998, Sherif 2006, Lugtenberg 2009, Taylor 2013) relatable to and understandable by clinicians and patients; as opposed to mechanistic processing of data (Brooks 2017).

The introduction of computer-based analytical and modeling tools (Grando 2010, Latoszek-Berendsen 2010, Papagregoriou 2012, Peleg 2013), including artificial intelligence tools, in the generation and interpretation of clinical practice guidelines utilizing electronic health records (EHR), holds promise for incorporating the ever-growing volume of data from different disciplines. These approaches, however, must adhere to these established principles that govern practice at all times and maintain the privacy and anonymity of patients' confidential information.

## 2.6 Summary

Clinical practice guidelines remain instrumental in promoting professionalism and ensuring high value in healthcare by providing rigorous analysis of the available scientific evidence relevant to and impacting diseases and interventions with the goal of promoting the cornerstones of quality in healthcare: safe, appropriate, reliable, reproducible and affordable care through patient-specific, disease-specific, time-dependent interventions towards the goal of improving survival, preventing disability and improving quality of care. The utilization of advanced tools for data analysis is promising for the possibility to utilize the vast volumes of available healthcare data, while adhering to the fundamental principles of quality and professionalism in the practice of medicine.

# Chapter 3

# BASIC MEDICAL DECISION-MAKING

## 3.1 Quality in Healthcare

Since ancient cultures, physicians were held in high regard because of their beneficence and altruism (Beauchamp 2007) in offering treatment towards preventing harm and promoting the benefit of mankind.

This deep-rooted concern for the safety and well-being of patients is at the very foundation of the practice of medicine (Miles 2005) and constitutes its core mission: To reduce harm, pain and disability, to improve survival and the quality of life. The ancient and modern versions of the Hippocratic Oath both stipulate: "…*for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice".*

Quality of healthcare (Kimberly 2000, Harteloh 2003, Porter 2010) can be simply defined as "what matters for patients and is a common interest for all stakeholders in the healthcare system". As such, it is the nominator in the value equation, with the denominator being the cost of healthcare and its delivery. Since healthcare is primarily concerned with improving survival and quality of life, the principles of high-quality healthcare include:

- Safety: This is the most important criterion (AHRQ 2007, Mitchell 2008) The "first principle" is "do no harm" or "*primum non nocere*".
- Reliability: Healthcare interventions must have a high degree of reproducibility, which makes their effects reliable. (Cheng Lim

2000, AHRQ 2002) In other words, they must have a high probability of producing the same effect every time.

- Appropriateness: Healthcare interventions must be the best suited for the specific disease in a specific patient. (Joint Commission 1990 and 1997, Runciman 2012)

- Timeliness: (AHRQ 2002, Elixhauser 2005) Medical interventions should be dynamic, reacting in real time and evolving with the disease process.

- Outcomes: The central criterion of quality in healthcare (AHRQ 2002, Elixhauser 2005, Batalden 2007) improved survival, improved quality of life and freedom from disability and support.

## 3.2 Wisdom in Data Analysis

All actions and decisions are based on information (i.e., data) relevant to the specific situation or problem to be addressed (Rowley 2007, Frické 2009, Jifa 2014). The following principles from information engineering illustrate the hierarchy of levels of data analysis:

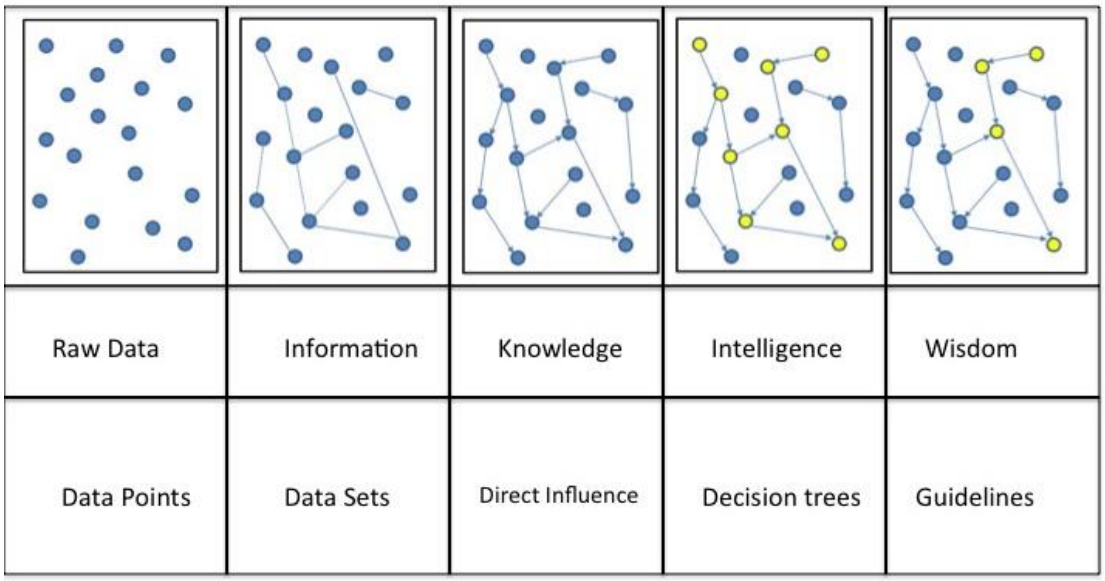



Figure 3 The hierarchy of information processing levels

Raw Data: This simply the identification of various data points observed or measured in the specified environment (Ackoff 1989, Rowley 2007). One example is the identification of the individual chess pieces and their positions on the chess board. Though vast in volume, (Schaller 1997) it is impossible to reach any meaningful conclusion from this disorganized data.

Information: The classification and categorization of the data points into data sets (Rowley 2006, Rowley 2009, Aven 2013). This requires describing logical or mathematical relationships between two or more data points. Such as grouping of the chess pieces in related categories: Pawns, Rooks, Bishops, etc. Grouping data points in categories is the first step towards identifying associative relationships.

Knowledge: Associative, influence and perhaps causative relationship between small data sets, and their hierarchy can be recognized here as direct or multi-linear relationships. In the chess example, we know that the pawns have the lowest level of

influence, and the Queen has the highest level of influence. Other pieces' influence on the chess board activities falls in between these two limits.

Rife with simplistic assumptions, this is the lowest level of scientific evidence and the domain for rule-based decision-making (Bellinger 2004, Rowley 2006, Rowley 2009, Bernstein 2011). Interestingly, several clinical practice guidelines are still based on such one-dimensional rules.

Intelligence: By examining the relationships between data in multiple dimensions, sequential cause-and-effect relationship patterns emerge among moderate size data sets (Hey 2004, Rowley 2009, Bernstein 2011, Aven 2013) and in networks. In the chess example, moving the Knight in a certain direction to a specific location on the chess boards creates a specific benefit for the player and risk for the opponent. Thus, each event (piece movement or activity) is a 'critical event'; with its own specific impact on the course of the chess game as a whole.

Since they rely on higher-order mathematical analysis of the relationships between different data sets, the level of scientific evidence is higher and more reliable. This is where clinical pathways and management algorithms are developed and, with a vision for automated medical practice—since such well-structured flowcharts are better suited for computer-based decision-making (Bergmann 2002, Jankowski 2008, Bernstam 2010), hence the term "artificial intelligence".

Wisdom or Higher Intelligence: Often described as an area of philosophy, this may be better termed "strategic planning". This is where chess masters excel: coordinating multiple combinations and variations of individual pathways towards formulating a successful strategy for winning the game.

Making a “wise” decision (Towle 1999, Bornstein 2001, Rothman 2017) requires the ability to formulate the optimal realistic, fact-based pathway to reach the desired goal in the safest way, with the best utilization of resources. Examples of this approach include the decision to implant a ventricular assist device in a moderately sick patient, whether to replace the ascending aorta in cases of Turner syndrome, and other controversial situations.

This hierarchy of knowledge or hierarchy of information serves as a basic platform for processing or “making sense of” observational and measured data. In business, this is referred to as “operationability”, or the ability to produce beneficial results (Melé 2010) according to planned goals, in the environment (system, organism or organization) based on the optimal utilization of data and pathways.

The key principle thus becomes the definition of the goal towards which the structure for data analysis should be directed. This can take the form of a research question, a hypothesis or a specific outcome. In all these cases, this goal must be the primary drive for the analytic methodology. In other words, the goal should always be: ”How does evidence (data) support the answer to this specific research/clinical question?”.

Reliance on standard statistical approaches has its shortcomings, resulting from general, unguided statistical data-driven analysis. Two papers (Austin et al 2006, Austin et al 2008) demonstrate the dubious yet statistically supported conclusion that the zodiac sign does indeed influence patients’ risk for congestive heart failure or pelvic fracture.

A recently introduced approach is the “bottom-up”, which relies on identifying patterns (obvious or hidden) in raw data and using these results as the foundations for

decisions. This approach is often based on neural networks, which rely on assumed simplistic universal connections (“edges”) between data entities (“nodes”). Though this can be useful in large volumes of data, it is based on statistical generalizations or “universal statements”, with the basic understanding of “inference” that these data points are “true”.

The random data associations between large numbers of nodes along numerous edges in neural network models (Hayes 2015, Nguyen et al 2015) sometimes produce unrealistic results (Google DeepDream project 2017) of non-existing patterns in images of hillsides or cloud formations. Basing healthcare interventions on such results of data analysis in a clinical environment can be catastrophic to patients’ outcomes.

This highlights the difference between astrology and astronomy as two different approaches to data analysis. Both rely on the same data set of the positions and trajectory of heavenly bodies. In astrology, assumed relationships between stars have produced entire non-existent universes of gods and other creatures. This is a poorly structured, non-goal-driven approach that relies on unfounded assumptions about data truth, validity and association. In contrast, an intricate device known as the Antikythera Mechanism, (Freeth et al 2006) was constructed 2000 years ago using a complex set of gears to calculate the position of stars and other heavenly bodies for the purpose of safe and precise navigation. This methodology uses a scientific, purpose-driven approach to properly organize data according to realistic, fact-supported assumptions

The result of these two methodologies to analyze the same data set could not be more different or more significantly impactful on peoples’ lives and safety. Those

who follow recommendations from the astrologers or the daily horoscopes would almost certainly get lost during their journey, if they ever decide to take it in the first place. Meanwhile, those relying on sound, scientific, purpose-driven navigation tools would be more assured of reaching their destination safely.

Paraphrasing the words of Popper (1963): *starting with pure observation in nature alone without any theory is absurd*. In less strong words, however, simplistically relying on raw data alone without having a logical structure is not sound and can actually be misleading or even harmful.

The more realistic approach is to start by identifying the problem that needs to be solved and the goal of our solution, or the desired outcome. This will guide the optimal, most efficient methodology to analyze and utilize the data at hand to reach that goal. Insights from Game Theory are invaluable in producing the optimal "yield" or "reward" in this regard. In other words, these insights should provide a plan to best play the hand that one is dealt in order to win the card game or formulating the most successful strategy to reach this goal with the most efficient utilization of resources, which is defined as resource management.

### 3.3 Wisdom in Healthcare Decisions

*"It is much more important to know what sort of a patient has a disease than what sort of a disease a patient has."* --Sir William Osler.

This quote summarizes the essence of healthcare: How to best address the impact of the disease or injury on that specific patient being examined. The nursing profession has recognized this foundational principle (McKie 2012), since the 1960s, describing the underpinning of the nursing theory:

Scientific knowledge (or episteme) is coupled with a thorough understanding of current technology (techne) and guided by ethics (phronesis) to form a basic framework of caring (sophia). Interestingly, "sophia" is traditionally translated as "wisdom".

The definition of wisdom according to Matney et al (2011) can thus be modified to describe wise healthcare decision-making as the "application of information through technology; mediated and guided by ethics and values, toward the common good (goal) for the entire healthcare team, centered around the patient".

In this context, the Berlin Wisdom Paradigm, developed around 1993 (Baltes & Staudinger, 1993; Smith, Dixon & Baltes 1989; Baltes & Staudinger 2000) offers insight into the application of wisdom in processes that require "judgment", typically involving complex and/or high-risk environments.

The Berlin Wisdom Paradigm describes a methodology to integrate information (or data) organized in different "themes", as a framework for optimal utilization of any set of data, guided by ethics and person or patient-specific interests, values and goals.

According to this model, a huge volume of population data can be "filtered" or adapted according to the specific problem addressed at the time, for which an effective, realistic solution is being sought. This application of data derived from a large data set is guided by the specific criteria for quality which govern the safety, appropriateness, reliability, and cost-effectiveness of the possible diagnostic and/or therapeutic interventions).

These influences are then processed and organized to formulate a planned action, which then requires an "action management plan" (McKenna 2005), which is

then appropriately implemented. The results of this implementation are then reviewed, providing feedback towards adjustments and corrections of the entire process.

Thus, the role of wisdom reflects the important principle of "*multum, non multa*" or "Much, Not Many" (Wright 1979). The sheer volume of data in itself creates a dilemma as to how to "make sense" of it all. The great Einstein reminds us that "information is not knowledge", and Dr. Osler also details how information (or data) is but bits and pieces of "building blocks", if you will, that bear no resemblance to the end result, much like how wheat resembles bread. Full knowledge of all the available parts (data sets) still requires a sound, process-based and goal-directed methodology to process it, in order to reach a meaningful, effective and safe outcome in clinical practice.

### 3.4 Summary

The emerging principle of patient-empowered, patient-centered decision-making emphasizes collecting every bit of information (i.e., data) about the patient, their family, their support system, their values and their wishes as the central stakeholder (Lindman 2014) in making decisions about interventions that have a significant impact on his/her longevity and quality of life. In this context, the role of the clinician in identifying and correlating these data points is paramount in advising the patient about the best decision regarding the plan of management that will lead to the highest benefit as defined or desired by the patient. This approach in wise decision-making integrates scientific knowledge, empathy and ethics towards improving the quality of care offered to the patient. In contrast, reliance on mechanistic data analysis has the risk of producing unrealistic or unrelated results,

which can have a harmful impact on the patient, against the foundational principles of healthcare practice.

# Chapter 4

# THE CORBIN-STRAUSS DISEASE TRAJECTORY MODEL

## 4.1 Background

Since its decisions and outcomes have a significant impact on patients' survival and quality of life, the practice of medicine has traditionally been closely intertwined with the supernatural, since effecting a positive change by reversing the effects of disease or injury was regarded as a "miracle". In ancient civilizations, physicians were also priests of the gods, and sometimes seen as gods themselves (Sherif 2014). Their decisions were unchallenged, with no accountability for adverse outcomes. In the Middle Ages, European medical practitioners were almost exclusively members of the clergy. Hence, medical practitioners remained above reproach and immune from accountability (Digby 1994).

The improved education in medical schools, with well-structured didactic and clinical teaching and training, and exams for competency, reinvented the practice of medicine as a profession rooted in the scientific method (Pelling 1997, Raach 1944). The Age of Enlightenment further asserted this basis for a safe and effective practice and saw the emergence of professional organizations (guilds, societies and colleges). Such organizations took on the responsibility of:

1. protecting the public through ensuring that only qualified professionals were allowed to practice medicine,
2. developing scientifically-based practice guidelines to improve outcomes,

3. ensuring accountability for adverse outcomes resulting from inappropriate or unsafe decisions and practices, and, most recently,

4. improving resource utilization and promoting affordable, accessible, equitable and cost-effective healthcare delivery. These goals have come to form the foundation of quality healthcare.

## 4.2 Importance of Guidelines

The ultimate objectives of clinical practice guidelines as decision-support tools remain promoting the safety, health and welfare of the populace, as well as protecting the public from the decisions and practices of the unqualified and incompetent. These guidelines also provide a quantitative, scientific foundation for the timing, indication and expected outcomes of diagnostic and therapeutic interventions.

A more relevant definition to the current discussion of the goals of clinical practice guidelines is to halt the course of the disease (i.e., "cure") or slow its progression, thus improving survival, quality of life, independence and freedom from intervention (Porter 2010). This expectation of outcomes is fundamental for safe, effective, equitable and affordable utilization of diagnostic and therapeutic resources to address the disease process. In other words, having a more quantifiable expectation of outcomes is essential for providing a higher quality healthcare (Buck 1992).

The implementation of statistical methodologies for predictive modeling by Health Maintenance Organizations (HMOs), insurance companies and healthcare regulators has been well established, albeit for a different goal, namely, reducing cost of healthcare delivery, based on the mortality and morbidity risk of each patient. In many cases, this has caused a shift of healthcare delivery away from chronic ("pre-existing") conditions and towards preventive and palliative measures (Wagner 2000, Nolte 2008).

Recently, such practices have migrated into the clinical decision-making realm, where clinicians' decisions have been influenced by reimbursement or financially punitive measures from healthcare regulatory agencies and insurance companies, in some instances replacing or conflicting with evidence-based guidelines. The recent experience in cardiothoracic surgical critical care practice with the so-called "sugar window" (Fullerton 2014) provides a clear example, where one arbitrary measure was selected as the basis for regulating clinical decision-making (including financial penalty for the entire hospital) across the widely variable spectrum of individual patients undergoing cardiovascular surgical procedures.

### 4.3 Disease Trajectory and the Corbin-Strauss Model

Since the 1970s, Strauss and others observed the changes in functional status and need of support in patients with chronic illness as they approach the terminal phase or their disease, as a means to guide the strategies that must be developed by them, their families, their caregivers and healthcare professionals to manage these situations.

The term "trajectory" was introduced in a 1975 book (Glaser & Strauss 1975) to describe the course of an illness over time. This book also introduced the fundamental principle that the course (and effects) of a disease process can be addressed and changed by proper management, which is the essence of medical practice and the goal of practice guidelines. A disease course can be extended at its current level and kept stable, its symptoms maintained under control or even reversed through application of proper diagnostic and therapeutic measures.

Building on this principle and an extensive review of nursing literature, Corbin and Strauss introduced a nursing model (Corbin & Strauss 1991) for management of

chronic illness based on the trajectory framework. This model of medical practice, which is no longer limited to nursing, aims to provide a framework for developing management strategies for controlling the symptoms and optimizing adaptation to the decreased functional status (disability) incurred by the disease (e.g., as a result of a stroke) or to the impact of the psychological and societal changes that affect the patients and their families (e.g., advanced malignancy, frailty or congestive heart failure). To these goals can be added the often ambitious goal of completely reversing the course of the disease and returning the patient's functional status to the "normal baseline", thereby providing a "cure".

However, the objectives of this "theoretical" framework (Corbin 1998) are as follows:

- Providing insight and improving the understanding of the mechanistic aspects of disease progression and its impact on survival, functional status and psychological well-being.
- Providing a framework to help organize and apply the extensive and rapidly growing body of scientific evidence relevant to that specific disease.
- Improving the understanding of the "hardiness" or "resilience" of the organ, system or patient affected by the disease, as in being able to adapt to and recover (partially or completely) from significant events in the course of the disease.
- Provide direction and guidance to develop best practice models (i.e., Clinical Practice Guidelines) for healthcare professionals in all tiers and classes, medical and biomedical researchers, healthcare regulators and policymakers.

The trajectory framework has been further detailed by Corbin and others (Corbin & Strauss 1991) as not only describing the course of the disease over time, but also the actions taken by various participants (including the patient and their decision

maker) to impact, shape or control this course. To help achieve this goal, the disease trajectory is broken down into several phases, each of which is associated with specific characteristics based on causative or associated factors or events.

Different diseases demonstrate different trajectories. Advanced malignancy has a fairly stable course with rapid deterioration in functional status until death within a year.

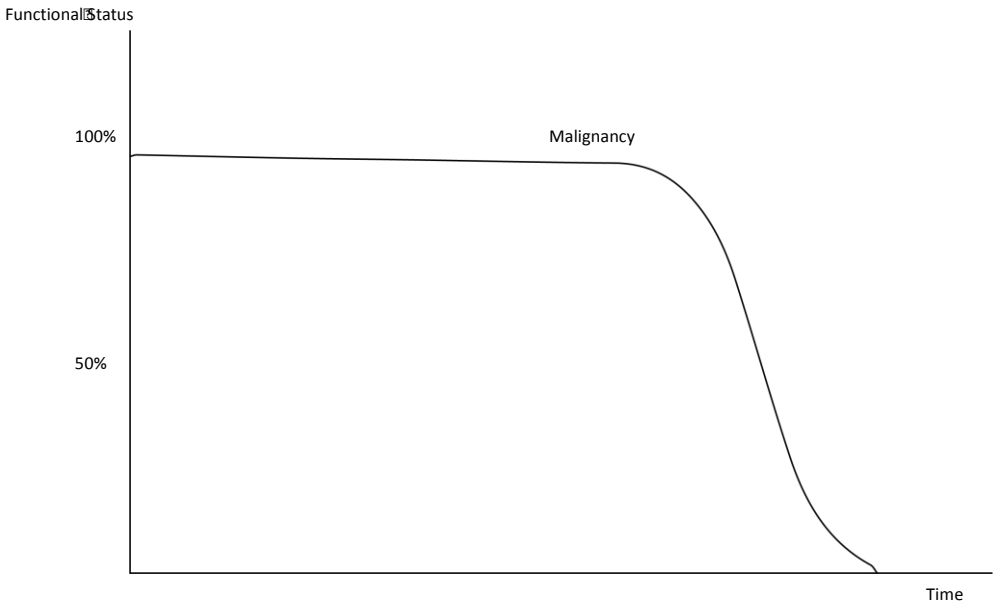



Figure 4 The Corbin-Strauss disease trajectory in advanced malignancy

Frailty secondary to malnutrition, for example, has a trajectory of progressive decline at a relatively steady pace, as in the following diagram (Figure 5).

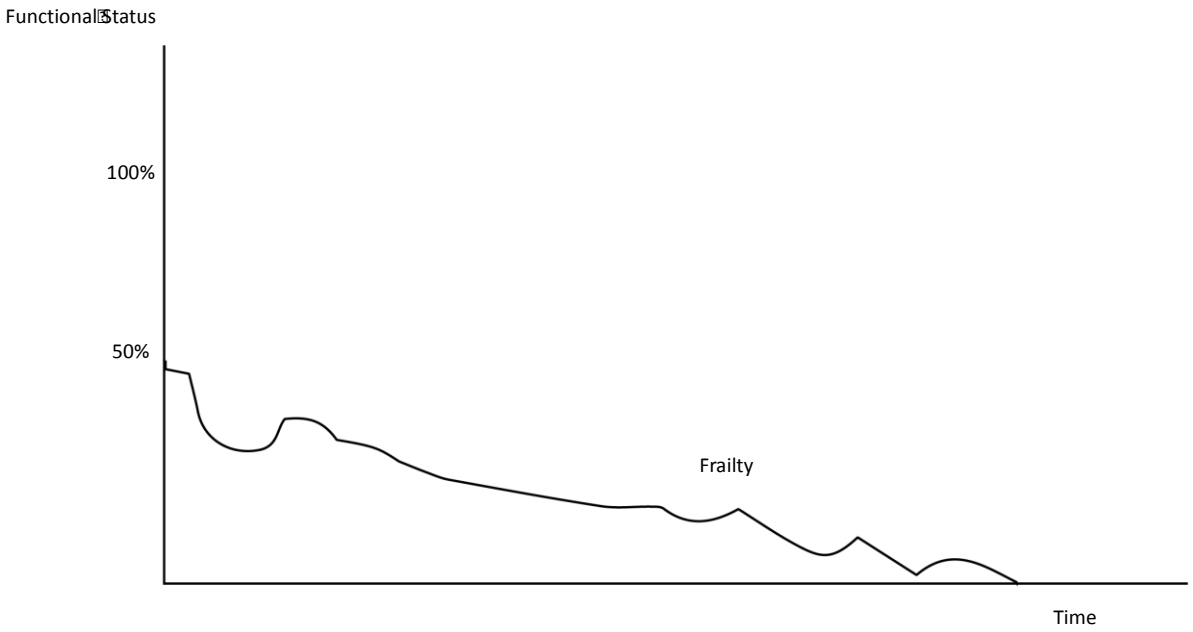



Figure 5 The Corbin-Strauss disease trajectory in frailty

Conversely, advanced organ failure, such as congestive heart failure, exhibits a trajectory of gradual decline in functional status but punctuated by episodes of periods of instability, decompensation or crisis, marked by partial recovery towards the original trajectory line. As organ failure progresses, the level of recovery from each episode of decompensation is lower than the previous one, until a limit is reached when recovery is no longer possible and functional status continues to deteriorate until death. The following diagram (Figure 6) illustrates this characteristic course:

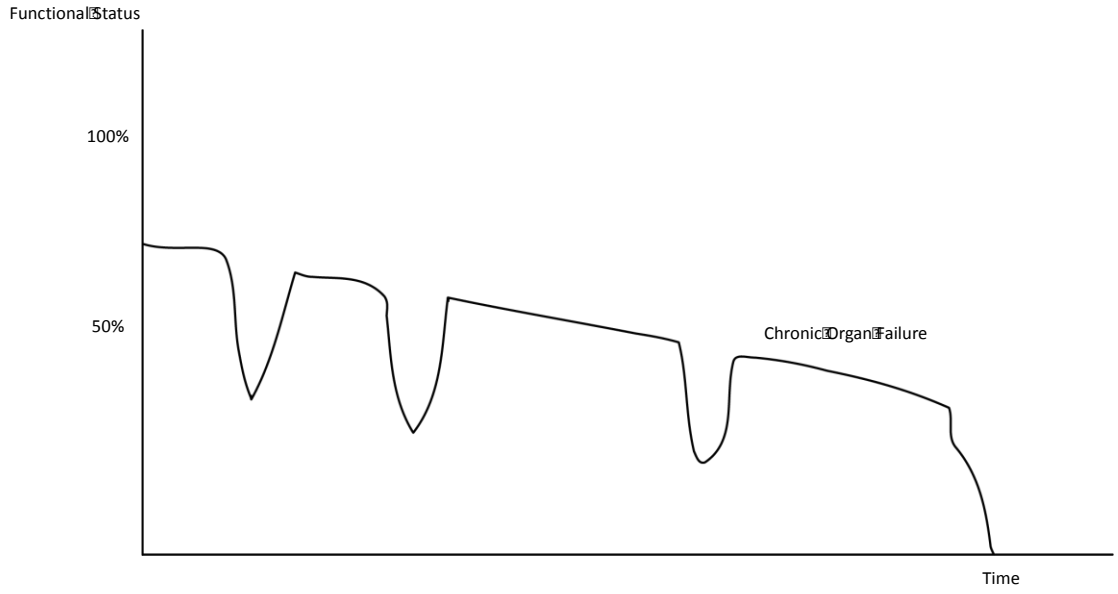



Figure 6 The Corbin-Strauss disease trajectory in advanced organ failure

Trajectories of other chronic conditions usually exhibit a steady trend towards worsening of survival or functional status over time, progressing at different rates ("slopes" of the curve) depending on the specific condition, and reaching recovery in response to intervention.

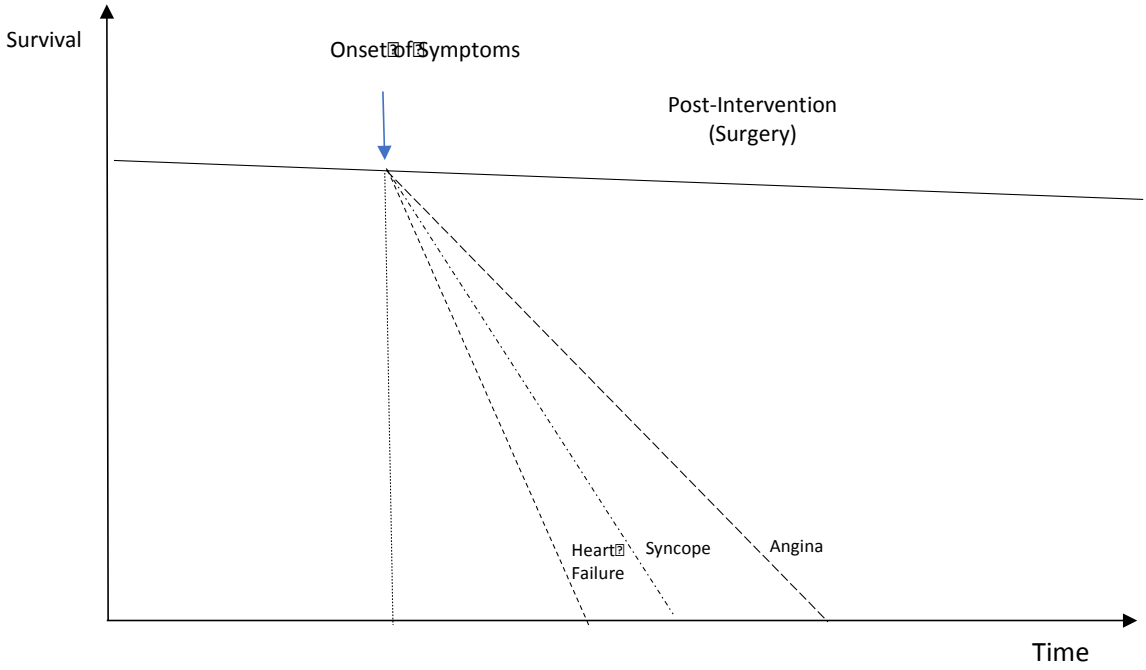
Each of the various stages in the Corbin-Strauss trajectory indicates a specific phase in the disease process, which is usually the result of a pathophysiologic set-up, a clinical event, a diagnostic or therapeutic intervention or other life events. As such, the specific goal of management at each phase is different from other phases in the course of the disease, depending on the precipitating causes for the change in course, the underlying mechanisms responsible for these events and—importantly—the expectations for survival, functional status and quality of life relevant to this particular

phase as well as the anticipated effect on the subsequent phases in the trajectory and the objective of medical management at each phase:

Table 2 Different phases in the disease trajectory

| **Disease Phase** | **Characteristics** | **Objective** |
|---|---|---|
| Baseline | Stable function | Prevent onset of disease |
| Onset | Initial symptoms or signs | Prevent loss of function |
| Unstable | Limited functional status | Return to baseline status |
| Recovery | Gradual return to baseline status | Support functional status |
| Crisis | Rapid deterioration of function | Remove threats to life<br>Sustain essential function |
| Downward slide | Difficulty controlling symptoms | Adapt to increasing disability |
| End-stage | Irreversible shutdown of function | Comfort, dignity |

Calcific aortic stenosis (Figure 7) demonstrates a nearly stable course (Horskotte 1988) until the onset of symptoms, at which point the trajectory changes to a rapid decline, with death in 2-3 years if untreated.




Figure

Figure 7 Trajectory of aortic stenosis

Abrupt, sudden catastrophic changes have been observed in the course of chronic diseases such as coronary artery disease (acute coronary thrombosis precipitating massive myocardial infarction causing cardiogenic shock) or Marfan syndrome (aortic dissection or rupture after a period of progressive aneurysmal dilatation). In such situations where the trajectory phases change unexpectedly and dramatically, the value of having an established trajectory projection and management plan becomes paramount in dealing with the new phase.

## 4.4 Systems Approach

A disease is considered to be an abnormal performance of a specific biologic system. In other words, it is a disruptive event that causes a decrease in the functional status/performance of the system, which—if unaddressed—leads to failure of the system. The "system" can be defined at the molecular, genetic, cellular, tissue, organ system or entire organism levels. Pslek (2001) defines a system as a "set of interacting parts to achieve a common goal".

In its 2010 recommendations for addressing "sentinel events" or medical errors, the Joint Commission (2010) provided the definition of root cause analysis as a "process for identifying the basic or causal factors that underlie variation in performance". This framework for investigating errors is designed to "assist organizations in improving processes and systems to prevent injuries from occurring". This definition is precisely the objective of clinical practice guidelines: to prevent harm and injury and disability and to improve the quality of life.

## 4.5 Process Line and Trajectory

A process is defined as a "series of actions, changes or functions bringing about a result", or "a series of operations performed in the making or treatment of a product". Hence, a process map is simply a graphical representation of how a given work flow happens or the order in which things occur. Therefore, a process line describes the sequence of events in any given process, from manufacturing to system performance to disease progression. The basic steps in defining a process line are: defining the boundaries (baseline conditions, onset, course and outcome); listing the steps in the process; listing the sequence of steps; then plotting the entire pathway or line.

This process line is punctuated by various points describing the time of occurrence and effect of events involved in the process (Eden 1992, Kenett 2014). This is the basis for establishing a graphical model of events that occur along the process timeline and their effect on the course and its direction.

Thus, a process line or trajectory (Figure 8) describes a linear system model, with blocks representing the essential steps and sequential arrows describing the direction of the process line towards its goal or result. The most important information from such diagrams is that each step or event is the result of one or more factors that cause it to happen, and it in turn sets the stage for the next event to occur when the appropriate input is introduced at the appropriate time. This sequence repeats, changing the system compartments as sequential inputs are applied. The final state of the system component is the planned or desired end-result. The following diagram (Graves et al 2010) illustrates the basic steps in medication administration.

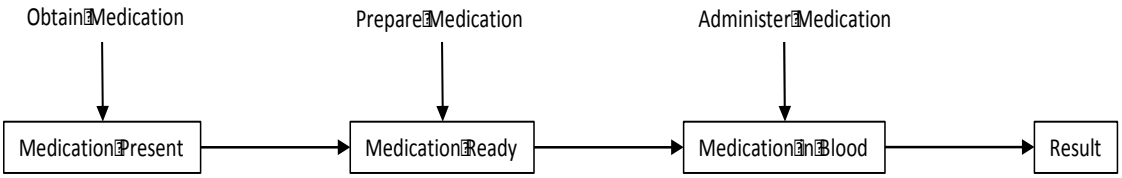



Figure 8 Basic process line. Modified from Graves et al (2010). Used with permission.

Understanding the sequence of events in any process and their relative position on the process trajectory is fundamental to the understanding of the performance of this particular system and any "error" or "failure" that adversely affects system performance. Errors and failures are events marked by a change in system performance and heralded by a shift of the process trajectory towards an unexpected, unintended and undesirable direction. Failure mode analysis has been well established in the science of safety and accident analysis (Stamatis 2003, Vincent 2004). Its main purpose is to provide a clear, evidence-based explanation for why the "error" occurred (the specific factor causing the event responsible for the trajectory shift), how it occurred (the point where the process trajectory has shifted) and to identify actions that must be put in place to ensure that it does not occur again. (Hambleton 2005, Graves et al 2010).

Since diseases and injuries are adverse events occurring along the course of a the lifetime of a person, group or population, such events have a significant impact on

the performance of the person, group or population (i.e., the health of such system) Each disease or injury has its own disease trajectory (the Corbin-Strauss trajectory) that provides a graphical representation of the sequence of events (and their causative factors) responsible for the genesis, progression and outcome of this condition in terms of death, disability and the change in the quality of life. This perspective on how diseases start and progress (etiology and pathogenesis) and how they affect quality of life (natural history, course or trajectory) provides the foundation for developing relevant, effective and comprehensive clinical practice guidelines. Understanding the origin and causative factors influencing each event in a disease process provides us with the foundational information to devise diagnostic tools to (a) predict this abnormal performance and its timing and (b) implement therapeutic tools to counter the effect of these factors that have caused the deviation from the expected course.

### 4.6 Critical Events

Partly as a result of the standard statistical interpretation of clinical and basic science research, clinical practice guidelines are frequently based on simplistic assumptions of a linear relationship between the cause and effect. In other words, a linear system configuration (DiStefano 2015) with a fixed input-to-output relationship is assumed, i.e., input *y* applied to the system component (compartment) A will result in a change in the status of system compartment B. Thus, the status of B is dependent on change in the status in A, which is the result of the input *y*.

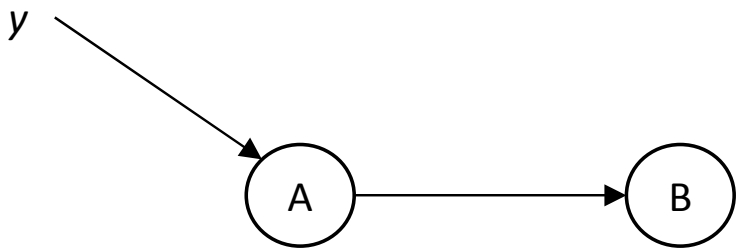



Figure 9 A 2-compartment linear system with a fixed input-output relationship

In this example, the change in the status of A is a critical event that has an impact on the definition of the next system compartment (B). Extending this example to a linear system with multiple compartments produces the sequential effect on the system as a result of a number of factors (inputs), each acting on a specific compartment at a specific time, producing a critical event that further acts as the subsequent input to the following compartment in the system.

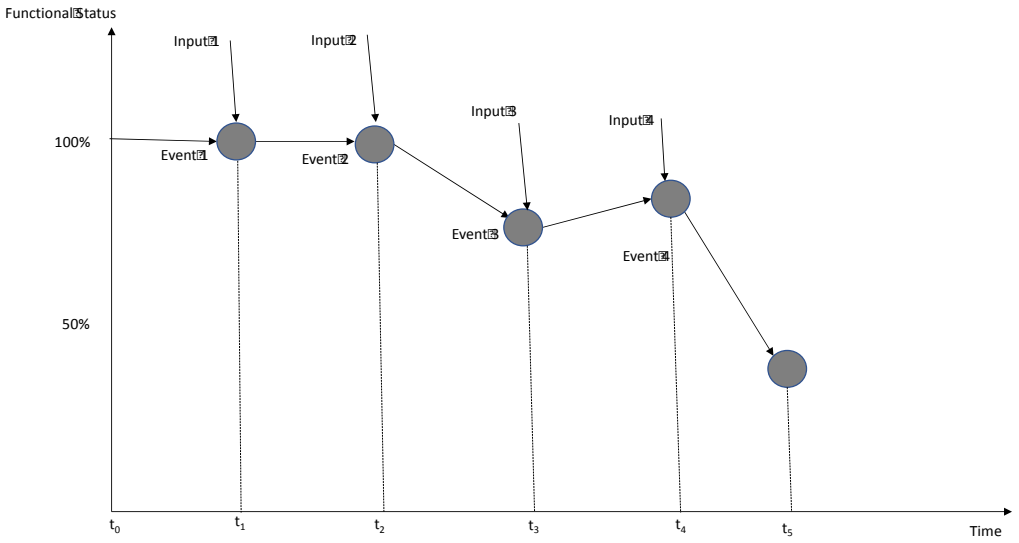



Figure 10 The effect of sequential events on the behavior of a multi-compartment system

Critical events in the disease trajectory can be due to a single factor or the combined effect of more than one factor. To better illustrate this, the trajectory for death due to venous thromboembolism (VTE-PE) is examined. The trajectory for this condition describes a progressive course (Nadkarni 2004) starting from the baseline condition of obesity.

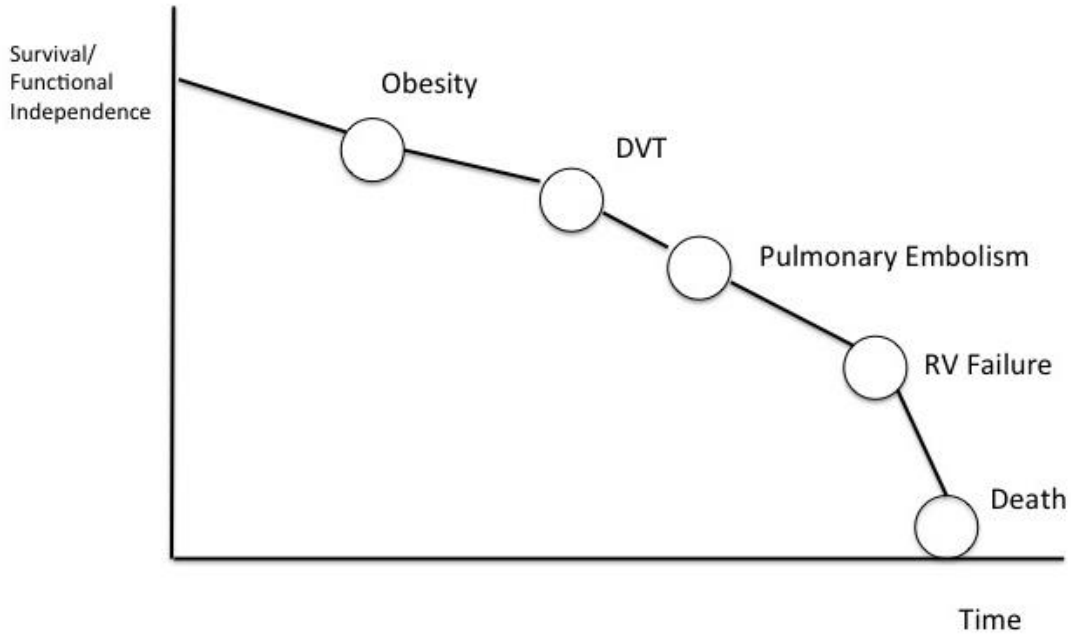



Figure 11 The Corbin-Strauss disease trajectory for death due to pulmonary embolism

The limited mobility associated with being obese places the patient at high risk for iliofemoral deep vein thrombosis (DVT). These thrombi in the large veins of the pelvis and thigh can detach, travel downstream to the pulmonary circulation and thus progress to pulmonary embolism. This repeated process causes chronic thromboembolic pulmonary hypertension (CTEPH) (McNeil 2007, Pepke-Zaba 2011). This, in turn, leads to chronic right ventricular strain because of the progressive increase in pulmonary vascular resistance. Untreated, CTEPH causes progressive right ventricular failure, which ultimately causes death. Each event can be the result of a single input or the combined effect of a number of factors. For instance, venous thrombosis is dependent on the presence of the three independent elements (Figure 12) of the classic Virchow Triad (Brotman 2004, Dickson 2004) of stasis, endothelial

injury and increased blood viscosity all acting in unison. Stasis, on the other hand, is dependent on decreased mobility and increased venous pressure.

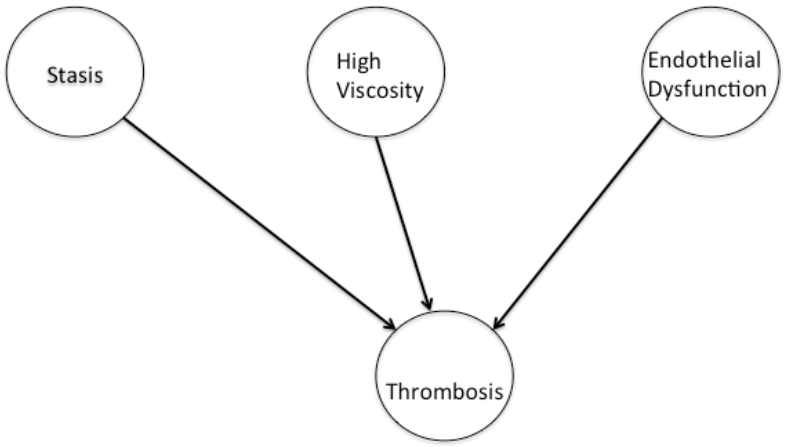



Figure 12 Genesis of thrombosis according to the Virchow Triad

Thus, in the Corbin-Strauss trajectory model described above, obesity is the precursor for the development of deep venous thrombosis (DVT). The direct precipitating factor for DVT, however, is the Virchow triad. In other words, obese patients are at a higher risk for developing DVT, but that event does not occur until the Virchow triad becomes a direct causative factor for this condition. Therefore, the shift in the disease trajectory due to obesity is not as significant as that caused by DVT.

### 4.7 Critical Events and the Disease Trajectory

The Corbin-Strauss trajectory presents a graphical model of the critical events in the course of the disease process, which occur as a result of a causative factor (input

at a specific point in time. The effect of this input is to shift the line of the trajectory in a different direction from the expected outcome towards a different outcome, akin to the change in the course of a billiard ball when struck by the cue or another ball. The force of impact (i.e., the magnitude of the effect of the input on the stability of the system) causes the object (or the process line) to shift at an angle away from the expected course towards a new, predicted course with a different outcome.

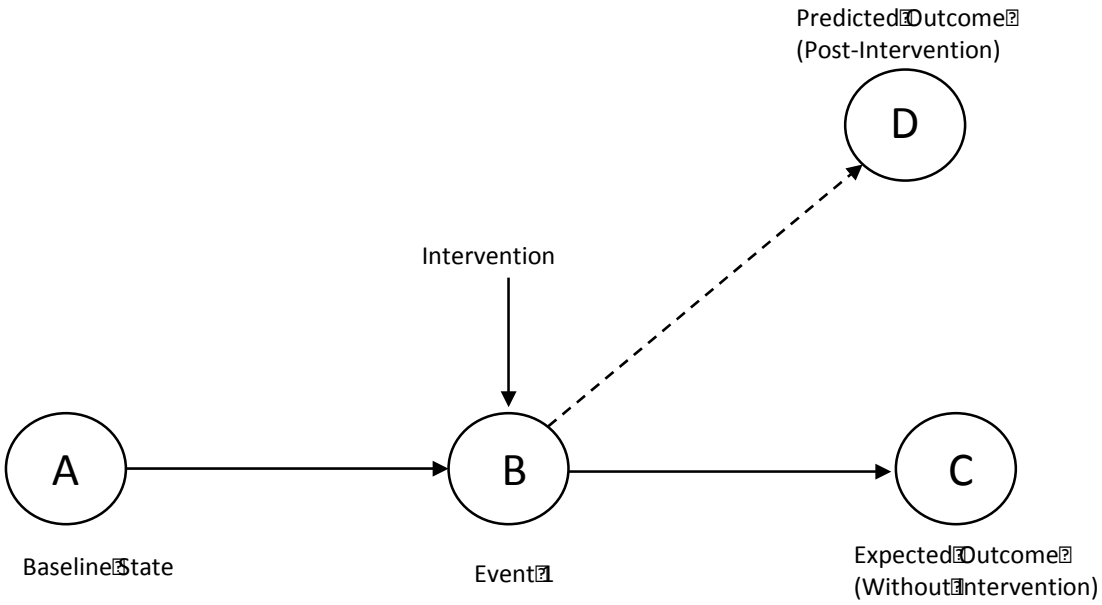



Figure 13 The shift of the process or disease trajectory as a result of critical events

This stimulus or input can be an external factor (e.g., infection, trauma, toxicity, drug intake, surgical or other invasive procedure), an internal event (e.g., effects of a gene mutation, internal bleeding, rupture of a cyst, hormonal surge, rupture of a vulnerable coronary plaque, etc.)

Each critical event that is precipitated by a specific stimulus also elicits a specific measurable effect or effects, such as symptoms, signs, imaging and laboratory data. These effects are also proportionate to the magnitude of the input and thus are related to its effect on the shift in the trajectory line. This makes it possible to stage the severity of the disease process by quantifying the degree of shift from the expected (e.g., historical or actuarial) point on the survival curve. A certain value of a specific biomarker (e.g., BNP in congestive heart failure) can thus be a staging as well as prognostic marker, given its correlation with the degree of severity and the stage of the disease.

In the following diagram (Figure 14), the system function is measured starting at the baseline time $t_0$. The system continues to function at a certain level until time point $t_1$, when Input 1 is applied (Event 1), thus changing the function level. The new level of function continues until another input (Input 2) occurs at time mark $t_2$ (Event 2). As a result, functional status changes over time to reach a different level at point $t_3$. At this point, another input (Input 3) exerts its effect to change the function level in another direction over time. Functional status continues in this new direction until time mark $t_4$, when the next event (Event 4) is precipitated by Input 4, resulting in another change of the trajectory line towards the last measurement at point $t_5$.

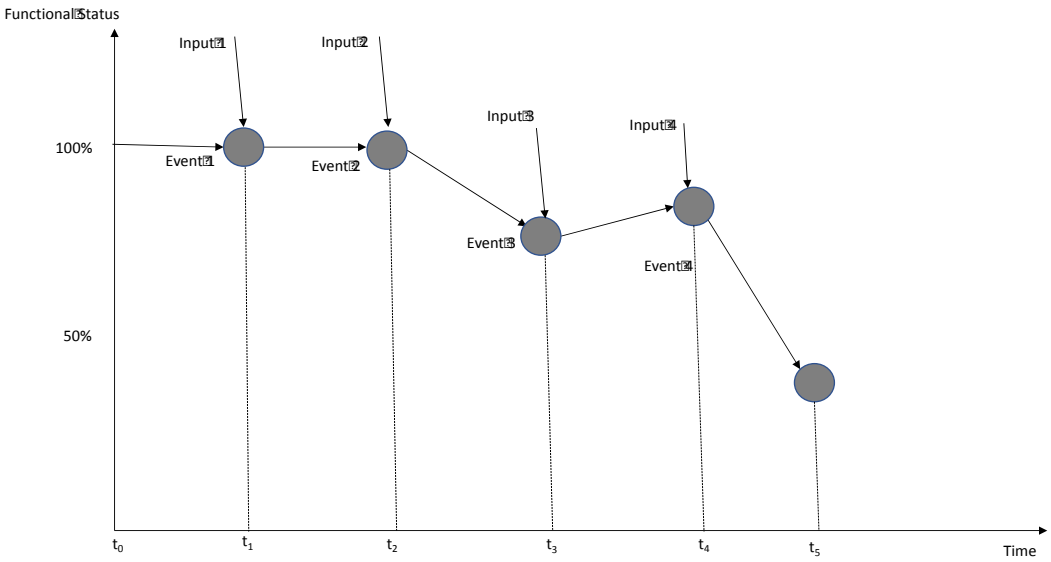



Figure 14 The effect of input on critical events in the trajectory

## 4.8 The Corbin-Strauss Model as the Basis for the Application of Resilience Engineering

The Corbin-Strauss model is a graphical representation of the performance of the entire system (in this case, the patient) over time, in the context of and as a result of a specific disease process or injury. Thus, the Corbin-Strauss trajectory can be considered a graphical representation of the system function Q over time Q(t).

Because of the inescapable effects of ageing, the absence of disease does not mean that the system performance of the human organism would remain at 100% throughout the person's lifetime. Thus, the Corbin-Strauss model for a healthy person will still reflect this gentle, gradual downward slope over the course of the person's lifetime. However, the added effects of an injury or disease process will alter this slope in various ways, depending on the pathophysiologic processes of the disease as

well as the coping and compensatory mechanisms (internal and external) within the human body.

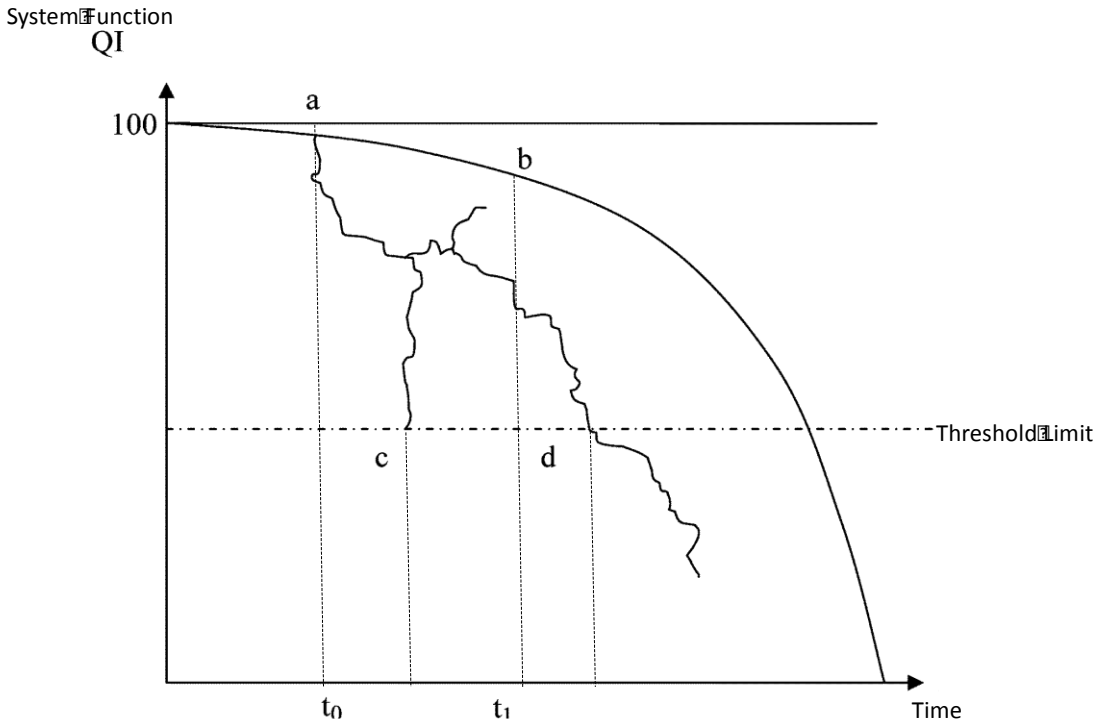



Figure 15 Resilience paths of a single infrastructure system. Modified from Attoh-Okine (2009). Used with permission.

Similarly, monitoring the function of complex systems (infrastructures, utilities, ecologic systems, etc.) demonstrates an almost identical trend. Figure 16 illustrates the different paths of performance (Quality Index or QI) of a single infrastructure system over time. Ideal function (at 100% performance) is represented by the horizontal line starting at point a. Realistically, normal function is represented by the gently sloping line a-b, reflecting the gradual decrease in function due to the

expected normal wear-and-tear occurring over a specific time interval from baseline status at time mark ($t_0$) to the end of the time period examined at time mark ($t_1$). The dashed line at points c and d represents the lowest level of function (the threshold limit) that the system reaches as a result of wear and tear and other factors causing degradation of system function.

Sudden, catastrophic failure is represented by the path a-c, which exhibits a much quicker decrease in functional level that reaches the threshold level well before the expected end of the time period examined. Another pattern of accelerated decrease in function (due to increased wear-and-tear) is represented by segment a-d, which illustrates the lower level of function at the end of the time interval examined ($t_1$).

### 4.9 Impact of Intervention on the Trajectory

Prediction of recovery versus failure after initiation of extra-corporeal membrane oxygenator in cases of severe respiratory failure remains a significant clinical challenge. The causes of acute respiratory failure are numerous and include trauma, adult respiratory distress syndrome, viral infection, and pneumonia, as well as toxicity. This clinical situation is extremely critical, requiring admission to the intensive care unit and aggressive supportive measures. In addition to its significantly increased risk for mortality, this also considerably impacts the physical and physiological well-being of the patient and their quality of life. In recent years, there has been an increase in the use of the extra-corporeal membrane oxygenator (ECMO) for support of ventilation and gas exchange until the recovery of native lung function. However, prediction of the success of this highly invasive and resource-intensive modality remains in need of improvement.

Zangrillo et al (2012) and Camboni (2011) reviewed the results of 12 studies conducted involving 1763 patients to evaluate 30-day mortality after implementation of ECMO.

A number of scoring systems (PRESERVE score; Schmidt et al 2013, Enger et al 2014, Pappalarado 2013) has been developed to help better quantify the risk of mortality after the initiation of ECMO as tools to help patient selection and clinical decision-making.

Data variables used in the development of these scoring systems were numerous and included historical, demographic and physiologic parameters. In each scoring system, each of these factors chosen was given a certain weight. For instance, in the ECMOnet scoring system (Pappalardo 2013), pre-intervention length of stay was given a weight between 0.5 and 2, the same range for serum hematocrit, while serum creatinine had a range of 0-3.5.

Data analysis relied on conventional statistical retrospective data analysis methodology. Statistical consistency was expressed in the familiar 95% confidence interval and 2-tailed *p* value estimates, in accordance with the assumed normal distribution.

Probabilities of survival were plotted using different methods: The Kaplan-Meier estimate curve was used to display the results of the ECMO PRESERVE study, while the area under the curve was used in the ECMOnet study.

The results of these predictive models provide varying levels of probability of survival, depending on the calculated severity score. The PRESERVE score, for instance, describes 14 levels of severity, which correspond to progressively decreasing

probability of survival: from 80% or above for a score of 0-2 to around 20% for a score >7.

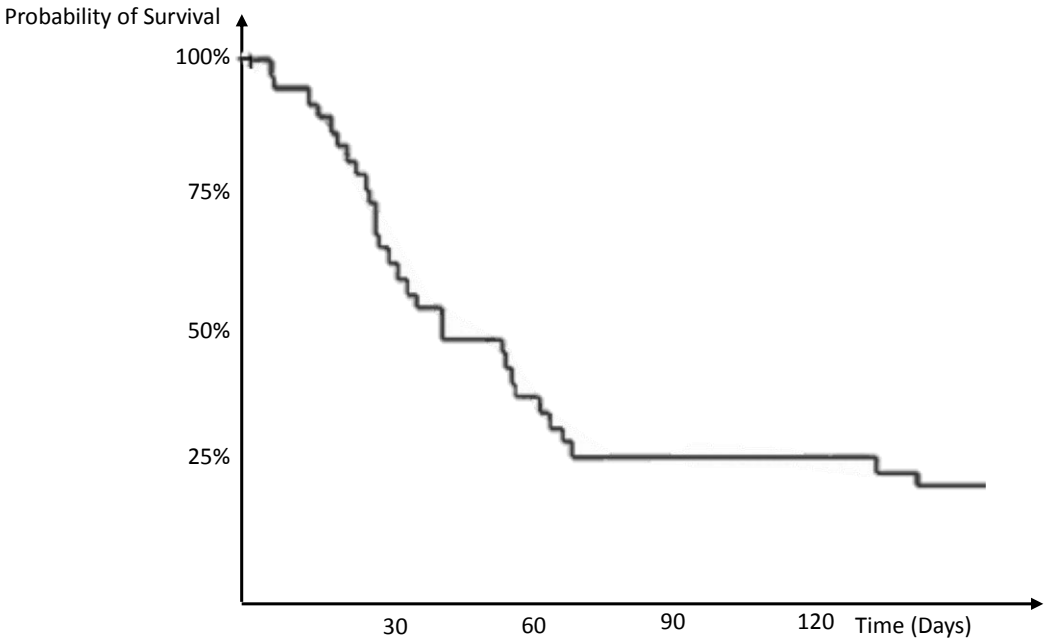



Figure 16 The Corbin-Strauss trajectory for probability of survival after ECMO. Modified from: Schmidt et al (2013). Used with permission.

Severe respiratory failure not responsive to conventional medical management and mechanical ventilation is a life-threatening situation and often even lethal if not promptly and effectively treated. The profound systemic metabolic effects due to this condition, remain the major contributing factor to the significantly increased risk of mortality in such extreme cases. This risk is even more elevated in certain patients whose pre-existing chronic conditions and limited or decreased physiologic reserves.

Therefore, it is often a great challenge to make the decision to implement the highly invasive, high-risk, resource-intensive therapeutic modality of ECMO towards a prompt, effective and reliable reversal of the disease insult and to allow the recovery of function of the lungs. Its inherent high risk for mortality within the early period after initiation of support, the high cost and impact on resource allocation and utilization all add to this challenge. Yet the most important challenge remains the prediction of the probability of the success of this therapy within the early period after initiation, since all these risks escalate significantly after the first 2-3 weeks.

As described above, current efforts to develop a predictive model for estimation of the probability of success of ECMO—understandably—continue to place the greatest emphasis in reducing morality within the early period after initiation of support. These scoring systems have relied on the analysis of the following parameters:

Parameters of function: These are indicators of the patient's expected functional status at the "baseline" or before the disease insult. Factors such as age, body mass index, immunocompromised status, etc. indicate the expected state of health before admission to the hospital. These are the same parameters that determine the patient's coordinates on the actuarial survival curve (Fig.), based on the known risk factors for mortality without the influence of the disease process.

These parameters are also the goals of therapy: to return the patient's functional status to or as close as possible to the functional level at which it was before the onset of disease. Thus, the parameters serve to measure the success of therapy in negating or eliminating the detrimental effects of the disease process.

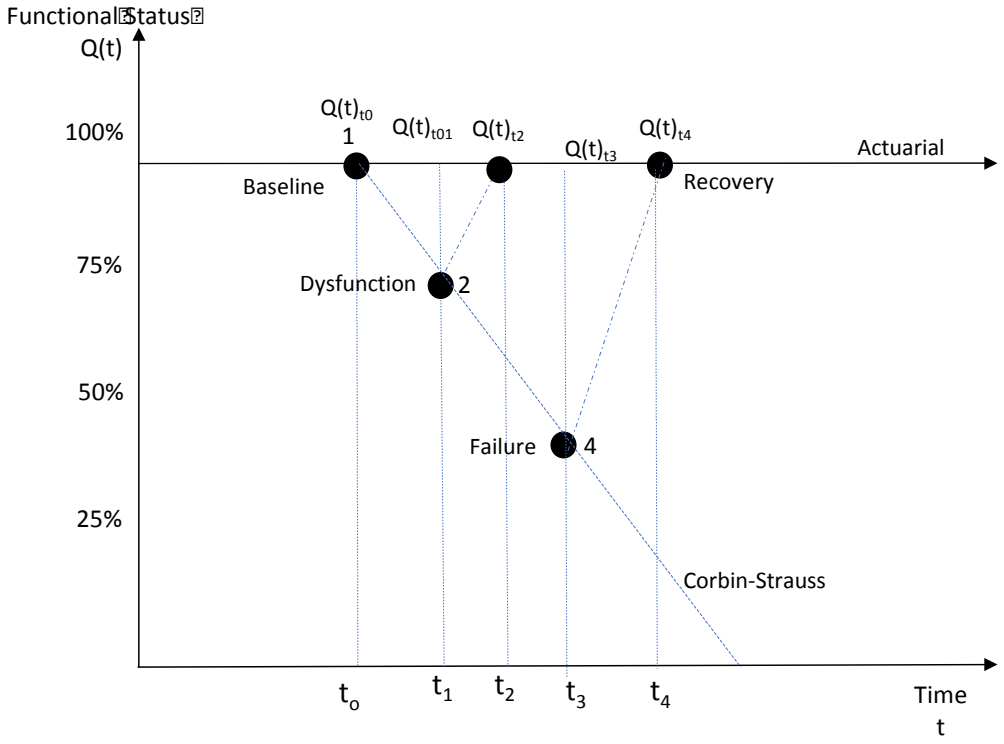



Figure 17 Parameters of function, dysfunction and failure

a. Parameters of dysfunction or failure:

These measurements and variables help quantify the magnitude of disturbance in the patient's physiologic balance and the extent and severity of the resulting organ and systemic loss or decrease in function.

For instance, the degree of acute lung injury can be quantified by examining the parameters of mechanical ventilation, supplemental oxygen and the need for other maneuvers. The degree of systemic malperfusion is estimated using such parameters as serum lactate and the total dose of sodium bicarbonate infusion needed for resuscitation.

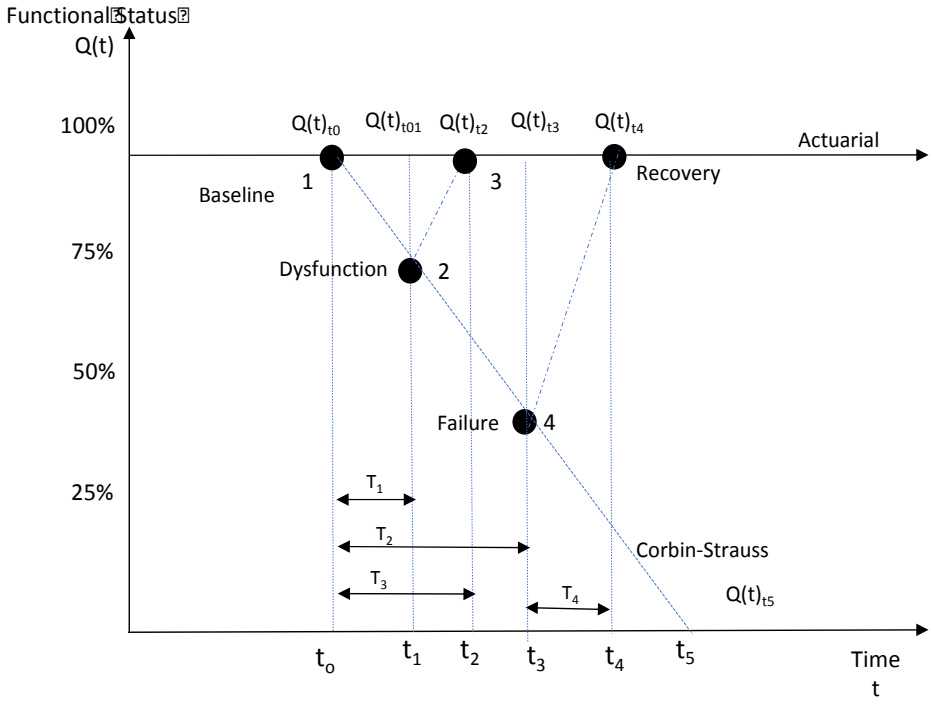



Figure 18 Coordinates of function (Point D), dysfunction (Point H) and failure (Point F) on the disease trajectory

Assumptions:

Time mark of disturbance: $t_0$

Time mark of dysfunction: $t_1$

Time mark of recovery: $t_2$

Time mark of failure: $t_3$

Time mark of recovery at failure: $t_4$

Time of deviation from normal: $T_1 = t_1 - t_o$ (dysfunction), $T_2 = t_3 - t_0$ (failure)

Time of recovery at dysfunction: $T_3 = t_2 - t_1$

Time of recovery in failure $T_4 = t_4 - t_3$

These parameters describe the factors influencing the patient's coordinates on the Corbin-Strauss disease model (Line DHF in Fig.) and their deviation from the expected coordinates on the actuarial or historical trajectory (normal or baseline status) as discussed above. The farther these coordinates diverge, the more significant the level of injury and disruption to the patient's physiologic balance has been. Subsequently, if the Corbin-Strauss coordinates are severely displaced from the actuarial coordinates, it becomes easier to predict the degree and aggressiveness of ECMO support needed to restore the patient's functional parameters to their pre-insult level or at least close to it.

The quantifiable level of functional status Q(t) corresponding to each point on the disease trajectory reflects the effect of the disease on the patient's physiologic status and reserve. Thus, the observed functional status $Q(t)t_1$ at point of dysfunction H represents the smaller effect of disease on the patient's status and thus probability of survival, while functional level $Q(t)t_3$ at point of failure F represents the lowest level of function, at which the system has depleted all its energy reserves and probability of survival is at its lowest. It follows, then, that the effort and energy required to return functional status to the baseline level $Q(t)_{to}$ is easier starting at point H than starting at point F, where the detrimental effects of the disease are more advanced.

The objective of healthcare in general and medical practice in particular is to eliminate, mitigate or reduce the effects of disease and injury on the organ-system, individual, groups or population. In other words, the goal of all medical interventions

(and the recommendations from the clinical practice guidelines) is to implement therapeutic modalities as critical events that will change the course of the disease towards improved functional status and survival. The timing of these events is of paramount importance, given the time needed for recovery. Also important is the cost of recovery, in terms of financial considerations, equipment and personnel as opposed to the expected yield of this intervention in improving quality of life, functional status and survival.

Therefore, an approach implementing the Corbin-Strauss trajectory model as the basis for devising to direct events in the natural history of the disease instead of being a response to these events is much more advantageous, as follows:

Table 3 Comparison between different approaches to planning medical interventions

| Traditional Approach | Resilience Approach |
|---|---|
| Reactive | Proactive |
| Reflexive | Predictive |
| Static | Dynamic |
| Passive | Active |
| "Snap-shot" | Time dependent |
| Task oriented | Goal oriented |

## 4.10 Summary

The Corbin-Strauss trajectory model provides a graphical representation of the change in functional status relative to time in different disease processes. The trajectory can be plotted over the entire lifetime of the patient, over the last few years of the patient or over a specific period of time; depending on the disease and interventions being examined. The course of this trajectory is determined by a series of critical events, each occurring as a result of an internal or external input. Due to its time-related nature, the Corbin-Strauss trajectory provides a valuable tool to quantify the level of functional status, correlating to the probability of survival, at different time points along the course of the disease. Comparing the Corbin-Strauss trajectory to the trajectory of functional status and/or survival in normal patients offers the foundation for quantifying the effort or energy required to implement interventions as inputs to shift the trajectory towards the normal or baseline course, thus producing recovery of function and/or improved probability of survival.

# Chapter 5

# FORMULATION

## Background

Aortic valve stenosis is the most common valve disease in the world. In this condition, the narrowed valve limits the flow of blood from the left ventricle to the aorta and the rest of the body. This reduced flow leads to specific symptoms, such as chest pain (due to decreased coronary flow), fainting or syncope (due to decreased flow to the brain), and progressive decline of heart function (congestive heart failure or CHF) due to the increased mechanical demands to overcome the obstruction at the aortic valve level and subsequent geometric changes in the heart. The patients usually remain free of symptoms for most of the course of the disease, and the condition is often discovered incidentally during evaluation for other conditions. Survival during this phase remains close or identical to the expected survival, given the patient's specific phenotype, history and risk profile. Thus, the probability of survival for 5 years in the absence of other factors is generally expected to be >75%.

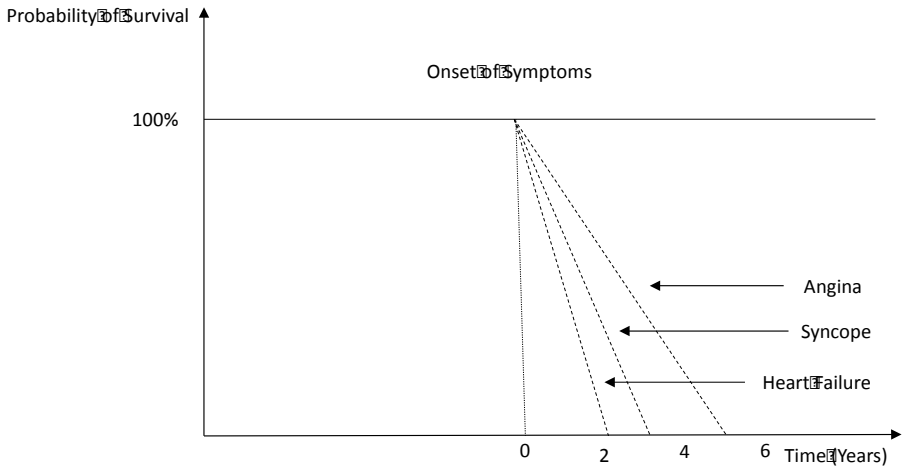



Figure 19 The course of aortic valve stenosis. Modified from Carabello and Paulus (2009). Used with permission.

The onset of symptoms (angina, syncope or congestive heart failure or HF) dramatically changes the probability of survival. Depending on the specific symptom, the probability of 5-year survival plummets to around 50% (Otto 1997, Rosenhek 2004, Pellikka 2005, Rosenhek 2010, Carabello 2009). The type of symptom also has an impact on the outcome. Angina or syncope is precipitated by the decrease in blood flow to the coronary arteries and the brain, respectively, but in both cases the function of the heart muscle (estimated by the left ventricular ejection fraction) remains stable or normal. Congestive heart failure is a serious indicator of the degree of decreased function of the ventricular muscle, which is the reason it correlates with the steepest decline in survival and/or functional status.

The most effective treatment for aortic stenosis is to replace the valve with an artificial (mechanical or biologic) valve that restores normal blood flow to the body.

Aortic valve replacement (AVR) is the most frequently performed valve surgery around the world. The survival rate changes significantly after aortic valve replacement, returning almost to the expected value according to actuarial estimates. Current clinical practice guidelines (Bonow et al 2008, Vahanian et al 2012, Holmes et al 2012, Lancellotti 2013, Nishimura et al 2014) are based on numerous studies demonstrating that aortic valve replacement is highly effective in reducing the risk of mortality and improving functional status from untreated aortic valve stenosis.

However, in some cases, surgery does not provide this expected high level of reduction of mortality risk (Otto 1997, Carabello 2002, Carabello 2004). In such cases, the timing of surgery becomes important because operating too late in the course of the disease will subject the patient to unnecessary surgical risk while the expected benefit remains small. Conversely, the benefit of early operation in asymptomatic severe or even moderate aortic valve stenosis remains unclear.

Therefore, justifying a highly invasive, high-risk procedure in a patient with aortic stenosis but has no symptoms is challenging. This clinical situation remains a point of debate (Brown 2008, Cioffi 2011) and has been one of the motivations for this work.

## 5.1 The Corbin-Strauss trajectory of aortic stenosis

The previous chapters have discussed the Corbin-Strauss trajectory model in detail. 30 illustrates the disease trajectory by plotting the probability of survival (as a surrogate for functional status) against time during each phase of the disease course.

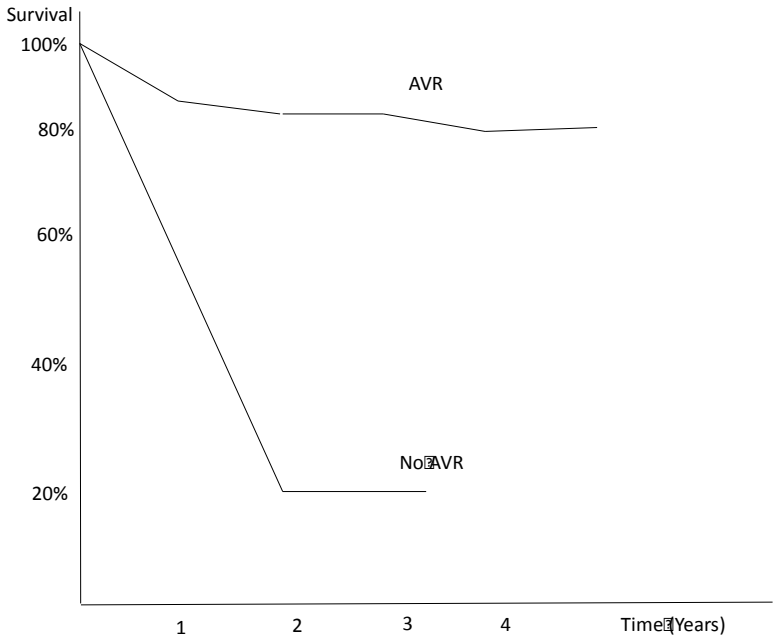



Figure 20 The probability of survival in aortic stenosis. Modified from: Carabello (2008). Used with permission.

## 5.2 Resilience Engineering Approach

The word "resilience" itself simply means "bouncing back". In other words, it describes the ability or capacity of a system or an organism to return to its normal functional state after a disruptive event or stimulus. Originally described by Holling (1973) as the "persistence of relationships within a system" and further defined by Lebel (2006), Hollangel (2014) and Walker et al (2004), it is the ability of a system to absorb disturbance and reorganize while undergoing change while still retaining the same structure and function. According to this definition, resilience is a time related phenomenon, where an event occurring at a specific point in time triggers a response

or a series of responses that adversely affect the structural and functional integrity and stability of the system, structure or organism.

Resilience is a functional property of the system more than a structural one. The maintenance and recovery of function, especially in complex, interdependent systems is entirely related to the responses within the system as a result of an external or internal disruptive event. That said, resilience is also related to the configuration of the system components, which directly impacts their functional capability. Thus, a resilient system exhibits the following aspects:

- A detailed process trajectory elaborating on the sequence of events necessary for the system to perform its function. This is the "blueprint" of the system, which allocates all components and their functional relationships and inter-dependencies. Especially important are the cause-and-effect relationships.
- Elemental capacity: This describes the components required for the system to properly function.
- Elemental function: Also known as the essential function, this describes the "bare bones" or very basic system components that can sustain minimal system function. These components are also the available, undamaged resources that will enable the system to recover its function.
- Full function: This is the full system configuration under normal operating conditions that allows for a full or a maximal system function.

Resilience systems can continue operating and/or recover their function after interruption by disruptive events due to certain functional attributes:

- Cushionability. This is the property that allows the system to reduce its function to a minimal level.
- Resistance: This property allows the system to negate the effect of hazards or disruptive events by redirecting its impact to less critical components and/or functional processes.
- Robustness: The property by which the system maintains a certain level of internal energy to support its function
- Redundancy: Complex systems incorporate several layers of functional components with overlapping and integrated functions. The loss of function due to disruptive events can be covered by other components within the system.
- Graceful extensibility: The system property that allows it to recover its function after partial failure due to an external or internal stressor

Resilience (Woods 2006, Woods & Hollangel 2006, Attoh-Okine 2016, Ayyub 2014, Nan 2017) describes the ability or capacity of a system or an organism to return to its normal functional state after a disruptive event or injury. According to this definition, resilience is a time-related phenomenon, where an event occurring at a specific point in time triggers a response or a series of responses that adversely affect the structural and functional integrity and stability of the system, structure or organism.

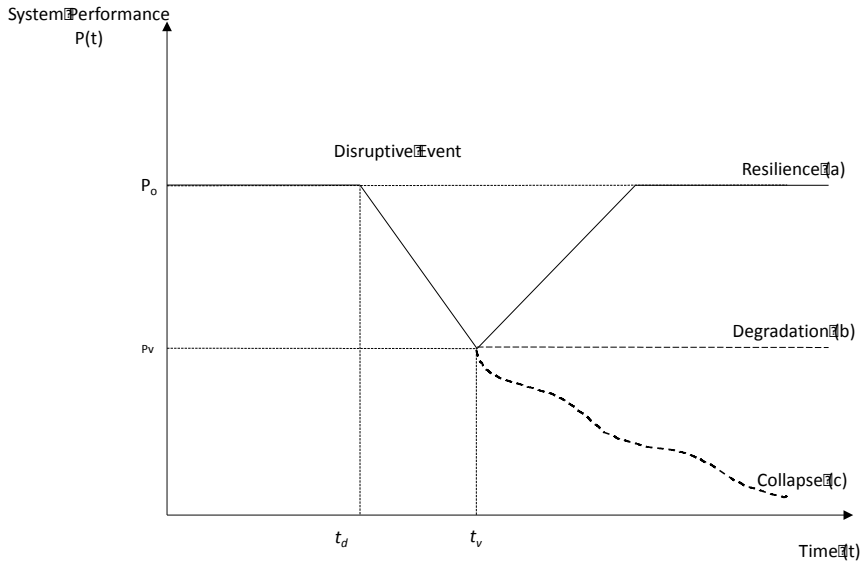



Figure 21 System performance in resilient and non-resilient systems. Modified from: Yodo, N., & Wang, P. (2016). Used with permission.

In Figure 21, as a result of the disruptive event at time point $t_d$, system function or performance (P) decreases at over time (degradation) from its baseline or optimal value ($P_o$) until it reaches a threshold level $(P_v)$ at time point $t_v$. In a resilient system (pathway a), the return of performance to its baseline level is observed in the ensuing time period. In non-resilient systems, the degradation of system performance continues over time beyond the threshold point, with inevitable collapse of the system without any recovery of function (pathway c).

Resilience has been described in many areas of human endeavor, as the following table illustrates:

Table 4 Comparison between the process of resilience in complex engineering and biological systems

| | **Civil Engineering** | **Biology and Healthcare** | **Cardiovascular Medicine and Surgery** |
|---|---|---|---|
| **Primary objective** | Safe performance of structures<br>Stable structural integrity | Successfully coping with external and internal stressors to maintain function | Maintenance of blood flow to the entire body and organs |
| **Elements** | Single structures<br>Complex systems | Multiple, interdependent practitioners, structures and systems | 4-chamber heart with one-way valves, aorta and arterial tree, capillaries, venous tributaries |
| **Stressor** | External forces | Internal mechanisms (disease processes)<br>External mechanisms (injury, infection) | Genetic defects<br>Age-related processes |
| **Innate repair mechanism** | Structural properties | Predictive homeostasis | Myocardial and vascular wall repair mechanisms |
| **Additional resources** | Maintenance | Reactive homeostasis | Up- or down-regulation of control mechanisms |
| **Acute energy shortage** | Severe accident | End-stage homeostatic failure<br>(Shock state. Depletion of resources) | Catastrophic events (dissection, hemorrhage) |
| **Chronic stress** | Progressive structural fatigue | Homeostatic overload<br>Chronic degenerative conditions | Progressive wall weakness, aneurysms<br>Dilated ventricle and congestive heart failure. |

## 5.3 Resilience in Biology

Resilience in medicine and biology is often referred to as “allostasis”, which is the process by which the organism maintains stability and equilibrium (McEwen 1998, McEwen 2003) within its internal environment through active, energy-consuming continuous adjustments and changes in its physiologic mechanisms and processes. These adjustments maintain all basic physiologic processes within a narrow, safe life-sustaining range. The maintenance of these physiologic parameters is called homeostasis. The process of change is mediated by various stress response mediators or compensatory mechanisms, mostly in the form of stress hormones and other related physiologic processes.

Homeostasis occurs at four different levels, described in the following table. Each level corresponds to the magnitude and duration of stressors, both internal and external, that the organism is subjected to during the course of its lifetime. The response to each stressor requires a certain level of energy expenditure (McEwen 2000) in order to shift these physiologic processes to meet the increased energy demands needed to maintain survival. This energy expenditure is also critically dependent on the available energy stores and resources of the organism at that time (physiologic reserve).

Table 5 Different energy levels required to maintain the normal function of the system in response to varying degrees of stressors

| **Homeostatic Phase** | **Stressor** | **Stress Response Activation Level** | **Energy Expenditure** | **Allostatic Energy (Energy Balance)** |
|---|---|---|---|---|
| Homeostatic Overload | Chronic, sustained, high-amplitude stress | Chronically elevated above normal level | Sustained high above normal level | $E_i$ |
| Reactive Homeostasis | Periodic, brief, low-amplitude stress | Short-term elevation, slightly above normal level | Brief, low-amplitude "spikes" | $E_2$ |
| Predictive Homeostasis | Recurrent, normal low-level fluctuations | Well within normal | Baseline energy expenditure | $E_1$ |
| Homeostatic Failure | Short-term, extremely high demand | Sustained at a very high level | Depletion of energy reserves | $E_0$ |

Normal, daily reparative mechanisms require very little energy ($E_1$) to address the normal fluctuations on a cyclic, daily or even seasonal basis. Brief periods of low-level stress (exercise, mild injury or infection) require a slightly elevated energy expenditure ($E_2$) that the organism can easily meet, drawing on its reserves without harming the system balance. Major stressors (severe injury, severe infection/sepsis, etc.) require a much higher level of energy expenditure ($E_i$) that may not be all available to the organism from its energy resources (Kline Leidy 1989). This is the level where interventions (pharmacologic, surgical or otherwise) are needed to assist in maintaining function. The energy resources required in severe or catastrophic stressors (aortic dissection, severe hemorrhage, end-stage organ failure with shut-down, etc.) occurring in a short period of time is usually so great ($E_0$) that the organism is in accelerated functional decline and eventually shut-off due to the severe depletion of energy reserves. External energy and support may fail to meet the demands to maintain function on a sustainable, long-term basis.

The relationship between homeostasis and the energy required to maintain the state of health at an optimal level is fundamental for determining the resilience response of the organism.

Under normal, everyday operating conditions, the small-scale fluctuations in energy requirements due to physiologic variations such as the circadian rhythm, exercise and sleep are easily met with the small adjustments in energy expenditure ($E_1$) through the predictive homeostatic process. This level of energy expenditure is the lowest and most affordable in the organism.

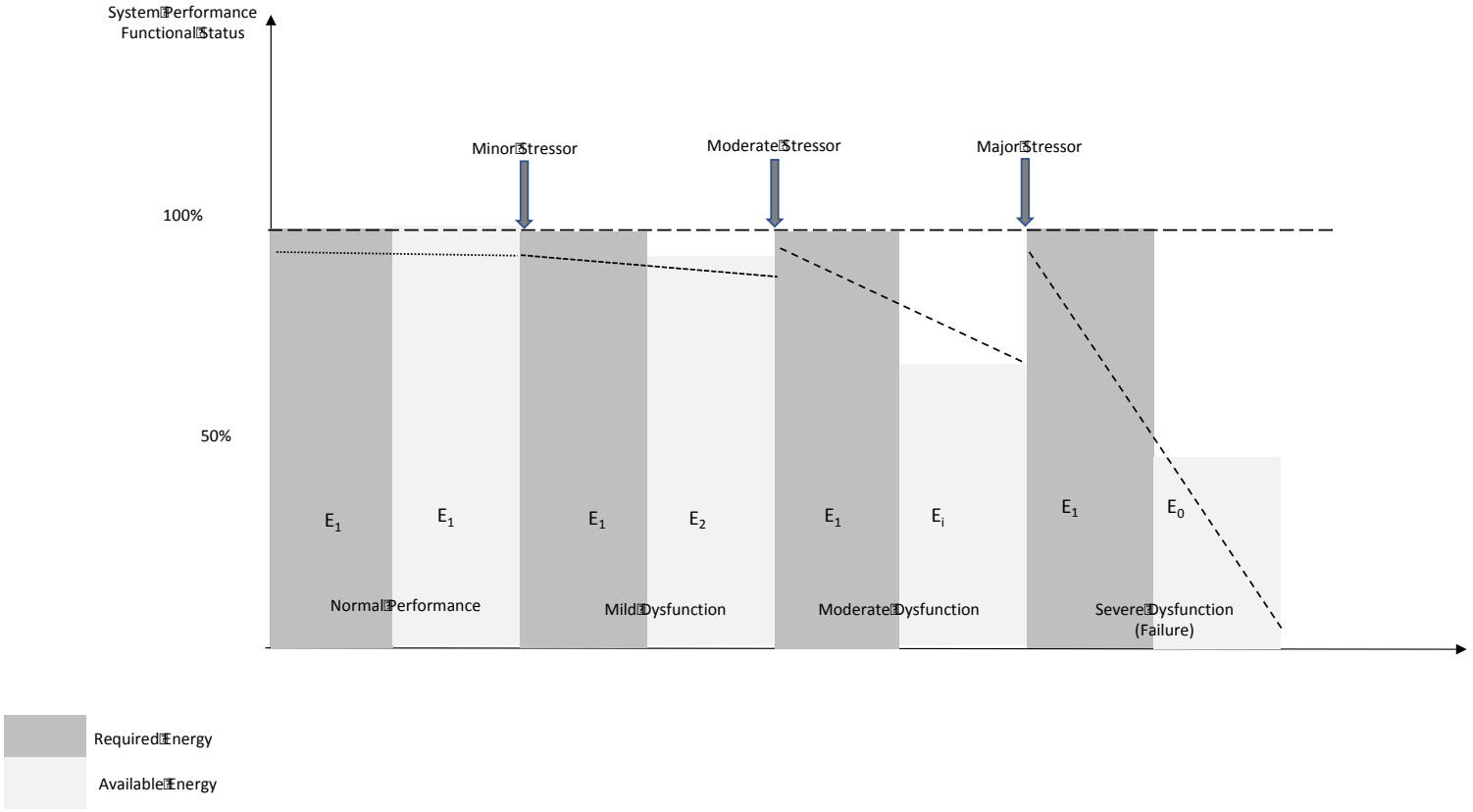



Figure 22 Change in system performance relative to the severity of stressor and the change of energy balance

The next higher level of energy requirement and expenditure is $E_2$, which is the level required to meet the metabolic demands of processes that require a slightly higher energy on a short-term basis in cases of short-term stress, such as approaching danger. During these brief periods of stress, the organism's regulatory responses easily provide the required "burst" or "spike" in energy level that only slightly exceeds the basic requirement level and only for a transient time.

On one extreme end of the energy spectrum are cases of homeostatic overload, where the entire organism is functioning under a "heightened state of alert", which is a chronic, sustained and prolonged period of the characteristic "fight or flight response". During this time, all mediators of stress and inflammation (from epigenetic and genetic control to neuro-hormonal pathways to local regulatory mechanisms) are maintained at a persistently high level. (McEwen 1999, Chrousos 2009) The results are sustained pro-inflammatory and pro-fibrotic changes in the organ systems that lead to long-term adverse changes. In the cardiovascular system, for instance, sustained long-term increases in heart rate, blood pressure, blood viscosity, ventricular wall fibrosis, vascular wall stress and coagulability, among other pathophysiologic changes (Tsigos 2000, Rich 2005), are all chronic active processes that divert the available "surplus" energy from the body's resources and direct it towards the perpetuation of these adverse effects, depriving other reparative and beneficial processes of their basic energy requirements. This lopsided energy distribution sets the stage for a situation in which any additional external or internal stressor (e.g., hypertensive crisis, thrombotic stroke, coronary thrombosis, hemodynamically significant dysrhythmia, etc.) will result in a significant increase in the energy requirements, thereby precipitating an "energy crisis" that further overloads the already strained energy resources, thus

causing significant general deterioration. This sudden and significant overload severely limits and reduces the organism's ability to adjust and maintain its baseline or normal state of health.

The other end of the energy homeostatic spectrum is homeostatic failure. This is the situation when energy sources and stores are depleted, commonly because of long-standing malnutrition, chronic debilitating illness or general frailty. As a result, and although there is a continued need for sustained energy expenditure, the organism cannot meet these energy requirements due to the severe, chronic depletion of its energy stores. Hence, it resorts to converting its own structural elements (e.g., fat and muscle) into useable energy, further exacerbating the energy "crisis" just to meet the requirements for daily activities, which are also down-regulated as a compensatory mechanism. This critical shortage of energy makes the organism and its regulatory/compensatory mechanisms very vulnerable to any sudden demand for energy in cases of serious illness or trauma. Such high-level stressors cause a catastrophic failure of energy supply and expenditure, and the organism's system experiences an accelerated failure (multi-system organ failure). Survival and quality of life fall drastically, and death becomes imminent.

Therefore, resilience in medicine and biology, or the ability to return to a normal or close to normal functional status, is entirely dependent on the energy required to counteract the effects of the stressor or disruptive event that has caused the deviation from the expected course of physiologic processes.

Since the effects of stressors are always time dependent, it then follows that the timing of intervention plays a fundamental role as well. As the Corbin-Strauss trajectory model as a process map demonstrates, all biologic and physiologic

processes are time dependent; the time of introduction of the stressor amplifies and increases its deleterious effects on the homeostatic mechanisms.

The recovery of function of the system depends on a favorable balance of the energy required for stable performance of the system versus the energy reserve (internally or externally provided) required to mitigate or reverse the effects of the disruptive event (sometimes called "surplus energy") (Attoh-Okine 2017, Costella 2009, Madni 2009) between the energy requirement and the available energy to recover and maintain normal system function after a disruptive event. More resilient systems have sufficient energy reserves to counteract the impact of the disruptive event (stressor) and thus minimize the degree and duration of the loss of function. Jeong et al (2017) have defined a metric of the resilience of a system (the Resilience Index) as the ratio between the surplus energy in the water distribution network and the input energy (amount of energy supplied to the system), given the energy loss during the operation of the system, which is increased as a result of the disruptive event.

## 5.4 The Stability-Injury-Recovery-Stability Resilience Pathway

Mathematical modeling of the resilience of any system is based upon the time-dependent property of system performance. Since resilience addresses the changes in system function over time, the graphical mathematical model for quantifying resilience plots system performance as a function over time: *P(t).* Therefore, the timing and pattern of change in system function can be estimated, as in the basic diagram below:

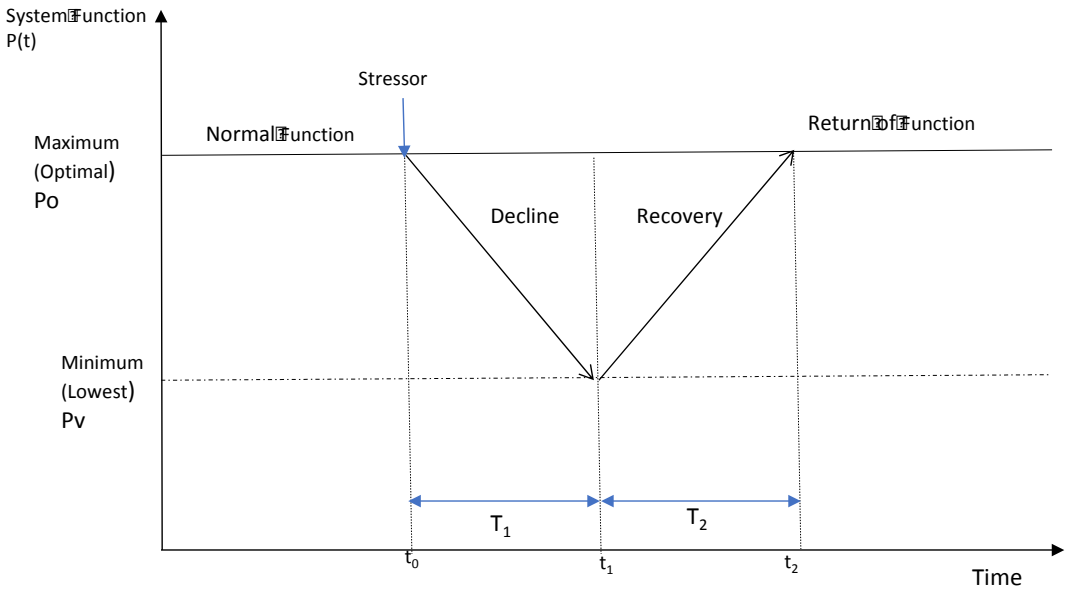



Figure 23 The sequence of events in the resilient response to injury. Modified from: Attoh-Okine (2016). Used with permission.

The process of resilience in any system describes four distinct and consecutive phases (Attoh-Okine 2016, Yodo 2016, Ayyub 2015, Ayyub 2014):

I. <u>First Stability Phase:</u>

This is the baseline condition at the start of examination of system performance. During this phase, all forces and factors acting on the structure are in a state of balance or equilibrium, known in biology as “homeostasis”. This favorable balance of forces maintains a stable environment within the structure that allows for its optimal functional status. In biologic or physiologic terms, this phase describes the “normal state of health”, where all body systems and organs are functioning at their expected level of performance, without increase or decrease in energy requirements or

expenditure outside the expected range needed for fulfillment of average daily activities and for growth.

In graphical representation, this phase is often expressed as a straight horizontal line, corresponding to its continuation over time (the X axis) and starting at the highest point of functional status (or survival) on the Y axis. Since all humans are mortals, in the survival versus time graph and depending on the specific time interval examined (i.e., an entire lifespan in chronic diseases versus a specific time interval for acute, short- or mid-term evaluations), this phase describes a line that slightly deviates downwards from the horizontal, thus representing the normal actuarial decrease in survival relative to age.

II. Injury or Unreliability Phase:

This phase is heralded by a point in time ($t_0$) at which a stressor exerts its effect on the process line. This is the point of onset. At this point, the process line (trajectory) begins its shift downwards at an angle α, thus assuming a different trajectory that is dependent on the magnitude of the stressor as well as the expected or predicted effect on the innate process at hand. The shift in the trajectory, indicating the degree of decrease in system performance, progresses at a variable rate. This is reflected by the wide variations in the angle α, ranging from a small acute angle in cases when the function loss is minimal and progressing at a slow rate, to a 90-degree angle, indicating a precipitous drop in system performance.

The effect of the stressor is a decrease in functional status or expected survival. As long as the stressor is in effect, the new trajectory continues downwards until it reaches the "nadir", which is the lowest level of decreased functional status or of

expected survival. This point ($t_1$) represents the maximal detrimental effect of the stressor on the process line.

III. Recovery Phase:

This begins at the point of intervention, whether diagnostic or therapeutic. Though not ideal, as the following discussion elaborates, healthcare interventions implemented at the point of worst decline in functional status mark the beginning of the trajectory representing the process line back to the expected course during this particular time interval. The full effect of recovery, i.e., a return to the expected level of survival and/or quality of life, intersects the original, expected process line trajectory at angle β, thus marking the successful completion of the recovery phase.

IV. Second Stability Phase:

This is the desired outcome or goal of intervention: to return the system or the organism to its previous state of stability and equilibrium. At time mark ($t_2$), the effects of the stressor on changing the trajectory will have been reversed by the effects of the intervention, thus restoring the balance of forces in the system At this point, the energy requirements and expenditure of the system decrease to their baseline level. Performance returns to its normal, baseline level. This is also the point where the outcome of the process (i.e., result of intervention or management plan) matches the expectation, thus indicating a success of intervention in meeting the stated/planned goal.

As such, the resilience pathway describes the sequence of events in the course of the treatment of a disease condition. The functional status of the subject (patient, group of patients or a community) declines at a variable pace in response to a stressor (disease onset, infection, trauma, epidemic, famine, etc.). Healthcare intervention (at a

molecular, cellular, tissue, organ or population level) reverses this trend of decline in functional status until the subject resumes its "normal" (i.e., expected based on historical, actuarial and risk adjustments) status.

Some reports in the engineering literature (Henry 2012, Ouyang 2012, Dessavre 2016) describe the resilience pathway as comprising five states: reliability (reflecting the normal or baseline functional state); unreliability (the stage immediately following the impact of the stressor, during which system performance continues to decline); disruptive state (a state of continued function at the lowest level, for a variable duration); recovery (the time period during which the system gradually regains its function) and recovered steady state, during which the system continues to operate at the previous, normal baseline level. (Figure 24)

This pattern of the resilience response may be applicable in the case of biological and medical situations. For example, after the resolution of the acute phase of a myocardial infarction, leading to a degree of damage to a certain area of the ventricular muscle, the ventricle continues to operate at a reduced level (i.e., in a disruptive state). After blood flow is restored to the heart muscle with coronary artery bypass surgery, ventricular function improves (recovery phase) to reach normal level.

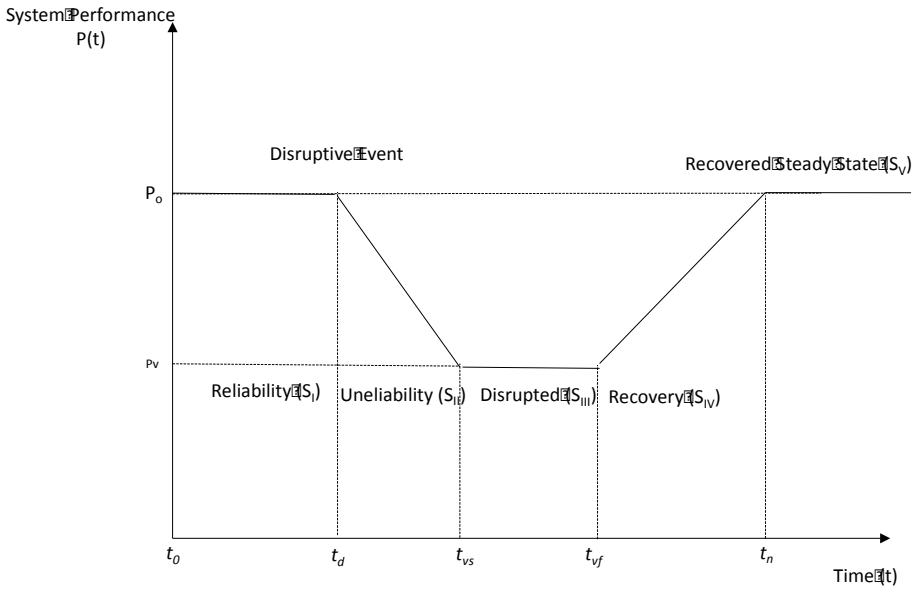



Figure 24 A five-state resilience pathway. Modified from: Yodo, N., & Wang, P. (2016). Used with permission

### 5.4.1 Patterns of Recovery

As established earlier, recovery of system performance is graphically plotted as a function curve. This curve has a starting point as the time mark when the deleterious effects of the disruptive event cease, and it continues until the system has regained its previous level of performance. Ideally, the recovery returns system performance to its previous level, without any residual decrease. Frequently, the disruptive event adversely affects system structure and functional relationships. This causes the recovery to lead to suboptimal level of performance. Conceptually (Yodo 2016, the structural-functional relationships, especially the system redundancies and backup mechanisms, may over-compensate for the injurious effects of the stressor. The result is the return of system function at a higher level than the baseline. While preferred to a lingering decrease in system, this may not occur in all cases.

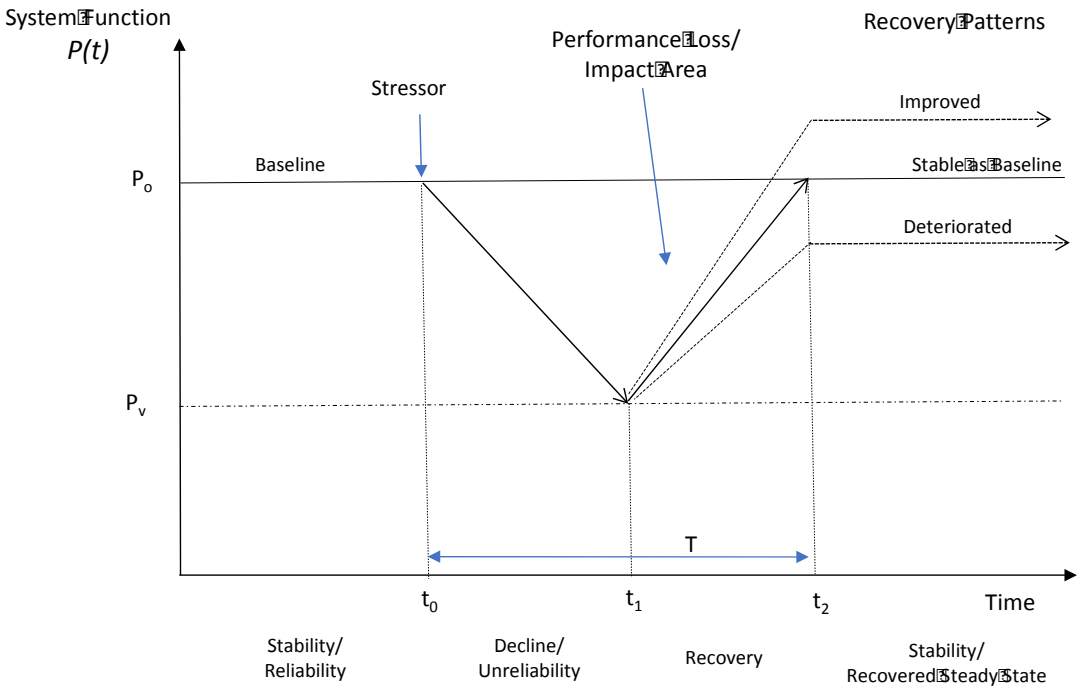



Figure 25 Different patterns of recovery curves. Modified from: Yodo et al (2016). Used with permission.

The difference in the pattern as well as the magnitude of recovery are highly dependent on specific system architecture and the governing functional relationships between its elements. There is a wide variation between the mathematical relationships governing the unreliability profiles and recovery profiles in complex systems, especially in biological systems. In addition, because of the presence of uncertainty in system performance affecting both the response to stressors as well as reliability and recovery, recovery curves are very often non-linear, exhibiting curved or irregular trajectories:

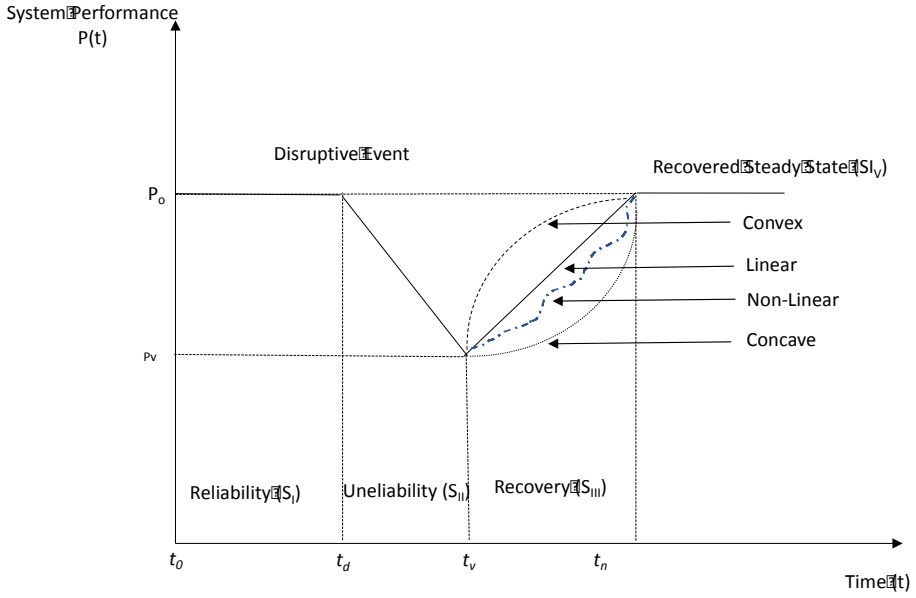



Figure 26 Different recovery curves. Modified from: Yodo, N., & Wang, P. (2016) after Munoz and Dunbar (2015). Used with permission

Another example of this variation in recovery patterns has been proposed by Sharma (2018) to demonstrate the different patterns of recovery of a system, reaching the same level of function within the same time period but along three different trajectories.

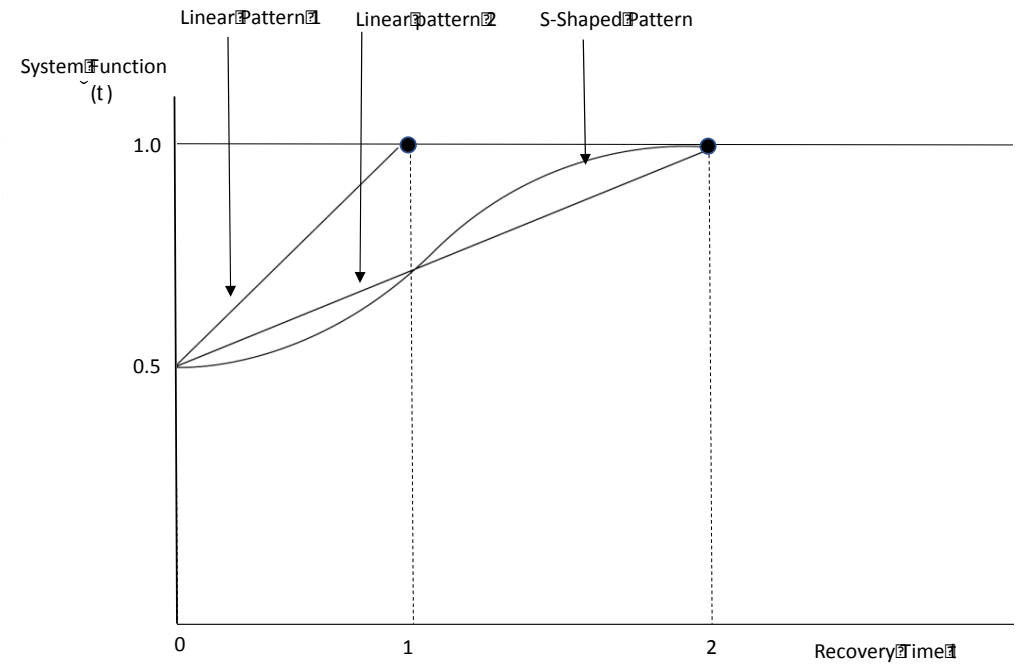



Figure 27 Different trajectories for the recovery curve. Modified from: Sharma et al (2018). Used with permission.

Assuming decline in system function occurs precipitously to its lowest level at $t_0$, the sustained return of function should—ideally—be expected at the earliest possible time ($t_1$) as opposed to a later point $t_2$. Hence, the recovery pattern described by Linear 3 in Fig 27. would be more desirable than Linear 2 or the S-shaped curve. In the case of gradual decline of function over time interval $t_0$-$t_1$, the expected recovery course to the point of sustained function ($t_2$) is the second half of the Linear 1 curve.

Most resilience models are based on the assumption that recovery is a continuous process that starts at the time of intervention and continues at different

rates and along different trajectories until recovery of function is achieved and sustained. However, this may not be the case in many systems that are susceptible to the impact of repeated disruptive events or "shocks" occurring in rapid succession.

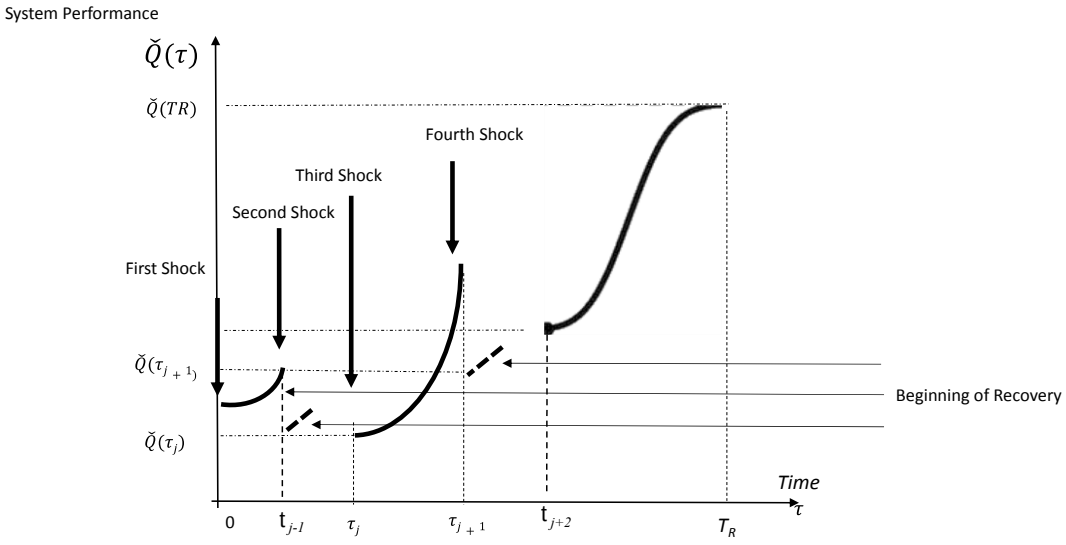



Figure 28 Impact of successive "shocks" to the system on recovery of function. Modified from: Sharma et al (2018). Used with permission.

Assuming the initial shock occurs at time mark 0, the recovery curve beginning at time mark $\tau_{j-1}$ is interrupted at time mark $\tau_{j-1}$. Recovery resumes at time mark $\tau_j$ but is interrupted again at time mark $\tau_{j+1}$. This repeating pattern of successive shocks to the system accentuates the effects of each shock on the structural components of the system and their functional relationships. The result is usually a recovery occurring over a longer period of time, and often with a suboptimal return of function. In their

2018 report, N. Sharma et al provide an equation (Equation 14, page 54) to estimate the overall resilience moments in such a model.

Examples of this situation include:

- Infrastructure in an area prone to frequent seismic activity,
- An urban power grid that is subject to repeated episodes of power interruptions,
- The brief loss of cardiac ejection due to the characteristic pause that follows "extra-systoles" or ventricular premature beats,
- The decreases in ventricular function as a result of multiple episodes of myocardial infarction
- the course of chronic obstructive pulmonary disease, which is characterized by recurrent episodes of "decompensation" or decreased performance of the pulmonary system.

## 5.5 The Resilience Curve

Quantification of the resilience is fundamental for the optimal design and construction of any engineering or complex system, including features that can predict, prevent or counteract the harmful effects of disruptive events (Yodo et al 2016). However, the development of standardized metrics for resilience is still a challenge (Hosseini 2016).

One of the important resilience metrics is the quantification of the effect of the disruptive event on the system performance. This metric, defined as Performance Loss or System Impact. This is the total time-related decrease in system function as a result of the stressor.

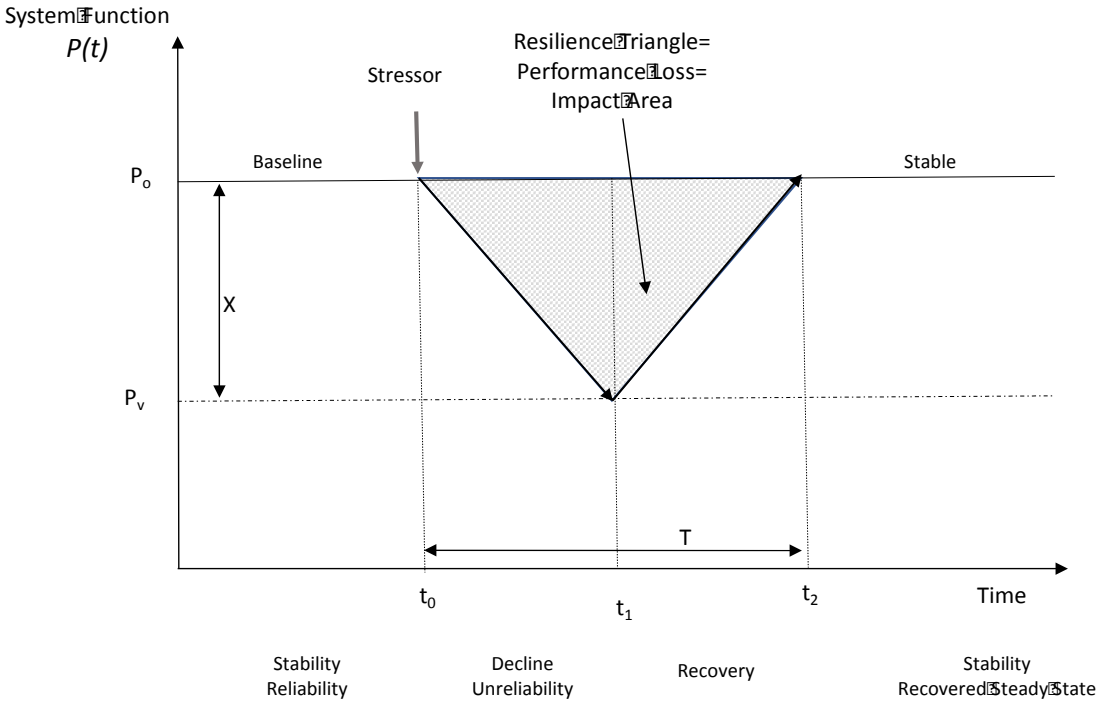



Figure 29 Performance loss as the area-under-the-curve. Modified from: Attoh-Okine (2016). Used with permission.

## 5.6 Resilience Equations

Yu and Hao (2008) developed a mechanism to calculate resilience based on the statistical analysis of two system components that reflect the resilient response in the system: (1) intrinsic resilience degree (direct effect on the system) and (2) special resilience degree (indirect effect on the system). Accordingly, they divided all variables contributing to or affecting the resilience of the system into these two groups based on their mechanism of effect, presumably along the lines of a process map or a decision tree. Their equation to calculate the resilience of a system is as follows:

$$\text{Resilience} = \sum_{i=1}^{n} f_i \, x\omega_i \qquad (1)$$

Where i = 1, …*n*; *n* is the amount of system assessment index variables, $f_i$ represents condition indices of contributing factors, *k* is a coefficient of transform and $\omega_i$ is the weighting coefficient of the index method.

A more relevant definition of resilience is the ability to prevent functional failure of the system. Thus, it becomes possible to measure the change in function of the system over time as an indicator of the system's resilient properties and performance in relation to specific stressors affecting specific system components for defined or predicted periods of time. The following model of the resilience response is modified from the original conceptual model proposed by Adams (2012).

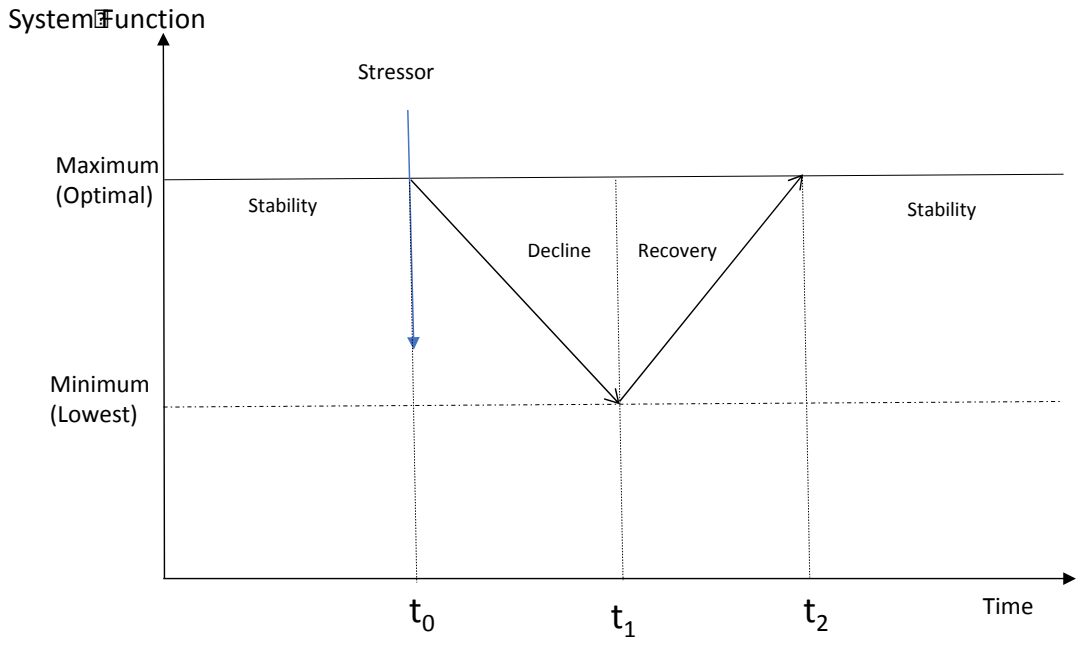



Figure 30 A simplified representation of the resilience response. Modified from: Attoh-Okine (2016). Used with permission.

Assuming resilience R is a function of quality (functional status or survival) over time *Q(t)*, then the change in this function over time relative to the stressor (Attoh-Okine 2016, Molyneaux 2016, Franchin & Cavalieri 2015, Adams 2012, Cimellaro 2016) can be expressed as follows:

$$R = \int_{t_0}^{t_2} \frac{[Q(t)]dt}{(t_2 - t_0)} \quad (2)$$

Which represents the integration of the area under the quality function *Q(t)* between different time intervals. Along similar lines, Bruneau (2003) described the following equation:

$$\mathrm{R} = \int_{t_0}^{t_2} [1 - Q(t)]dt \quad (3)$$

Using the same parameters as in Fig 27, Li and Lence (2007) redefined the resilience index originally described by Hashimoto (1982) as a vector of the time points in the resilience response curve as follows:

$$R_{(t_1,t_2)} = [\frac{g(t_2)\geq 0}{g(t_1)\geq 0}] \quad (4)$$

Where $R(t_1,t_2)$ represents the resilience of the system between time points $t_1$ and $t_2$, while $g(t_1)$ and $g(t_2)$ are the system performance at these time points, respectively.

Since resilience is an active, energy-demanding process, it becomes important to devise a formula to calculate the cost (in term of interventions, personnel, materials and money) of returning the system performance to a normal level.

In their 2009 report, Attoh-Okine et al used the quality index (i.e., the measured performance level as a percentage of the ideal 100%) to develop a resilience index as follows:

$$\text{Resilience} = \int_{t_1}^{t_2} (\frac{[Q(t)]dt}{100-(t_2-t_1)}) \quad (5)$$

## 5.7 Quantifying Resilience: The Resilience Triangle and the Area Under the Curve

The basic concept of the systemic impact (SI) (Vugrin 2014, Yodo 2016, Ayyub 2016, Nan et al 2017) is defined as the difference between the expected or target system performance (TSP) and the actual, observed system performance (SP). In medical terms, this represents the difference between the expected or desired functional status for the specific patient or patient population (coordinates on the actuarial/historical trajectory) and the observed or measured functional status (coordinates on the Corbin-Strauss trajectory). These observations are relative to points $t_0$, corresponding to the baseline functional status, and $t_f$ , corresponding to the

observed status. Thus, calculation of SI can be defined as the area under the curve for the resilience triangle, as follows:

$$SI = \int_{t_0}^{t_f} [TSP(t) - SP(t)]dt \quad (6)$$

Using the area under the curve as a representation of the energy required for recovery of function, the recovery effort (RE) or total recovery effort (TRE) can be calculated as follows:

$$TRE = \int_{t_0}^{t_f} [RE(t)]\, dt \quad (7)$$

This important metric RE(t) represents a valuable indicator of the degree of change in system function or performance during the entire resilience pathway (stability-injury-recovery-stability phases). A stable system performing normally (i.e., a healthy person) experiences no change of function over time. In this case, RE(t) = zero.

The following diagram illustrates the different parameters in the resilience pathway relating to a sudden loss of function caused by a disruptive event:

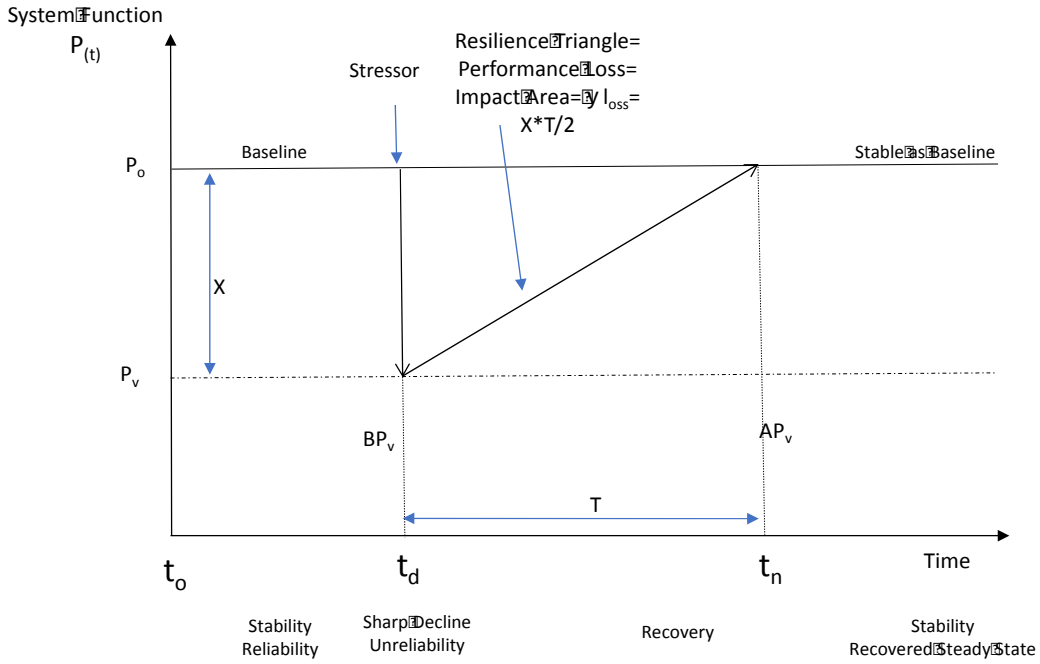



Figure 31 The resilience pathway with sudden decrease of function. Modified from: Yodo and Wang (2016). Used with permission.

Another model describes the parameters in the pathway characterized by gradual decrease of function and gradual recovery to normal state:

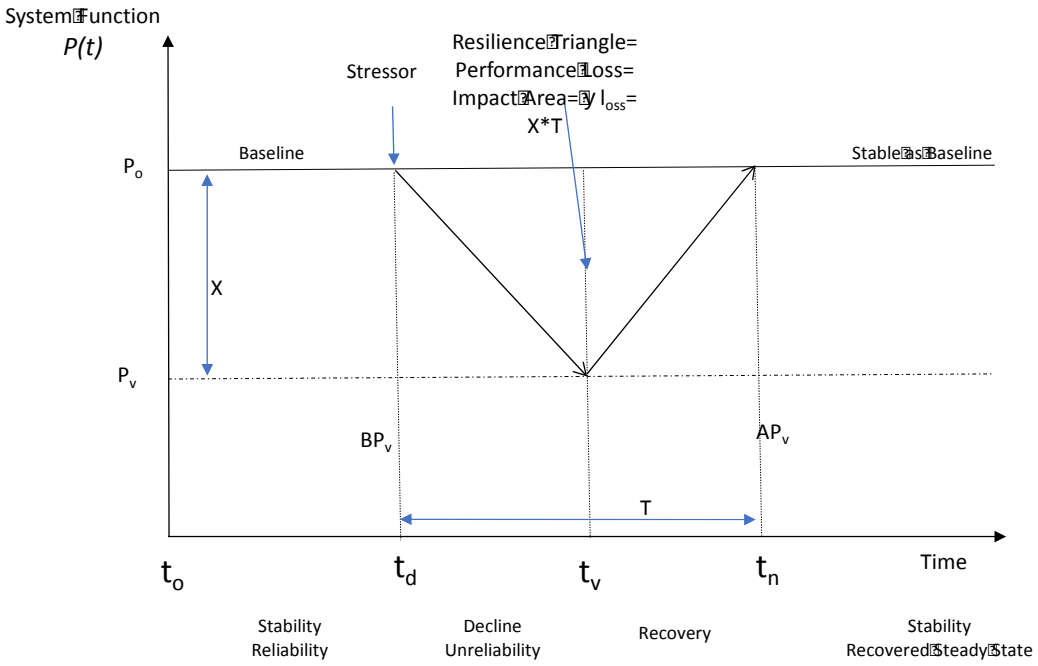



Figure 32 The resilience pathway demonstrating a biphasic gradual change in function. Modified from: Yodo and Wang (2016). Used with permission.

Where *P(t)* is the system performance as a function of time *(t)*, $P_o$ is the normal level of function, $P_v$ is the lowest level of function as a result of the event, $t_0$ is the time mark for the beginning of the process, $t_d$ is the time mark for the event, $t_n$ is the time mark for recovery, X is the degree of deterioration of function at the time of event ($P_0 - P_v$), AP(t) is the area under the curve for recovered stable state and T is the time period from the onset of the event until the return of function. In this model, the impact of the event on the system performance is the difference in performance before and after the disruptive event. Based on these diagrams, the following "dimensions of resilience" can be calculated:

Table 6 Three dimensions of resilience

| **Parameter** | **Description** | **Equation** |
|---|---|---|
| Impact | Effect of event on performance | $P_o(t_0) - P_v(t_v)$ |
| Performance loss | Total loss of function until recovery | $(t_n - t_d) \times P_o(t_0) - \int_{t_d}^{t_n} P(t)\mathrm{dt}$ |
| Recovery | Time required to return to normal function | $t_n - t_d$ |

Impact = [Initial performance level $P_o$ – Post-event level $P_v$] (8)

Relative to the time of event and the time of recovery, the loss of function is the area under the curve as bounded by the optimal level of function, interval X (degree of loss of function) and interval T (time to recovery). This area is called the resilience triangle, representing the total loss of function until the system recovers. This is calculated as follows:

Impact area = Loss of Function = $\psi_{loss} = \frac{XT}{2}$ (9)

$$\psi_{loss} = \int_{t_d}^{t_n} [Po(t_0) - P(t)]dt \quad (10)$$

Based on this, the resilience of the system $\psi$ can be calculated as follows:

Resilience $\psi = \int_{t_d}^{t_n} \frac{AP(t)}{T}\, dt$ (11)

This equation describes resilience in a single "snapshot" instance of the system performance. Assuming multiple events occur throughout the service time or lifetime of the system T*, it becomes possible to calculate the resilience of the system during this time as follows:

Resilience $\psi = Po\,(t_0) - (\frac{XT}{T^*})$ (12)

Using the parameter $\lambda$ in a Poisson process to represent the average number of events per unit time, the resilience can be calculated as follows:

$$\text{Resilience } \psi = 1 - \lambda E[IA] \quad (13)$$

Where E[IA] is the expected impact area (i.e., loss of function or the resilience triangle) occurring with each event.

Similarly, Ayyub (2015) describes another equation based on a modification of the following figure.

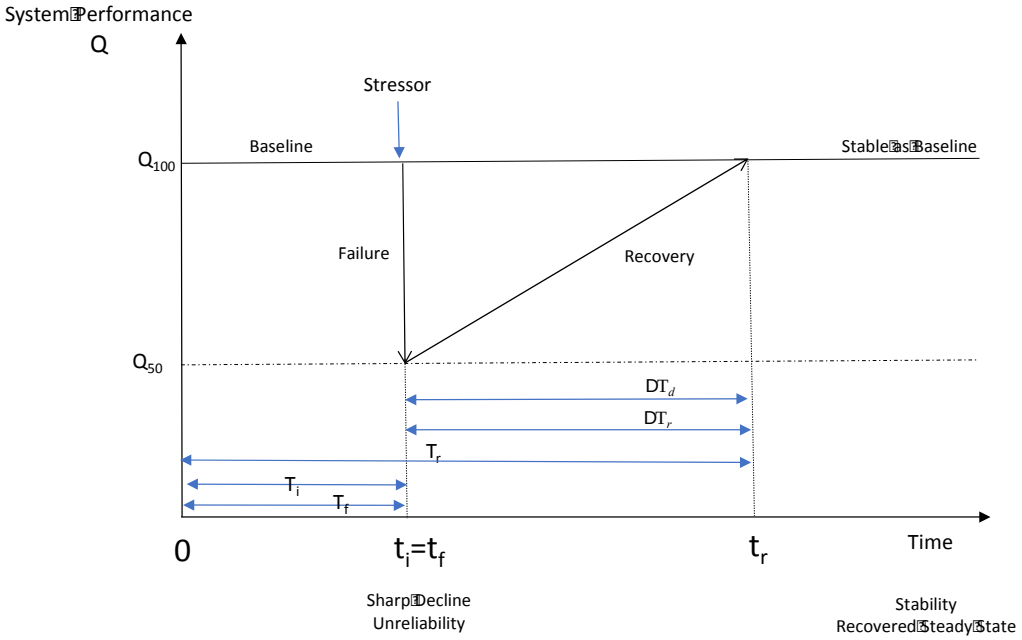



Figure 33 Resilience pathway with a sudden decrease in function. Modified from: Ayyub 2015. Used with permission.

As a Poisson process with a rate λ, an event occurring at time $t_i$ may cause failure F at time $t_f$, after a time interval $\Delta T_f$ and followed by a period of recovery at time interval $\Delta T_r$. Therefore, the duration of total disruption $\Delta T_d$ (loss of function D) is:

$$\Delta T_d = \Delta T_f + \Delta T_r \tag{14}$$

Given the time to incident $T_i$, time to failure $T_f$ and time to recovery $T_r$, the resilience of the system relative to the event $R_e$ can be calculated as:

$$R_e = \frac{T_i + F\Delta T_f + R\Delta T_r}{T_i + \Delta T_f + \Delta T_f} \tag{15}$$

This approach applies to situations where there is a precipitous drop in system performance over an extremely short period of time with an almost instantaneous start of the recovery phase. In this model, the time of loss of function (disruption duration or $\Delta T_d$) is identical to the duration of recovery or $\Delta T_r$. In biologic systems, this is most commonly associated with trauma or acute injury, but it can also be associated with other catastrophic events such as acute aortic dissection. A classic example is loss of function due to a fracture of a bone. Up to this point, the system function remains at the highest level, dropping suddenly and precipitously as a result of the disruption of the mechanics of the limb. Bone healing allows for the gradual return of function to its previous level.

Resilience engineering is an estimate of the system's property of experiencing a disruptive event, minimizing its impact on loss of function and returning to normal steady-state performance. (Attoh-Okine 2009, McDaniles 2008, Ayyub 2016, Yodo 2016, Nan 2017, Koliou et al 2018). Todman (2016) further defines the resilience response as dependent on the degree of return to normal function, the time needed to return to normal function, the rate of return (performance per time) and the efficiency (loss of function relative to the disturbance, ideally at zero) thus providing the foundation for devising preventive and/or corrective measures to preserve optimal system function. Hence, the purpose of resilience engineering is to:

a. Predict and quantify the potential and probability of failure of function in a system

b. Formulate plans for prevention of catastrophic system failures

c. Conceptualize and formulate corrective and reparative plans and processes for preservation of optimal system performance

d. Project the cost of reparative and corrective measures over the service life of the system

Resilience engineering (O'Rourke 2007, Reed 2009, Bocchini 2013, Ganin 2016, Frangopol 2016) discusses the performance of complex systems in ecology and infrastructure. By definition, these systems comprise multiple, highly organized, autonomous components (sub-systems) that are highly connected, inter-related and interdependent. For instance, an urban healthcare system describes a highly developed network of practitioners, support staff, diagnostic and therapeutic equipment and medical records. This system has its own resources, rules and regulations, feedback and overall mission of providing optimal healthcare to the population. Yet, this complex, autonomous system is highly dependent on other equally complex systems in the urban environment or a "network of networks" (Attoh-Okine 2017), such as the electricity power grid; the physical streets and traffic signal systems; transportation systems, including ambulances; the water supply and a myriad of other industries providing medical gases, instruments and equipment. The success of the urban healthcare system in performing its mission is highly dependent on the complex relationships within itself as well as within the larger network of systems in the urban environment.

Similarly, the human body is an autonomous, functionally independent, complex organism that comprises a number of autonomous complex subsystems ("system of systems") working in concert to facilitate optimal performance of the entire person, i.e., maintain the state of health. The entire body, for instance, is dependent on the stable and sustained adequate level of blood flow from the cardiovascular system for its very survival and continued function. The maintenance of blood flow at an optimal rate and volume (i.e., a healthy, fully functional

cardiovascular system) is dependent on a number of structural (anatomic), functional (physiologic), regulatory (neural and hormonal feedback) and global (age-related, genetic, inflammatory and degenerative processes) mechanisms that involve other sub-systems (brain, central nervous system, autonomic nervous system, adrenal glands, etc.).

Since "health" is defined as the maintenance of a normal function of the human body and/or its sub-systems, especially in response to harmful stimuli, injury and external and internal disease processes, the study and implementation of the resilience of complex systems (Rose 2013, Orwin 2004, Alipour 2016, Yodo 2016, Cimellaro 2017, Cimellaro 2018) provides the fundamental underpinnings of the conceptualization, formulation, implementation and evaluation of materials, instruments, methodologies, procedures and protocols as interventions for the diagnosis and treatment of conditions that affect the function of the human body, i.e., medical decisions and interventions and the practice guidelines that govern their use and implementation.

This model (Ayyub 2016, Yodo 2016) also allows for estimation of the predictive properties of the system performance. For this, the following two definitions are described:

- Robustness of the system: This is the ability of the system and its elements/components to withstand the disruptive event without a significant loss of performance.

- Redundancy of the system: This is the extent to which the system and its elements can sustain function during the disruptive event.

Thus, failure events are a measure of decreased robustness of the system. The failure profile F can be estimated as follows:

$$F = \frac{\int_{t_i}^{t_f} f\ dt}{\int_{t_i}^{t_f} Q\ dt} \quad (16)$$

Based on a biphasic resilience pathway model, Nan et al (2017) described another integrated resilience metric estimating the measure of performance (MOP, referred to as Q in Ayyub [2016]) and defined as the time-average performance loss (TAPL). This is calculated as follows:

$$\text{TAPL} = \frac{\int_{t_d}^{t_{ns}} [Q(t_0) - Q(t)]dt}{(t_{ns} - t_d)} \quad (17)$$

Where $t_0$ is the time of baseline performance, $t_d$ the time of onset of disruption, $t_r$ the time of lowest performance (failure) and $t_{ns}$ the time of return to normal status.

The importance of providing a mathematical resilience model for predicting failure and catastrophe in critical infrastructure has been highlighted in recent years (Linkov and Palma-Oliveira 2017, ASCE 2017, Linkov et al 2018). Incorporating resilience engineering in designing buildings and other infrastructure is valuable in assuring the continuation of functionality and reducing the time needed for repair as a requirement for return to full function. In biologic terms, this means providing preventive measures to anticipate and prevent system failure (i.e., disability) due to disease or injury, ensuring preservation of functional status (i.e., health) and reducing the recovery period and its attendant resources.

Sharma (2018), quoting Bonstrom and Corotis (2016), builds on the typical resilience metric described in the following equation:

$$R = \frac{\int_{t_I}^{t_L} Q(t)\,\mathrm{dt}}{T_R} = \frac{\int_0^{T_R} \breve{Q}(\tau)d\tau}{T_R} \quad (18)$$

This equation has been based on a typical resilience model, describing an abrupt and significant decrease in system performance from its highest (baseline) level

*Q(t)* as a result of a severe stressor ("shock") applied to the system at time mark $t_I$. The system performance at that time is lowest, at a level $Q_{res}$, reflecting the residual function at the beginning of the s-shaped recovery curve over the period $t_I$ to $t_L$.

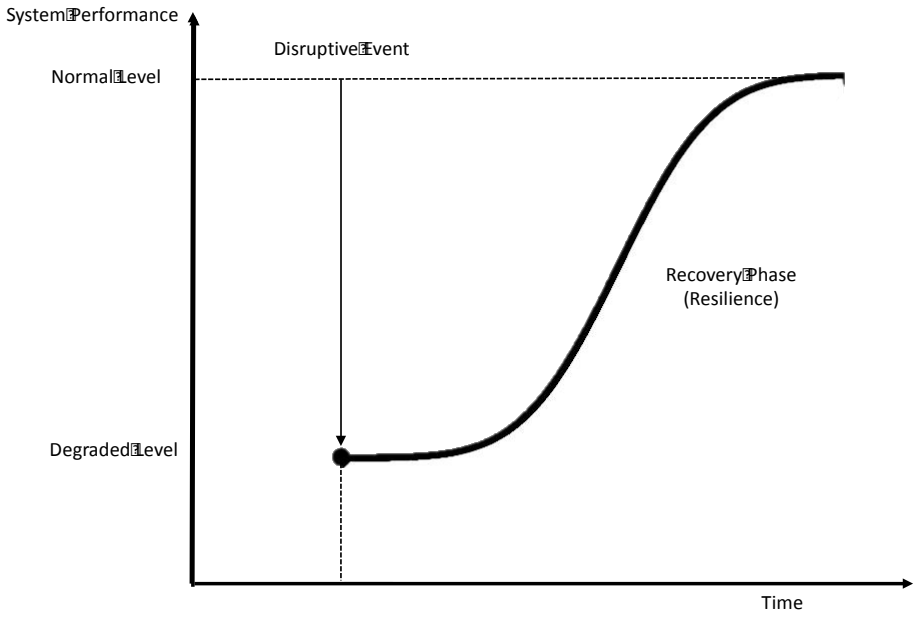



Figure 34 Recovery curve in a typical resilience model. Modified from: Sharma, Tabandeh, & Gardoni (2018). Used with permission.

This time interval τ reflects the recovery time as in Equation 18, used to calculate the resilience metric R. This is based on the assumption that recovery time $T_R = t_L - t_I$. This is the basis for defining system performance as a function of time. $\tilde{Q}(t) = Q(t)$.

One of the limitations of using such above-listed equation to quantify of resilience is that these assumptions lead to the same result of the resilience metric R, regardless of the different combinations of $\breve{Q}\ (t)$ or $T_{R.}$

This is because assuming that $\breve{Q}\ (t) = Q(t)$ approximates the recovery function curve to a linear function. As detailed in the previous chapter, the recovery curve varies widely in different scenarios. N. Sharma (2018) provides this illustrative example of three different patterns of recovery in this resilience pathway:

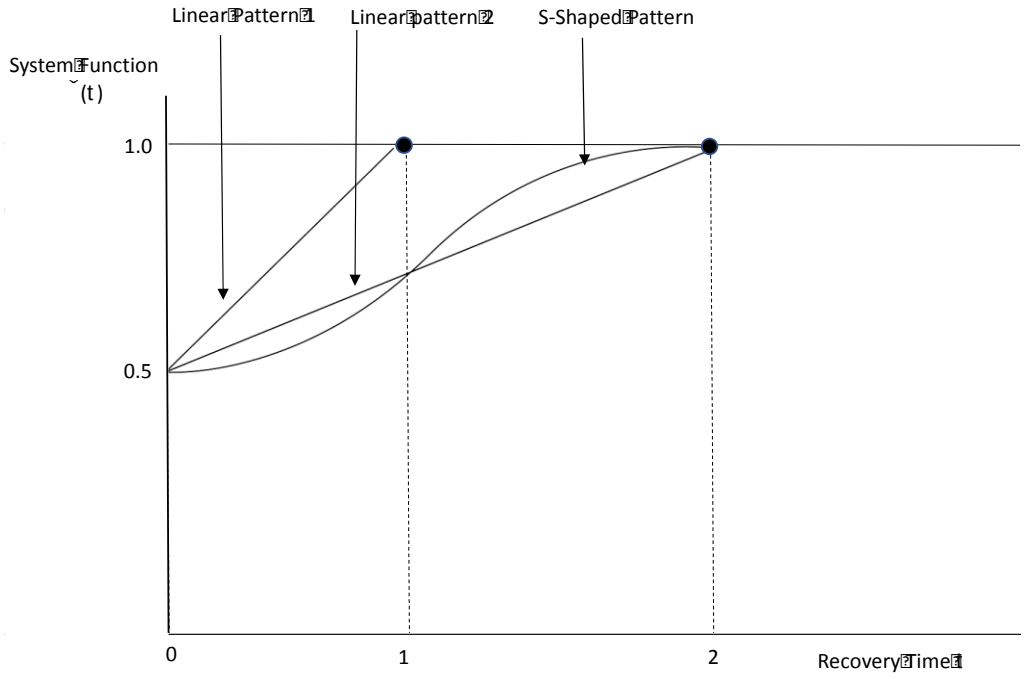



Figure 35 Impact of different recovery curves on the resilience metric. Modified from: Sharma et al (2018). Used with permission.

In this monophasic resilience model (focusing on the recovery phase), all recovery curves begin at the same time mark, (0). Linear 1 curve describes a straight line reaching recovered steady state at time mark 1 and continues at that level to time mark 2. Linear 2 curve is also a straight line, beginning at the same time but has a different angle, thus reaching the same functional level at a later time period (2). The third recovery curve also begins at time mark (0) and ends at time mark (2), but it describes a sinuous, S-shaped curve with the change of phase from a gradual increase to a more robust increase coinciding with time mark (1).

7 presents the mathematical relationship they described to calculate the recovery function. According to their calculations, all three curves reflect the same resilience metric R.

Table 7 Mathematical relationships for different recovery curves. After Sharma et al (2018. Used with permission.

| Curve | $T_R$ | Recovery Function | R | $R(T_H=2)$ | $R(T_H=3)$ |
|---|---|---|---|---|---|
| Linear 1 | 1-0 = 1 | $0.5 + 0.5\ t$ | 0.75 | 0.87 | 0.92 |
| Linear 2 | 2-0= 2 | $0.5+0.25\ t$ | 0.75 | 0.75 | 0.83 |
| S-shaped | 2-0= 2 | $0.75-0.25 \cos(\pi\ t/2)$ | 0.75 | 0.75 | 0.83 |

As an attempt to compensate for this discrepancy, various researchers (Reed et al 2009, Cimellaro 2010a, Decò et al 2013) have replaced $t_L$ in Equation 18 with a fixed time horizon denoted $t_H$. Subsequently, the resilience metric $R(t_H)$

By implementing this change, the resilience metric is set at $R(T_H = 2)$ or as $R(T_H = 3)$. Calculating for these values, the resilience metric for the three different curves Linear 1, Linear 2 and S-shaped are listed in the right-hand columns of the table.

According to this example, the resilience metric $R(T_H)$ corresponding to a fixed time horizon $T_H$ does not differentiate between different recovery patterns (in this case between linear and S-shaped curves)

The authors then proposed a new resilience metric to quantify resilience given a specific recovery curve in terms of partial descriptors of $\breve{Q}(\tau)$. This new metric (Cumulative Resilience Function or CRF) represents the overall recovery by time $\tau$ and defines the time interval to recovery as $T_R$ ( $t_L - t_I$). The overall recovery time for any resilience pathway is defined as $\tau$.

Thus, the cumulative recovery function (defined as a continuous function of quality Q over time) can be represented as follows:

$$q(\tau) = d\frac{\breve{Q}}{d\tau} \qquad \text{for all} \quad \tau \in [\,0, T_R] \tag{19}$$

Table 8 List of equations reviewed

| # | Reference | Equation | Comment |
|---|---|---|---|
| 1 | Nan 2017 | $q(\tau) = d\frac{\breve{Q}}{d\tau}$ for all $\tau \in [0, T_R]$ | Cumulative recovery function |
| 2 | Yodo 2016 | $\psi = \int_{t_d}^{t_n} \frac{AP(t)}{T}\, dt$ | Resilience |
| 3 | | $\psi = Po\ (t_0) - (\frac{XT}{T^*})$ | Resilience |
| 4 | Attoh-Okine 2016 | $\mathrm{SI} = \int_{t_0}^{t_f} [\mathrm{TSP}(t) - \mathrm{SP}(t)]\, dt$ | System impact |
| 5 | Yodo 2016 | $(t_n - t_d) \times P_o(t_0) - \int_{t_d}^{t_n} P(t)\mathrm{dt}$ | Performance loss |
| 6 | | $TRE = \int_{t_0}^{t_f} [RE(t)]\, dt$ | Total recovery effort |
| 7 | Bonstrom and Corotis 2016 | $R = \frac{\int_{t_I}^{t_L} Q(t)\mathrm{dt}}{T_R} = \frac{\int_0^{T_R} \breve{Q}(\tau) d\tau}{T_R}$ | Resilience |

Table 8 Continued

| # | Reference | Equation | Comment |
|---|---|---|---|
| 8 | Attoh-Okine 2016 | $\int_{t_0}^{t_2} \frac{[Q(t)]\mathrm{dt}}{(t_2 - t_0)}$ | Resilience |
| 9 | Ayyub 2015 | $R_e = \frac{T_i + F\Delta T_f + R\Delta T_r}{T_i + \Delta T_f + \Delta T_f}$ <br> $\text{Resilience} = \frac{\int_{t_0}^{t_1} Q(t)\mathrm{dt}}{100(t_0 - t_1)}$ | Resilience |
| 10 | Attoh-Okine 2009 | $R = \int_{t_0}^{t_1} \left( \frac{[Q(t)]\mathrm{dt}}{100(t_2 - t_1)} \right)$ | Resilience |
| 11 | Yu and Hao 2008 | $\text{Resilience} = \sum_{i=1}^{n} f_i \, x\omega_i$ | Resilience |
| 12 | Liu and Lence 2007 | $\text{Re}\,(t_1, t_2) = \left[ \frac{g(t_2) \geq 0}{g(t_1) \geq 0} \right]$ | Resilience |
| 13 | Bruneau 2003 | $R = \int_{t_0}^{t_1} (1 - Q(t)dt)$ | Resilience |

### 5.7.1 Data Analysis

Table 9 A sample of the data variables as collected. Non-numeric data have been converted to numeric code

| | Gender | Age | Mortality | Days | Location | Survival | GenderDef | Place |
|---|---|---|---|---|---|---|---|---|
| 1 | Male | 67 | Alive | 3 | DE | 100 | 1 | 1 |
| 2 | Male | 67 | Unknown | 5 | DE | 50 | 1 | 1 |
| 3 | Male | 69 | Alive | 11 | DE | 100 | 1 | 1 |
| 4 | Male | 67 | Alive | 18 | NJ | 100 | 1 | 2 |
| 5 | Female | 66 | Alive | 7 | DE | 100 | 2 | 1 |
| 6 | Female | 81 | Alive | 9 | DE | 100 | 2 | 1 |
| 7 | Male | 74 | Alive | 6 | DE | 100 | 1 | 1 |
| 8 | Male | 81 | Unknown | 21 | PA | 50 | 1 | 3 |
| 9 | Male | 81 | Alive | 8 | DE | 100 | 1 | 1 |
| 10 | Female | 85 | Unknown | 14 | DE | 50 | 2 | 1 |
| 11 | Female | 86 | Alive | 12 | NJ | 100 | 2 | 2 |
| 12 | Male | 88 | Dead | 22 | NJ | 0 | 1 | 2 |
| 13 | Male | 81 | Unknown | 11 | DE | 50 | 1 | 1 |
| 14 | Male | 70 | Alive | 8 | DE | 100 | 1 | 1 |
| 15 | Male | 64 | Unknown | 6 | DE | 50 | 1 | 1 |

Table 9 Continued

| | Gender | Age | Mortality | Days | Location | Survival | GenderDef | Place |
|---|---|---|---|---|---|---|---|---|
| 16 | Male | 50 | Unknown | 16 | PA | 50 | 1 | 3 |
| 17 | Male | 73 | Unknown | 7 | DE | 50 | 1 | 1 |
| 18 | Male | 80 | Alive | 7 | DE | 100 | 1 | 1 |
| 19 | Male | 81 | Unknown | 8 | DE | 50 | 1 | 1 |
| 20 | Male | 85 | Alive | 5 | DE | 100 | 1 | 1 |

## 5.8 Patient Cohort

The Society of Thoracic Surgeons Adult Cardiac Surgery Database (Executive Summary 2017) is the world's largest registry for cardiac surgery patients. Since its establishment in 1989, it now has over 6.3 million records submitted by over 31000 surgeons around the world. This registry has been instrumental in evaluating the outcomes of different treatment modalities and different operative techniques and devising indications for surgery. It serves as the repository of scientific evidence for the development and revision of clinical practice guidelines (Brown et al 2009, Dewey et al 2008, Wendt et al 2009, Tommaso et al 2012, Mack et al 2015).

After obtaining the necessary permission from the local administrator of the Society of Thoracic Surgeons Adult Cardiac Surgery Database, the electronic health records of 500 patients who had undergone aortic valve replacement within the last 3 years were reviewed. All patient identifiers were removed, and data was anonymized and retained in secure storage with access limited to the primary investigator. Data from 153 patients were excluded due to incomplete follow-up. Data from the remainder 347 records were analyzed.

## 5.9 Data Variables

- Age
- Gender
- Geographic location: Delaware, Pennsylvania, New Jersey or Maryland
- Time interval from decision to surgery (in days)
- Survival status (also expressed as mortality percentage) at 30 days after surgery

Table 10 Summary of the data variables and their characteristics

| | **Characteristics** | **Comments** |
|---|---|---|
| Number of data entities | 347 | Study cohort |
| Age | Discrete variable | |
| Gender | Categorical variable | Coded as Male/Female |
| Geographic location | Categorical variable | Coded as: DE, NJ, PA, MA |
| Time from diagnosis to surgery | Continuous variable | |
| 30-day survival | Categorical variable | Coded as: Alive, Dead, Unknown |

Data from the 347 patient records was used, with columns representing each data variable and rows representing each patient. Non-numeric data (gender and location) were represented in separate columns by numeric equivalents. Survival status was expressed numerically as percentage values (0, 50 and 100%) in a separate column. Gender data was defined as (Male=1, Female=2), Location data was specified as detailed above.

The following parameters were calculated: minimum, maximum, mean, median, 1st quartile, 3rd quartile, standard deviation, variance.

Table 11 Calculated parameters

| | Min | 1st Qrt | Median | Mean | 3rd Qrt | Max | Variance | Std Dev |
|---|---|---|---|---|---|---|---|---|
| Age | 20.00 | 66.50 | 76.00 | 73.85 | 83.00 | 97.00 | 167.1934 | 12.93033 |
| Days | 2.00 | 7.00 | 11.00 | 11.63 | 16.00 | 30.00 | 31.0666 | 5.573742 |

## 5.10 Graphical Representation of Statistical Analysis

## 5.11 Comments

Exploratory data analysis of this small group of patients reveals a survival rate of 87.6%, reflecting a postoperative mortality rate of 2.5%. This is excluding the patients with an unknown survival status (9.7%). These findings correlate with the published reports (Brown 2009 [risk of 2.7%], Swinkles 2011 [risk of 2-5%], Iturra 2014 [risk of 2.8%], Reardon 2017 [risk of 4.4%]), which list the national average of <2 and 2-5% for low and intermediate risk, respectively. Considering the lack of a

specific risk assessment for each patient in this cohort, the patient population examined is assumed to have an intermediate risk for aortic valve replacement. The expected operative risk (30-day mortality risk) for this mixed group of patients is 2-5%.

In examining the data analysis, the distribution of survival and of the time to surgery is skewed. According to Ogunnaike (2009), this can be addressed as a log-normal distribution. Given the skewness of the distribution (the shape of which is related to the standard deviation $\beta$), its height is related to the arithmetic mean $\alpha$; the change in which changes the height or scale of the distribution but not its shape. Therefore, the median is a better indicator of the central tendency in this distribution.

Given the arithmetic mean of the random variable as $\alpha$, the median $m$ is calculated as:

Median = $m = e^{\alpha}$.

## 5.12 Proof of Concept

In cardiothoracic surgery, survival at 30 days after surgery has been established as the benchmark measure of quality (Monte 2018, Krumholz 2006, Shroyer 2003). This metric has been expressed alternatively as the probability of survival (as a percentage) or the probability of mortality (also as a percentage). This principle provided the basis to construct a resilience model incorporating the Corbin-Strauss trajectory to estimate the change in probability of survival relative to surgery in an index case of aortic stenosis.

Step 1:

The first part of the mathematical proof of concept was to construct the Corbin-Strauss trajectory for untreated aortic stenosis using historical large-population

studies. In constructing this model, the time-related probability of survival in untreated aortic stenosis, based on data from the published literature (Brunwald 1990, Carabello 2008, Varadarajan 2006, Rosenhek 2010), was assumed to be as follows: 1-year survival 62-75% (average 68%), corresponding to 1-year mortality of 26-48% (average 37%). Extrapolating from these findings, the rate of decrease is assumed to be 5.7% per month, correlating to a daily rate of approximately 0.19%. Based on these observations and his own findings, Carabello (2008) estimates a monthly mortality risk of ~2%.

Assuming a constant rate of decline, the probability of survival *Q(t)* was assumed to be as a decay function representing the Corbin-Strauss trajectory in this situation. This function was plotted as a linear decay function.

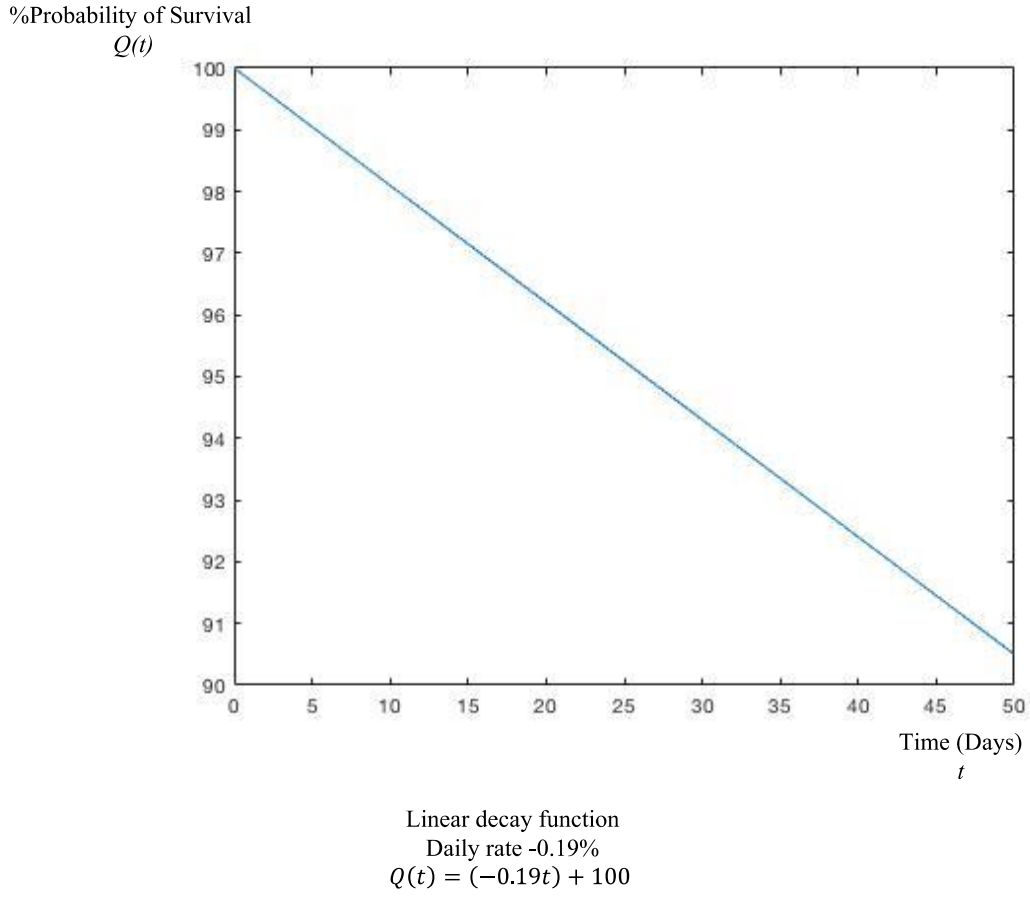
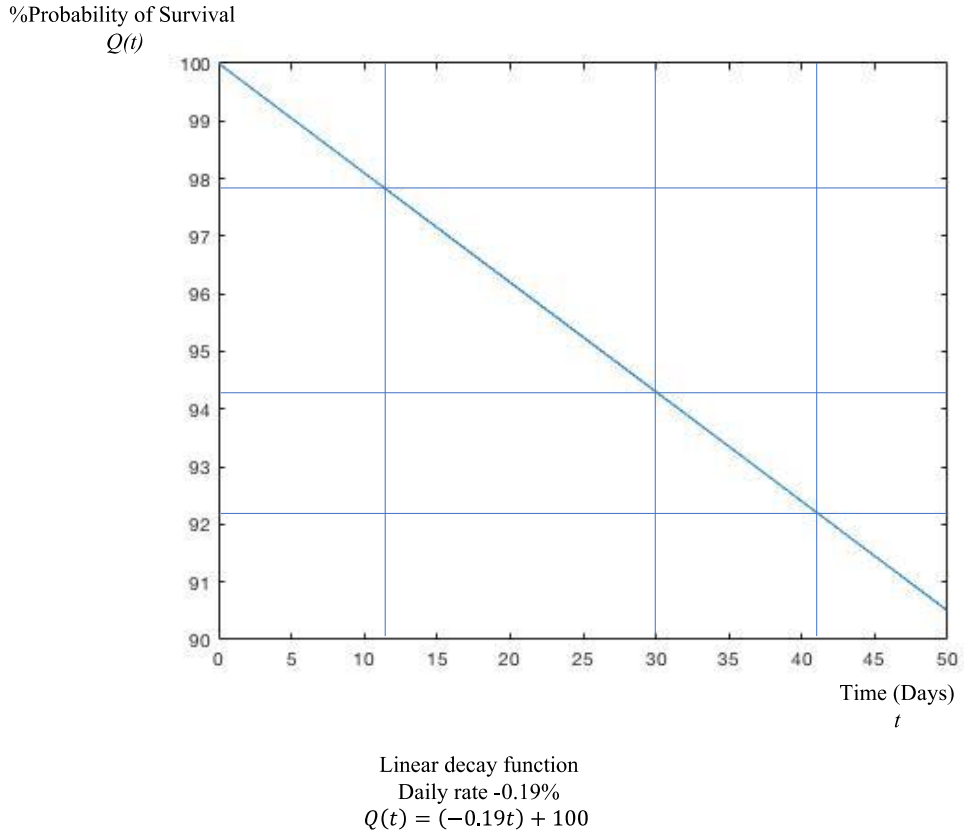



Figure 49 The Corbin-Strauss trajectory for aortic stenosis

The expected or predicted probability of survival (based on this model) is projected on the graph as 97.9% at 12 days, 94.3% at 30 days and 92.1% at 42 days. In addition to these predictions from the trajectory, the results of the exploratory data analysis of our local data set, reflecting the probability of survival at specific time

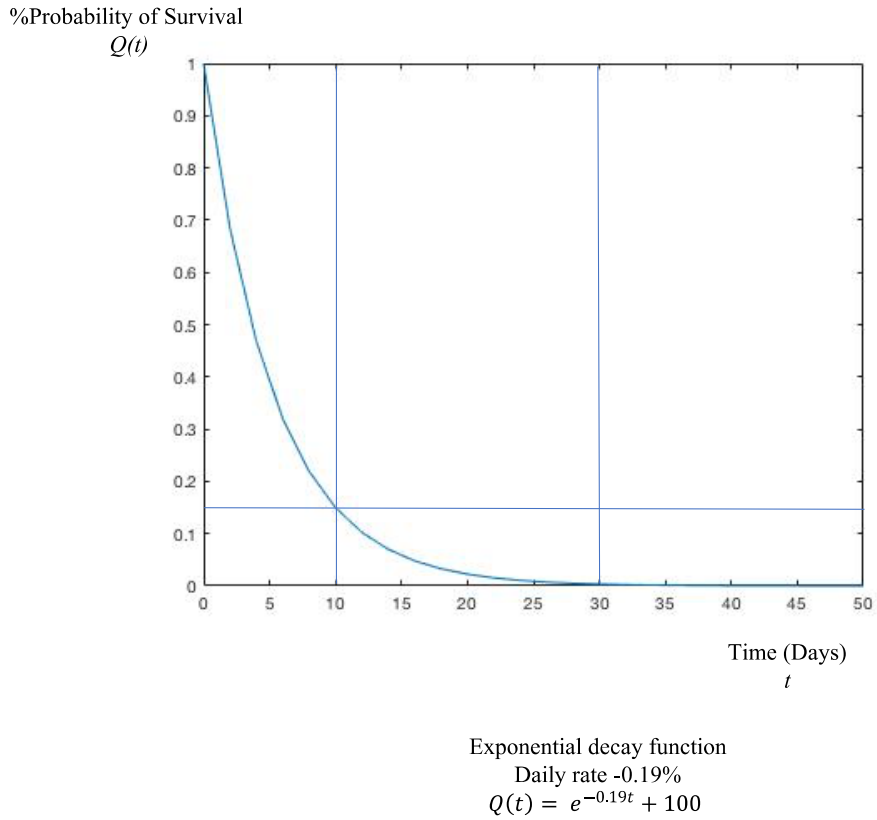
points (time of diagnosis [$t_0$], time of surgery [$t_1$] and 30 days after surgery [$t_2$]), were calculated and the results tabulated in the graph.




| t | Q(t) |
|---|---|
| 0 | 100 |
| 12 | 97.7 |
| 30 | 94.3 |
| 42 | 92.0 |

Figure 50 The Corbin-Strauss trajectory plotted as a linear decay function

Alternatively, we explored the assumption that the Corbin-Strauss trajectory may be an exponential decay function. Accordingly, the mathematical relationship in this situation was also plotted in Figure 51.




| t | Q(t) |
|---|---|
| 0 | 100 |
| 12 | 15 |
| 30 | 0.0 |
| 42 | 0.0 |

Figure 51 The Corbin-Strauss trajectory plotted as an exponential decay function

However, this assumption suggests an unrealistically accelerated rate of decrease in the probability of survival, which is predicted to reach 0.0% at 30 and 42 days. These predictions significantly contradict the published results and estimations

based on the analysis of data from large-scale clinical studies. Therefore, this assumption was not applied in the comparison of results, which follows below.

Step 2:

For the purpose of comparison of the results from the Corbin-Strauss trajectory model and our own analysis, a composite graph was constructed, plotting the Corbin-Strauss trajectory as a linear decay function with the parameters specified above. The predicted probability of survival at the three time intervals described (12, 30 and 42 days) were plotted along the trajectory line (grey circles in Figure 35). In addition, the estimated probability of survival -without treatment- at those same time points (according to the results of our data analysis of a decrease in survival of 2.5% at 42 days) were also plotted as clear circles in the same figure. The results of our data analysis were noted to fall within a range of 2.0 percentage points from the predictions of the Corbin-Strauss model. Notably, in this model, our findings represent an observed survival of 87.6% and mortality of 2.5%, likely due to the censored or excluded patients with an “unknown” survival status.

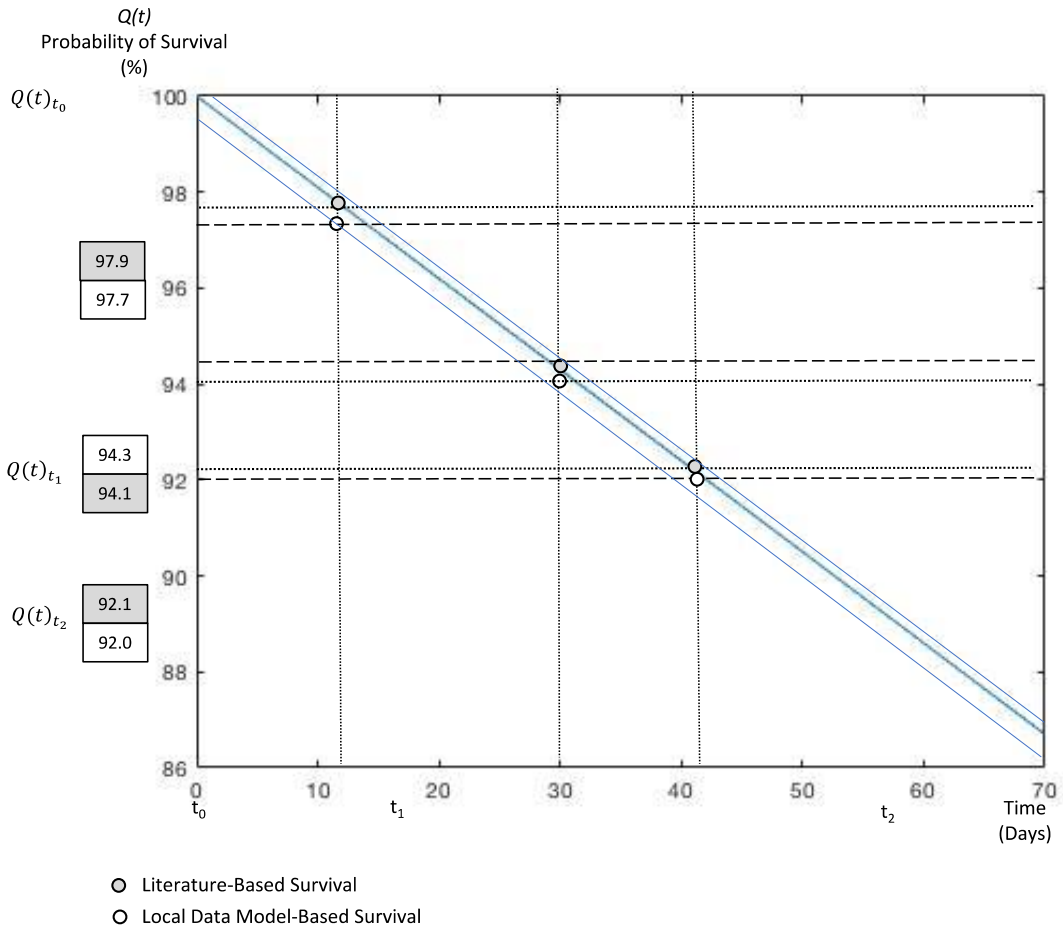



Figure 52 Comparison of results of data analysis and the Corbin-Strauss trajectory

Step 3:

A biphasic resilience model was constructed according to the time marks along the trajectory. Q(t) or the probability of survival at the time of diagnosis $t_0$ was highest at 100%. The expected probability of survival at the endpoint of 30-days after surgery or $t_2$ was 92%.

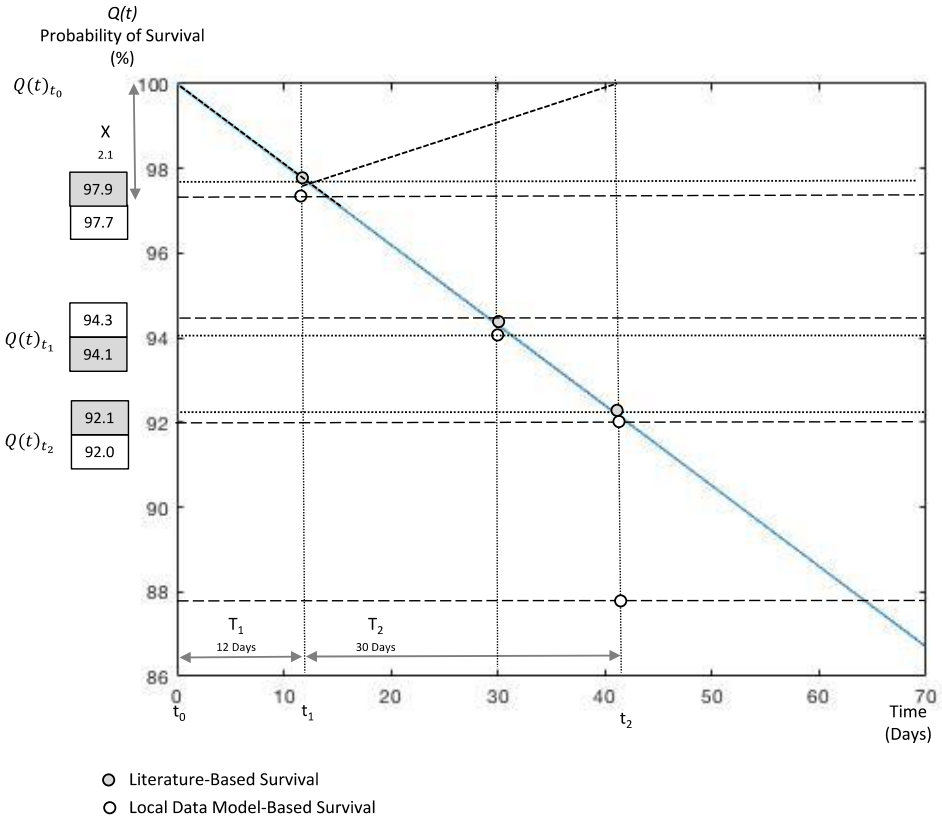



Figure 53 The resilience model incorporating the Corbin-Strauss trajectory.

Time intervals $T_1$ and $T_2$ were plotted to describe the time from diagnosis to surgery and the 30-day period after surgery, respectively, while X represents the degree of change in the probability of survival between baseline and the time of surgery.

For the purpose of this work, the probability of survival has been implemented as a surrogate measure of the system performance *Q(t).* Therefore, normal system performance $Q(t)_0$ at baseline corresponds to survival status of 100%. Meanwhile, the projected or expected survival status of 98% as a result of the onset of symptoms (time mark $t_0$) is represented as $Q_v$, or the lowest expected performance of the system

(corresponding to the expected reduced quality of life). The estimation of the progressive decrease in system performance over time due to the effect of untreated aortic stenosis is here represented as a decline in expected survival. The slope of this line is based on the assumption that patients have presented with symptoms of either angina or syncope, reflecting a preserved left ventricular function and the absence of congestive heart failure. Time interval to surgery ($t_1 - t_0$) is represented as $T_1$, and postoperative time to recovery of function ($t_2 - t_1$) is represented as $T_2$, both in days.

Assumptions:

$Q_0 = Q(t)_{t_0}$ =100%

$Q_v = Q(t)_{t_1} = 98\%$

Change in system performance $X = Q_0 - Q_v = 2\%$

$T_1 = (t_1 - t_0) = (12\text{-}0) = 12$ days

$T_2 = (t_2 - t_1) = (42\text{-}12) = 30$ days

$T_1 + T_2 = (t_1 - t_0) + (t_2 - t_1) = 42$ days

Documented mortality rate 2.5%

The following equations were solved to estimate the resilience of the system as represented by the total impact on the system performance (i.e., the resilience triangle or the area under the curve) or expressed in percentage of the baseline (optimal or full) system performance:

Loss of Function = System Impact = Resilience Triangle $= \Psi_{loss} = \frac{XT}{2} = 42$

Total recovery effort:

$$\text{TRE} = \int_{t^0}^{t_f}[RE(t)]dt = \int_{t_0}^{t_1}[Q(t)]dt = (Q_{t_0} - Q_{t_1}) = 100 - 98 = 2\%$$

Resilience:

$R = \int_{t_0}^{t_2}[1 - Q(t)]dt = \int_{t_0}^{t_2} 1\, dt - \int_{t_0}^{t_2} Q(t)dt$ = $(t_2\text{-}t_0)$ -$[Q(t_0)- Q(t_2)]$

= 42-[100-100] = 42

Resilience:

$$R = \frac{\int_{t_0}^{t_2}[Q(t)]\mathrm{dt}}{(t_2 - t_0)} = \frac{[Q(t)]dt}{42} = \frac{98}{42} = 2.3\%$$

Resilience:

$$R = \int_{t_0}^{t_1}\left(\frac{[Q(t)dt}{100(t_2 - t_0)}\right) = \frac{\int_{t_0}^{t_1}[Q(t)]dt}{1(t_2 - t_0)} = \frac{98}{1(42)} = 2.3\%$$

Resilience:

$R = \int_{t_0}^{t_2}[\, Q_{0(t_0)} - Q(t)]\, dt = \int_{t_0}^{t_2} Q_{0(t_0)} - \int_{t_0}^{t_2}[Q(t)]dt = 100 - 98 = 2\%$

Resilience as performance loss:

Performance loss = $\int_{t_d}^{t_n}[P_o(t_0) - P(t)]\,\mathrm{dt}$ = [100-98] = 2%

Change in performance:

The change in performance = $\int_{t_0}^{t_f}[TSP(t) - SP(t)]dt$

= $\int_{t_0}^{t_f} TSP(t)dt - \int_{t_0}^{t_f} SP(t)dt$ = 100 – 98 = 2%

Based on the parameters defined in the model, several equations were used to calculate the resilience in the described model. The results are summarized in the following table:

## 5.13 Findings

Table 12 Summary of equations applied

| | Equation | Calculated Resilience | Calculated System Impact | Documented Change in Survival | Comment |
|---|---|---|---|---|---|
| 1 | $\Psi_{loss} = \frac{XT}{2}$ | | 42 | 2.5% | |
| 2 | TRE = $\int_{t^0}^{t_f}[RE(t)]dt$ | 2% | 42 | 2.5% | Within 5% margin |
| 3 | R = $\int_{t_0}^{t_2}[1 - Q(t)]dt$ | | 42 | 2.5% | |
| 4 | R= $\int_{t_0}^{t_2} \frac{[Q(t)]\mathrm{dt}}{(t_2 - t_0)}$ | 2.3% | | 2.5% | Within 5% margin |
| 5 | $R = \int_{t_0}^{t_1} (\frac{[Q(t)dt]}{100(\ t_2 - \ t_0)})$ | 2.3% | | 2.5% | Within 5% margin |
| 6 | R = $\int_{t_0}^{t_2}[\ Q_{0(t_0)} - Q(t)]\ dt$ | 2% | | 2.5% | Within 5% margin |
| 7 | Resilience= $\int_{t_d}^{t_n}[\boldsymbol{P}_o(t_0) - \boldsymbol{P}(t)]\ \mathrm{dt}$ | 2% | | 2.5% | Within 5% margin |
| 8 | Change in performance= $\int_{t_0}^{t_f}[TSP(t) - SP(t)]dt$ | 2% | | 2.5% | Within 5% margin |

The following table lists the equations not applied to this model:

| | **Equations Not Evaluated** |
|---|---|
| 1 | $q(\tau) = d\frac{\breve{Q}}{d\tau}$ for all $\tau \in [0, T_R]$ |
| 2 | $\psi = \int_{t_d}^{t_n} \frac{AP(t)}{T}\, dt$ |
| 3 | $R = (t_n - t_d) \times P_0(t_0) - \int_{t_d}^{t_n} P(t)dt$ |
| 4 | $R = \frac{\int_{t_I}^{t_L} Q(t)\,\mathrm{dt}}{T_R}$ |
| 5 | $R = \frac{T_i + F\Delta T_f + R\Delta T_r}{T_i + \Delta T_f + \Delta T_f}$ |
| 6 | $\text{Resilience} = \sum_{i=1}^{n} f_i x \omega_i$ |
| 7 | $\text{Re}(t_1, t_2) = \left[\frac{g(t_2) \geq 0}{g(t_1) \geq 0}\right]$ |

A total of 15 equations were examined. Seven equations were not applied. Of the 8 equations applied, equations 1 and 3 calculate the system impact measure as identical to the assumed model parameter of 42. Equations 2, 6 and 8 calculate the resilience (as the change in system performance) as 2%, within a 0.5% difference from the documented results. The results of equations 4 and 5 are each 2.3%, also within a 0.5% range. The results of all equations applied fall within a 5% range of the documented change in survival.

## 5.14 Limitations

This study appears to be among the earliest applications of theoretical principles and equations of resilience engineering to a real-world model of assessing the outcomes in an individual clinical situation.

Some assumptions and limitations of this study:

1. The resilience model is a mathematical approximation of the measurements and parameters influencing the clinical process. For instance, the projected survival trajectory of untreated aortic stenosis (the Corbin-Strauss trajectory) is described as a straight line, while actual, real-life data from population studies are almost always a curvilinear trajectory. The following diagram illustrates the Corbin-Strauss trajectory in the case of medical management versus aortic surgical management (aortic valve replacement or AVR) for aortic stenosis. The trajectory describes a curvilinear line, with a variable slope of the curve depending on the time scale (days to months or years)

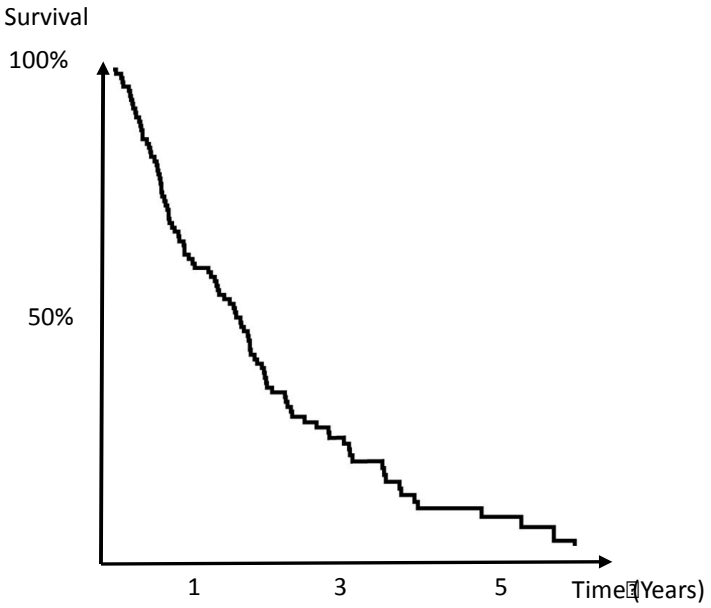



Figure 54 Corbin-Strauss trajectory of survival in aortic stenosis. Modified from: Rosenhek et al (2010). Used with permission.

2. The slope of the Corbin-Strauss trajectory varies depending on age. Older patients exhibit a Corbin-Strauss trajectory line with a steeper slope, with the predicted survival decreasing more rapidly than in younger patients. The trajectory in our model is a mathematical construct, based on the assumption that patients have a mean age of 76 years.

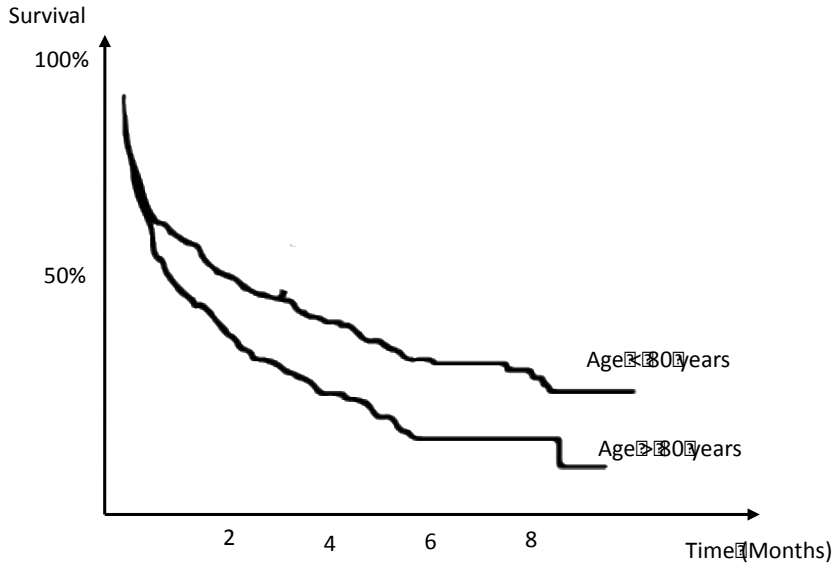



Figure 55 Corbin-Strauss trajectory in patients above and below 80 years of age. Modified from: Varadarajan et al (2006). Used with permission.

3. Several other factors also influence the shape and slope of the Corbin-Strauss trajectory. An important factor in this regard is the ventricular function, typically estimated by measuring the ejection fraction or EF. Patient with congestive heart failure (CHF) often have a reduced ejection fraction and reduced survival expectancy. The presence of severe aortic stenosis further reduces the predicted survival in these patients, as reflected by the change in the shape and slope of the Corbin-Strauss trajectory:

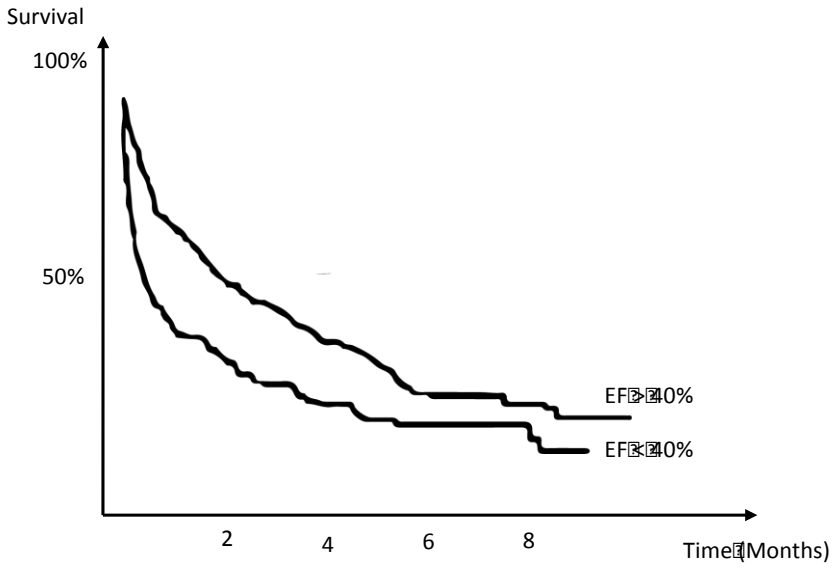



Figure 56 Impact of ventricular function on the Corbin-Strauss trajectory. *Ibid.*

4. The Corbin-Strauss trajectory of most chronic illnesses very often does not describe a regular straight or curvilinear pattern, especially when examined over an extended period of time, such as the patient's lifetime or the last years of life. In clinical practice, the change in functional status due to chronic diseases has a widely variable course, depending on the individual patient's phenotype and specific disease-related and other co-existing factors.

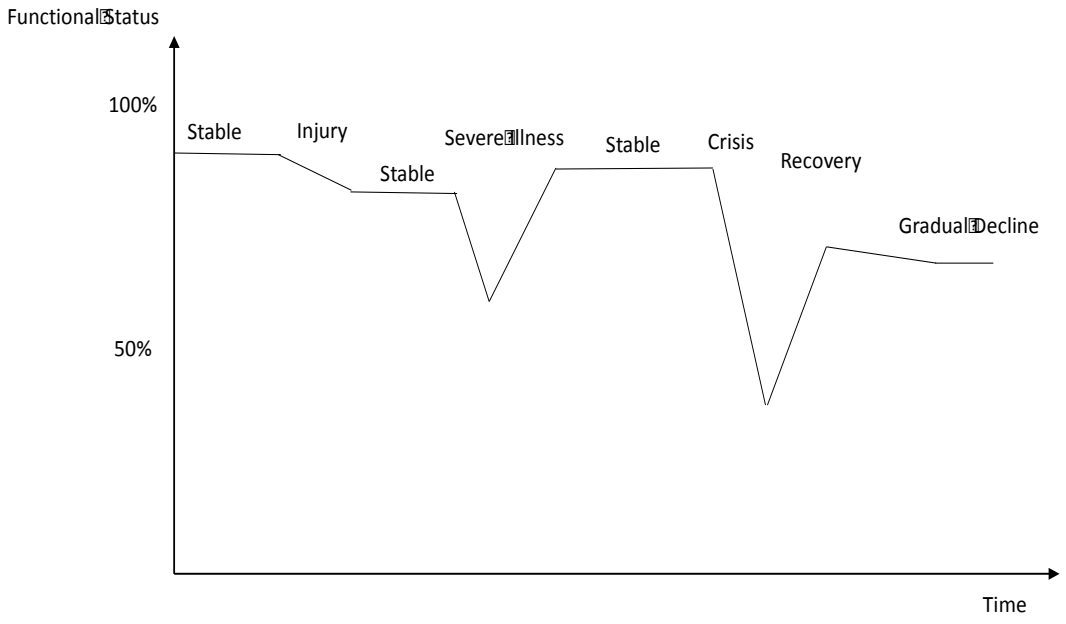



Figure 57 Change in functional status in chronic illness. Modified from: Baker and Heitkemper (2016). Used with permission.

5. The Corbin-Strauss trajectory is continually affected by various life events, physiologic changes, interventions and complications and their treatment. Loss of loved ones, which have varying degrees of impact on functional status.

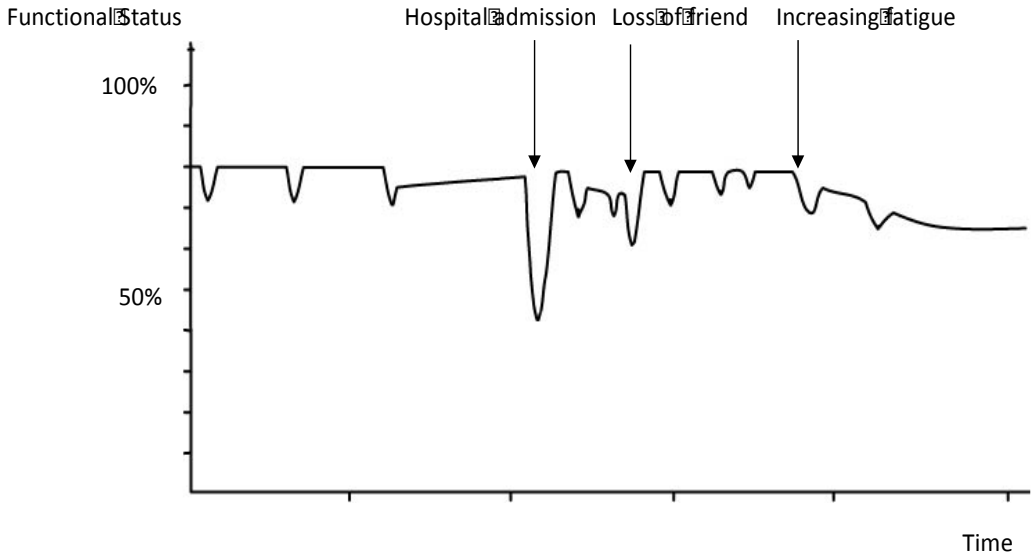



Figure 58 Impact of different events on the Corbin-Strauss trajectory. Modified from: Reed, E., & Corner, J. (2013). Used with permission.

6. The impact of these events on the change in functional status can be quite pronounced; especially in older patients with multiple co-morbidities and therefore a higher operative risk. Hence, careful consideration (Müller-Mundt 2013, Metzelthin 2013) is always given for the benefits of surgery to better determine the benefit of the results of this high-risk intervention in light of the expectations of improvement of functional status and decreasing disability as opposed to just the prolongation of life.

7. Due to the progressive impact of chronic diseases on the functional status, the need for pharmacologic and physical support and the level of independence of the patients, expectations for improvement of functional status are often limited.

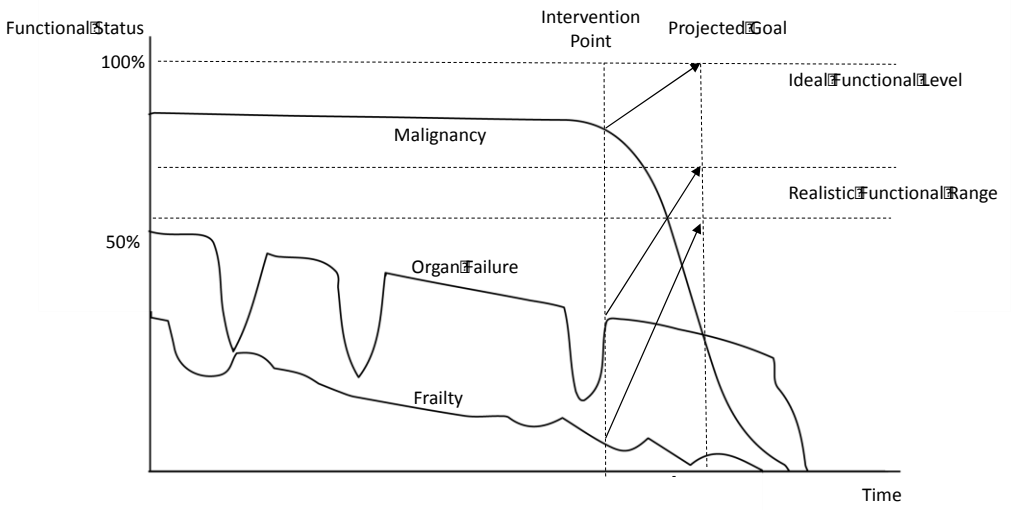



Figure 59 Different expectations for the result of intervention in different chronic diseases. Modified from Murray et al (2008). Used with permission.

This is very common in clinical practice, especially in older patients or those with aggressive disease; the optimal outcome desired by the patient is not to return to the full functional status but rather to ameliorate their functional status as much as possible, reduce their dependence on support or palliate symptoms. The definition of the goal of management makes defining the resilience triangle challenging.

8. In this model, the time of diagnosis is assumed to be the time of onset of symptoms. This assumption simplifies the calculations but does not relate to the real-world findings. There is a relative lack of data about functional status and survival in patients with known aortic stenosis who do not have symptoms. In fact, the decision to operate on such patients is an area of controversy (Amato 2001, Brown 2008, Monin 2009) within the cardiothoracic surgical community and a motivation for this work.

9. The expected probability of survival at the time of surgery in this study is assumed to be 98%, corresponding to an estimated average mortality risk of 2% for untreated aortic stenosis. This is based on approximation of published data from large, often multi-center, trials. According to our exploratory data analysis, the observed mortality rate at 42 days was estimated at 2.5%. In addition to being small, the study cohort describes a mixed group of patients across a range of ages, as explained

in the exploratory data analysis. This variation in age, as well as other factors, affects the survival probability or mortality risk for individual patients.

10. Furthermore, the data set in this study did not include specific individual patient risk factors, which are fundamental in calculating the specific mortality risk for each patient, according to the Society of Thoracic Surgeons or the EuroSCORE risk scoring systems. These risk assessment tools have become the benchmark tools for evaluating 30-day mortality risk after cardiac surgical procedures, and they continue to undergo modifications and improvements to their accuracy and individualization. Thus, the estimated probability of survival, reflecting the 30-day mortality risk used in this study should be seen as an approximate representation of the mixed risk of a heterogeneous group of patients. It is our expectation that future iterations, modifications and possible expansions of this model application will allow for inclusion of more patient factors and parameters, permitting a more precise assessment of mortality risk.

11. This study is a retrospective, chart-review study, based on collecting a limited number of variables from the electronic health records of a small number of patients in a single center. This small data set, which decreases the accuracy of statistical analysis and limits the application of compensatory statistical methodology. The endpoint in this study was the recorded death at 30 days after aortic valve replacement surgery. In addition, the data does not differentiate between different types of operations for aortic valve replacement (i.e., open surgical approach versus the trans-catheter approach) As such, the endpoint does not differentiate between death due to surgery or due to other factors. This is extremely important in constructing a mathematical model to investigate the effects of surgical intervention on changing the mortality risk for specific patients or patient groups.

## 5.15 Summary

Real-life retrospective data were obtained from the medical records of a local cardiac surgery group. Exploratory data analysis was conducted and its results discussed. The probability of survival at 30 days after aortic valve replacement was estimated. A model of the Corbin-Strauss disease trajectory was constructed to

quantify the probability of survival without valve replacement surgery. Predicted values for the probability of survival according to the Corbin-Strauss model and the exploratory data analysis were compared. A resilience engineering model was constructed to examine the probability of survival at 30 days after aortic valve replacement. A literature review was conducted, and a total of 15 different equations for calculation of the resilience of systems, both in terms of impact on the system performance (area-under-the-curve) or the percentage of change in system performance, were found. Eight different equations were chosen to be implemented to quantify the resilience response in this index case. The results of our calculation correlated within an acceptable range with the documented change in probability of survival as per the constructed Corbin-Strauss model as well as our exploratory data analysis.

# Chapter 6

# CONCLUDING REMARKS

## 6.1 Introduction

The majority of the existing literature discusses resilience engineering in various fields and enterprises; including infrastructure, ecology, interconnected network systems and civil engineering. This study appears to be among the emerging works examining the increasing role of resilience engineering in medical decision-making and the prediction of outcomes of interventions in terms of change in functional status and/or survival.

The main goal of medical practice is to provide high-quality care at a reasonable cost. This means providing care that is safe, efficient, reproducible and reliable at optimal resource utilization, in terms of financial cost, personnel and equipment allocation and utilization. Since healthcare aims to maintain the health status for the individual, the group and the population at large, the goal of all interventions remains to provide the highest beneficial yield of interventions in terms of improvement in survival and/or functional status, based on the stated wishes and goals of the patient. These principles have established foundation for the national mandate for precision medicine, requiring the introduction of novel data analytical tools and methodologies towards the improvement of clinical decision-making towards providing recommendations and interventions that are tailored to the patient at specific points in time in their specific disease, which conform to the patient's specific wishes, values and goals.

## 6.2 Discussion

Considering the human organism is a highly complex "system of systems", healthcare management can then be defined as measures taken to predict, prevent, detect and address disruptive events at different levels of this system (molecular, cellular, tissue, organ, system, individual, group or population). The overarching goal of all these measures and interventions is to maintain and/or optimize the function of the system at any level against the effects of disruptive events. Examples include maintenance of societal function in the case of an influenza epidemic, maintenance of mobility in the case of an acute fracture of the lower extremity bones, optimization of health status in the context of congenital cardiac defects, etc. Given these objectives, resilience engineering metrics present the healthcare professionals with valuable tools to reach these goals.

Resilience engineering provides mathematical tools to predict and quantify the change in the system performance in response to disruptive events; thus, it is a platform for devising and selecting measures and interventions to address the known and/or expected effects of such disruptive events to prevent harm and maintain normal or optimal function. It is an added methodology to assist in effectively coordinating the allocation and utilization of personnel, skills, experience, technology, equipment, rules and regulations and finances against the effects of known or possible disruptive events.

Resilience engineering metrics are always time-dependent estimates of the system performance, (e.g., the course of an injury or an infection or plans for end-of-life care in geriatric population) or across the entire lifespan of the system (e.g., maintenance of health in specific populations, such as Turner syndrome patients, or optimization of health status in patients with single-ventricle physiology). Since

medicine deals primarily with human subjects, who sustain the effects of disease and injury and stand to benefit from diagnostic and therapeutic interventions, the importance of quantifying the benefit of the intervention for each patient cannot be overstated. Thus, the emerging guiding principle of patient-centered care, based on patient-empowered decision-making has become central to the formulation and implementation of a management plan, with patients' interests and wishes at the foreground. In engineering terms, resilience analysis of the complex systems in healthcare must focus on engaging the ultimate stakeholders, i.e., patients. The formulation and implementation of a patient-specific, disease-specific, time-dependent management plan is the definition of precision medicine.

This correlates well with the recently introduced concept of "endogenous preference", which describes the level of system performance desired by the stakeholder at a specific time, especially in the context of an actual or projected disruptive event. It is often challenging to present patients and their families with easily quantitative models of the risk versus benefit of such interventions that are tailored to their specific condition, in terms of survival and quality of life. The same is true in the case of professional organizations and regulatory agencies considering or examining scientific evidence to provide recommendations for safe, effective, reliable and scientifically sound clinical practice guidelines. This is especially relevant in the situations where experimental or even observational evidence is insufficient, as in the cases of rare or incompletely understood conditions. Resilience engineering can provide helpful modeling of the disease course and the projected effects of interventions on survival and quality of life.

The current body of scientific literature in resilience engineering grants insight into the study of past experiences of disruptive events and the analysis of the system responses to the type, magnitude, duration and quality of the event. The study of the available resources and the processes that were recruited to cope with the effects of disruption provide the necessary data for quantifying the system's potential for adaption ("adaptive reserve") and is fundamental for assessing the system's response to future disruptions by the same events or variations thereof. This is also the basis for assessing how far the system resources can be "stretched" before failing. Repeatedly stressing the system or triggering its adaptive mechanisms into multiple, successive adaptive cycles can precipitate system decompensation, where the time needed by the system to recover increases (critical slowing down). This is indicative of the progressive exhaustion of the system's adaptive ability and is nearing the point of "irreversible" failure, and it is also an indicator of the high system impact or loss of function due to disruptive event(s). The quantification of this process is very helpful in understanding and modeling clinical situations characterized by multiple relapses and recovery phases.

## 6.3 Conclusions

This work has achieved its main objective, which has been to formulate a novel model based on the Corbin-Strauss disease trajectory model and resilience engineering.

The first sub-objective has been reached through the identification and formulation of a mathematical model of a disease-specific Corbin-Strauss trajectory.

This model was further quantified by the implementation of the results of analysis of data obtained from real-world patient records from the local chapter of the national cardiac surgery database.

This has offered us the opportunity to estimate the probability of survival relative to the specific time points along the disease process, as defined by the Corbin-Strauss trajectory specific to the phase of disease management being examined, thereby achieving the second sub-objective.

A resilience engineering model was then constructed to predict the change in the probability of survival as a result of the intervention. The model was tested using established equations from the resilience engineering literature.

The results of the Corbin-Strauss model and the resilience engineering model were compared to the observed results from the literature. The results of our models fell within an acceptable range from the published results from national large-scale studies. This has achieved the third sub-objective.

We conclude that this novel hybrid model for clinical decision-making, based on the Corbin-Strauss model and resilience engineering is both feasible and fairly accurate.

## 6.4 Recommendations

In 1986, the manual of preoperative and postoperative care published by the American College of Surgeons included a chapter with useful pearls of advice for young surgeons and surgical trainees as they launch their clinical career. One such statement advised the surgeon to “avoid surprises!”

Medical practice in general, and surgical practice in particular, involves making decisions dealing with the highly complex, high-risk environment of disease effects on the complicated system of the human organism. Instead of focusing (in practice, metrics, rules, policies, guidelines and regulatory and accountability measures) on adverse outcomes or errors as the definition of safe practice, the goal has shifted to measures, policies and methodologies designed to promote the maintenance of optimal function, based on the wishes and goals of the stakeholder. In other words, the focus is changing from "what goes wrong" to "what is going right" as the basis for monitoring and adjusting system performance.

Resilience engineering presents valuable tools to further our knowledge and expertise in the following areas where much research is still needed:

- How diseases affect the function of human or healthcare systems,
- How human and human-technical systems maintain function or fail to adapt,
- What mechanisms need to be developed, identified or supported to ensure optimal system function at all levels and in all configurations,
- How to predict and anticipate risks and surprises in order to prepare the system to manage their effects,
- How to improve system architecture and functional relationships to better adapt to disruptive events.

Whether on the individual human system level or the complex human-socio-technologic healthcare system level resilience engineering offers valuable tools for the maintenance of sustained optimal system performance that produces the best yield for

patients (in terms of favorable outcomes), healthcare teams (effective, cohesive, high-performance teamwork with minimal or no tension or disruption) and healthcare delivery systems (affordable, cost-effective care that adapts for emergency situations and significant disruptions). This relies on the implementation of the four basic qualities of resilient systems:

1. To continuously monitor system performance in terms of meeting the stated goal at the time,
2. To respond to expected and unexpected changes in performance,
3. To learn from successes and failures in system performance in terms of how it meets its goal,
4. To anticipate short- and long-term changes that can have a disruptive effect on the system.

## 6.5 Future Directions

Resilience analysis is not limited to resilience as "rebound", i.e., the assessment of system function and how it changes over time in response to disruptive events and interventions. In fact, the study and application of resilience engineering provides valuable insights into "graceful extensibility" or the basic architecture of the system as it is designed to adapt and compensate for the loss of function due to disruptive events. This particular area examines the availability and recruitment of anatomic and physiologic redundancies and 'back-up" systems ("system reserves") that can recover function during and after disruption. Examples include neural area crossovers in cases of stroke, muscle transfer in cases of limb injury, lung ventilator reserve in cases of severe respiratory failure, etc.

A key to graceful extensibility is predictive modeling: Similar to the virtual reality constructs in flight simulation, the introduction of low-, intermediate- and high-impact events in a mathematical or computer model of system failure is essential for the design and implementation of adaptive and responsive structures and processes that can or should be activated in such events. These metrics of system performance are based on incorporating the probability of occurrence of disruptive events. These models examine system performance and are designed to predict the probability and impact of a disruptive event (either as an anticipated effect based on system architecture or as a random event) that can have a catastrophic impact on the system structure and function. Resilience engineering models can provide an additional layer of certainty in anticipating such serious events, such as acute coronary syndromes due to sudden coronary artery stent thrombosis or acute aortic dissection.

These two conditions are examples of catastrophic, often life-threatening events for which current statistical models are sometimes insufficient in predicting the risk, which is reflected in the inadequate, incomplete or generalized and vague recommendations in the literature. Utilizing data from the scientific literature and experimental studies, quantification of the effect of each of the most important factors affecting the structural integrity of the aortic wall (through organization and maturation of its structural proteins collagen and elastin) is a prerequisite to calculate the Young modulus relative to each factor. Data from longitudinal and experimental studies can be utilized for quantification of the change in Young modulus due to growth, the force of pulsation, chronic hypertension as well as other metabolic conditions. This will facilitate the estimation of the resilience of the aortic wall relative to specific time periods in the life of specific patients. Thus, the risk of acute

aortic dissection, typically affecting young and otherwise healthy patients, can be predicted as a random event.

. As is the case with investigating any complex system, the study of failure is fundamental to ensuring success. In fact, failure is the other normal alternative outcome of the system performance. Understanding how, when and why complex systems fail and the effects of system failure on the connected systems and environment is essential for maintenance of health and safety for individuals, groups and the population at large. This is dependent on a thorough understanding, analysis and modeling of the entire process line and the sequence of events along its trajectory for the system as a whole or for any specific component. Events that alter the optimal sequence in this trajectory are plotted against time, and their effects on the system performance are noted, as is the degree of impact they have on the overall outcome. Failure of a system is the result of an error. An is defined as an unexpected or unintended event that alters the course of the process examined. Thus, an error is a function of the system architecture; some systems exhibit a higher risk for errors: the "Vulnerable System Syndrome". Woods reminds us that adverse outcomes ("errors") result from the brittleness (reduced robustness) and complexity (and thus hidden or unrecognized interdependencies) of the system rather than an error or the abnormal behavior of one of its components. In ensuring successful performance of the system, the probability of an error should be—ideally—reduced to zero. Resilience engineering has emerged as a more suitable approach in complex, dynamic, time-dependent systems as opposed to other linear-based risk assessment methodologies. This is by definition, since resilience analysis requires the understanding of how different system components respond to disruptions (unexpected events or "errors").

One of the properties of resilient systems is robustness, or the ability of the system to adjust its performance to changes and/or disturbances. In other words, it is a measure of the system to absorb perturbations to maintain performance. This is especially important if the perturbation is not well modeled, thereby challenging the system's adaptive capacity. Thus, resilience engineering offers a useful platform for the identification of critical parts or sequences in the system that can predict specific abnormal behavior, which is a valuable tool for predicting errors, assessing and quantifying their impact on system function, and devising and implementing mechanisms to minimize their occurrence. In addition to identifying the critical structural and process vulnerabilities of the system, resilience analysis is also useful in identifying and/or predicting the time as well as the frequency at which these errors are generated, thus determining their projected impact on the system performance. This is especially important in situations when some seemingly random events (e.g., coronary thrombosis, cerebrovascular embolism, intimal tear of the aorta, etc.) can have significant or life-threatening consequences. In healthcare terms, this means an increased capacity to predict structural and/or functional errors in molecular pathways, organ function or time-dependent processes (e.g., impact of genetic errors on embryonic development or metabolic errors on ageing) and predict their effect on the health of the individual.

By providing valuable insights and models into how complex human, human-technical or socio-technical systems function or fail, resilience engineering is proving to be beneficial for healthcare planning, decision-making and interventions. It is a novel, active area where clinical medicine, healthcare and engineering (especially

biomedical engineering) join efforts towards their common goal to further advance human health and well-being.

## REFERENCES


1. Abidi, S. S., & Chen, H. (2006, August). Adaptable personalized care planning via a semantic web framework. In *20th International Congress of the European Federation for Medical Informatics (MIE 2006), Maastricht, the Netherlands.*

2. Ackerknecht, E. H., & Haushofer, L. (2016). *A short history of medicine*. Baltimore, MD: JHU Press.

3. Ackerknecht, E. H., & Haushofer, L. (2016). *A short history of medicine*. Baltimore, MD:JHU Press.

4. Ackoff, R. L. (1989). From data to wisdom. *Journal of applied systems analysis*, *16*(1), 3-9.

5. Adams, T. M., Bekkem, K. R., & Toledo-Durán, E. J. (2012). Freight resilience measures. *Journal of Transportation Engineering*, *138*(11), 1403-1409.

6. Ahmed, A. (2003). American College of Cardiology/American Heart Association chronic heart failure evaluation and management guidelines: relevance to the geriatric practice. *Journal of the American Geriatrics Society*, *51*(1), 123-126Ahmed A. American College of Cardiology/American Heart Association chronic heart failure evaluation and management guidelines: relevance to the geriatric practice. Journal of the American Geriatrics Society. 2003 Jan 1;51(1):123-6.

7. AHRQ PSNet Patient Safety Network. Patient safety. Available at: https://psnet.ahrq.gov/search?Site2Search=PSNet&q=guidelines Last accessed May 15th, 2018.

8. Alipour A., Shafei B. (2016). Seismic resilience of transportation networks with deteriorating components. *Journal of Structural Engineering, . 2016 Jan 4;142*(8):C4015015.

9. Alston, R. P. (1997). Guidelines and cardiac anaesthetists. *Anaesthesia*, *52*(4), 328-331.

10. Amato, M. C. M., Moffa, P. J., Werner, K. E., & Ramires, J. A. F. (2001). Treatment decision in asymptomatic aortic valve stenosis: role of exercise testing. *Heart*, *86*(4), 381-386.

11. American Society of Civil Engineers (ASCE). (2017). *Minimum design loads and associated criteria for buildings and other structures (ASCE/SEI 7-16)*. Reston, VA: ASCE.

12. Angell, M. (2008). Industry-sponsored clinical research: a broken system. *Jama*, *300*(9), 1069-1071.

13. Ashley E. A. (2015). The precision medicine initiative: a new national effort. *JAMA, . 2015 Jun 2;313*(21), :2119-20.

14. Ashley, E. A. (2015). The precision medicine initiative: a new national effort. *JAMA*, *313*(21), 2119-2120.

15. Attoh-Okine, N. (2016). *Resilience Engineering: Models and Analysis*. Cambridge University Press, Cambridge, UK.

16. Attoh-Okine, N. O. (2017). Big Data and Differential Privacy: Analysis Strategies for Railway Track Engineering. John Wiley & Sons. Hoboken, NJ.

17. Attoh-Okine, N. O., & Bowers, S. (2006, June). A Bayesian belief network model of bridge deterioration. In *Proceedings of the Institution of Civil Engineers-Bridge Engineering* (Vol. 159, No. 2, pp. 69-76). Thomas Telford Ltd.

18. Attoh-Okine, N. O., Cooper, A. T., & Mensah, S. A. (2009). Formulation of resilience index of urban infrastructure using belief functions. *IEEE Systems Journal*, *3*(2), 147-153.

19. Attoh-Okine, N. O. (May 2017) Bayesian Analysis. Big Data and Differential Privacy: Analysis Strategies for Railway Track Engineering, 207-223. John Wiley & Sons. Hoboken, NJ.

20. Audet, A. M., Greenfield, S., & Field, M. (1990). Medical practice guidelines: current activities and future directions. *Annals of Internal Medicine*, *113*(9), 709-714Audet AM, Greenfield S, Field M. Medical practice guidelines: current activities and future directions. Annals of Internal Medicine. 1990 Nov 1;113(9):709-14.

21. Austin, P. C., & Goldwasser, M. A. (2008). Pisces did not have increased heart failure: data-driven comparisons of binary proportions between levels of a categorical variable can result in incorrect statistical significance levels. *Journal of clinical epidemiology*, *61*(3), 295-300.

22. Austin, P. C., Mamdani, M. M., Juurlink, D. N., & Hux, J. E. (2006). Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health. *Journal of clinical epidemiology*, *59*(9), 964-969.

23. Authors/Task Force Members, Vahanian A., Alfieri O., Andreotti F., Antunes M. J., Barón-Esquivias G., Baumgartner H., Borger M. A., Carrel T. P., De Bonis M., Evangelista A. (2012). Guidelines on the management of valvular heart disease (version 2012) The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *European Heart Journal, 2012 Aug 24;33*(19), :2451-96.

24. Aven, T. (2013). A conceptual framework for linking risk and the elements of the data–information–knowledge–wisdom (DIKW) hierarchy. *Reliability Engineering & System Safety*, *111*, 30-36.

25. Aven, T. (2013). A conceptual framework for linking risk and the elements of the data–information–knowledge–wisdom (DIKW) hierarchy. Reliability Engineering & System Safety, 111, 30-36.

26. Aven, T., Renn, O., (2009a). On risk defined as an event where the outcome is uncertain. *Journal of Risk Research 12,* 1–11.

27. Ayyub, B. M. (2014). Systems resilience for multihazard environments: definition, metrics, and valuation for decision making," *Risk Anal*., *34*(2), 340–355

28. Ayyub, B. M. (2015). Practical resilience metrics for planning, design, and decision-making. *ASCE-ASME J. Risk Uncertainty Eng. Syst. Part A: Civ. Eng*., 1(3), 04015008.

29. B. Chaib-Draa, Causal maps: Theory, implementation, and practical application in multiagent environments, *IEEE Transactions on Knowledge and Data Engineering, 14*, No.6 (2002).

30. Baker, M. (2016). 1,500 scientists lift the lid on reproducibility. *Nature News*, *533*(7604), 452.

31. Baker, M. and Heitkemper, M. (2016). Chronic illness and older adults. Available at: https://nursekey.com/chronic-illness-and-older-adults/

32. Balk, S. J., Landesman, L. Y., & Spellmann, M. (1997). Centers for Disease Control and Prevention lead guidelines: Do pediatricians know them? *The Journal of Pediatrics*, *131*(2), 325-327.

33. Baltes, P. B., & Staudinger, U. M. (1993). The search for a psychology of wisdom. *Current directions in psychological science*, *2*(3), 75-81.

34. Baltes, P. B., & Staudinger, U. M. (2000). Wisdom: A metaheuristic (pragmatic) to orchestrate mind and virtue toward excellence. *American psychologist*, *55*(1), 122.

35. Bane, F. (1952). Occupational licensing legislation in the states. *Chicago: Council of State Government*.

36. Banja, J. (2010). The normalization of deviance in healthcare delivery. *Business horizons*, *53*(2), 139-148.Banja J. The normalization of deviance in healthcare delivery. Bus Horiz. 2010; 53(2): 139.

37. Batalden, P. B., & Davidoff, F. (2007). What is "quality improvement" and how can it transform healthcare?

38. Bardhan I., Oh J. H., Zheng Z., Kirksey K. (2014). Predictive analytics for readmission of patients with congestive heart failure. *Information Systems Research*, *26*(1), 19-39.

39. Beauchamp, T. L. (2007). The 'four principles' approach to health care ethics. *Principles of health care ethics*, 3-10.

40. Bellinger, G., Castro, D., & Mills, A. (2004). Data, information, knowledge, and wisdom. Available at: http://www.systems-thinking.org/dikw/dikw.htm Last accessed May 15th, 2018.

41. Bergmann, R. (2002). Experience management: foundations, development methodology, and internet-based applications. Springer-Verlag, Germany.

42. Bernstam, E. V., Smith, J. W., & Johnson, T. R. (2010). What is biomedical informatics?. *Journal of biomedical informatics*, *43*(1), 104-110.

43. Bernstein, J. H. (2011). The data-information-knowledge-wisdom hierarchy and its antithesis. *Nasko*, *2*(1), 68-75.

44. Bishop, P. B., Quon, J. A., Fisher, C. G., & Dvorak, M. F. (2010). The Chiropractic Hospital-based Interventions Research Outcomes (CHIRO) study: a randomized controlled trial on the effectiveness of clinical practice guidelines in the medical and chiropractic management of patients with acute mechanical low back pain. *The Spine Journal*, *10*(12), 1055-1064.

45. Black J, Hashimzade N, and Myles G. (2013). A Dictionary of Economics, 4th ed. Oxford University Press, UK.

46. Bertrand, M., Duflo, E., & Mullainathan, S. (2004). How much should we trust differences-in-differences estimates?. *The Quarterly Journal of Economics*, *119*(1), 249-275.

47. Bloche, M. G. (2002). Trust and betrayal in the medical marketplace. *Stanford Law Review*, 919-954.

48. Bocchini, P., Frangopol, D. M., Ummenhofer, T., & Zinke, T. (2013). Resilience and sustainability of civil infrastructure: Toward a unified approach. *Journal of Infrastructure Systems*, *20*(2), 04014004.

49. Bodenheimer, T. (1999). The American Health Care System: Physicians and the Changing Medical Marketplace. *New England Journal of Medicine*, *340*(7), 584-588.

50. Bonow R. O., Carabello B. A., Chatterjee K., de Leon A. C., Faxon D. P., Freed M. D., Gaasch W. H., Lytle B. W., Nishimura R. A., O'Gara P. T., O'rourke R. A. (2008) Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *Circulation, 118*(15), e523-661.

51. Bonnabeau RC. The Edwin Smith Papyrus from ancient Egypt. The world's first surgical treatise. *Minn Med*. 1985 Apr;68(4):277, 279-80.

52. Bonstrom, H., & Corotis, R. B. (2014). First-order reliability approach to quantify and improve building portfolio resilience. *Journal of Structural Engineering*, *142*(8), C4014001.

53. Bornstein, B. H., & Emler, A. C. (2001). Rationality in medical decision making: a review of the literature on doctors' decision-making biases. *Journal of evaluation in clinical practice*, *7*(2), 97-107.

54. Borum, R. (1996). Improving the clinical practice of violence risk assessment: Technology, guidelines, and training. *American Psychologist*, *51*(9), 945.

55. Bothwell, L. E., & Podolsky, S. H. (2016). The emergence of the randomized, controlled trial. *New England Journal of Medicine*, *375*(6), 501-504.

56. Boxwala, A. A., Tu, S., Peleg, M., Zeng, Q., Ogunyemi, O., Greenes, R. A., ... & Patel, V. L. (2001). Toward a representation format for sharable clinical guidelines. *Journal of biomedical informatics*, *34*(3), 157-169.

57. Braithwaite J., Wears R. L., Hollnagel E. (2015). Resilient health care: turning patient safety on its head. *International Journal for Quality in Health Care*. *2015 Aug 20*, *27*(5), 418-20.

58. Bramstedt, K. A. (2008). Destination nowhere: a potential dilemma with ventricular assist devices. *ASAIO journal*, *54*(1), 1-2Bramstedt KA. Destination nowhere: a potential dilemma with ventricular assist devices. *ASAIO Journal*, *54*(1), 1-2.

59. Brennan, T. A. (2000). The Institute of Medicine Report on Medical Errors-Could It Do Harm?. *The New England Journal of Medicine*, *342*(15), 1123-1125.

60. Briggs, A. (2005). *A history of the Royal College of Physicians of London* (Vol. 4). Oxford University Press, USA.

61. Brotman, D. J., Deitcher, S. R., Lip, G. Y., & Matzdorff, A. C. (2004). Virchow's triad revisited. *Southern medical journal*, *97*(2), 213-215.

62. Brown J. M., O'Brien S. M., Wu C., Sikora J. A., Griffith B. P., Gammie J. S. (2009). Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. *The Journal of Thoracic and Cardiovascular Surgery*, *137*(1), 82-90.

63. Brown, M. L., Pellikka, P. A., Schaff, H. V., Scott, C. G., Mullany, C. J., Sundt, T. M., ... & Orszulak, T. A. (2008). The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. *The Journal of Thoracic and Cardiovascular Surgery*, *135*(2), 308-315.

64. Browne L. (1935). Regulation of professions by the state. The right to regulate, reasons therefor, methods in use, and attitude of regulatory bodies and the courts, with relation thereto. *Cal West Med*, *43*(2), 119-123.

65. Bruneau, M., & Reinhorn, A. (2006, April). Overview of the resilience concept. In *Proceedings of the 8th US National Conference on Earthquake Engineering* (Vol. 2040, pp. 18-22).

66. Bruneau, M., Chang, S. E., Eguchi, R. T., Lee, G. C., O'Rourke, T. D., Reinhorn, A. M., ... & Von Winterfeldt, D. (2003). A framework to quantitatively assess and enhance the seismic resilience of communities. *Earthquake spectra*, *19*(4), 733-752.

67. Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., ... & Littlejohns, P. (2010). AGREE II: advancing guideline development, reporting and evaluation in health care. *Canadian Medical Association Journal*, *182*(18), E839-E842.

68. Buck, A. S. (1992). Defining quality in health care. *Military medicine*, *157*(5), 260-262.

69. Burgers, J. S., Grol, R. P. T. M., Zaat, J. O. M., Spies, T. H., van der Bij, A. K., & Mokkink, H. G. A. (2003). Characteristics of effective clinical guidelines for general practice. *The British Journal of General Practice*, *53*(486), 15–19.

70. Burgers, J. S., Grol, R., Klazinga, N. S., Mäkelä, M., & Zaat, J. (2003). Towards evidence-based clinical practice: an international survey of 18 clinical guideline programs. *International Journal for Quality in Health Care*, *15*(1), 31-045.

71. Bury, M. (2010). Chronic illness, self-management and the rhetoric of empowerment. In *New Directions in the Sociology of Chronic and Disabling Conditions* (pp. 161-179). Palgrave Macmillan, London: Palgrave Macmillan.

72. Cabana, M. D., Rand, C. S., Powe, N. R., Wu, A. W., Wilson, M. H., Abboud, P. A. C., & Rubin, H. R. (1999). Why don't physicians follow clinical practice guidelines?: A framework for improvement. *Jama*, *282*(15), 1458-1465.

73. Camboni, D., Philipp, A., Lubnow, M., Bein, T., Haneya, A., Diez, C., ... & Müller, T. (2011). Support time-dependent outcome analysis for veno-venous extracorporeal membrane oxygenation. *European Journal of Cardio-Thoracic Surgery*, *40*(6), 1341-1347.

74. Carabello, B. A. (2002). Aortic stenosis. *New England Journal of Medicine*, *346*(9), 677-682.

75. Carabello, B. A. (2002). Selection of patients with aortic stenosis for operation: The asymptomatic patient and the patient with poor LV function. *Advances in cardiology*, *39*, 49-60.

76. Carabello, B. A. (2004). Is it ever too late to operate on the patient with valvular heart disease? *Journal of the American College of Cardiology*, *44*(2), 376-383.

77. Carabello, B. A. (2008). Aortic stenosis: a fatal disease with but a single cure. *JACC. Cardiovascular Interventions*, *1*(2), 127.

78. Carabello, B. A., & Paulus, W. J. (2009). Aortic stenosis. *The lancet*, *373*(9667), 956-966.

79. Castillo, E., Gutierrez, J. M., & Hadi, A. S. (2012). *Expert systems and probabilistic network models*. Springer Science & Business Media.

80. Chan, K. J., Punjabi, P. P., Flather, M., Wage, R., Symmonds, K., Roussin, I., ... & Pepper, J. R. (2012). Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitationclinical perspective: Final results of the randomized ischemic mitral evaluation (RIME) trial. *Circulation*, *126*(21), 2502-2510.

81. Cheng Lim, P., & Tang, N. K. (2000). The development of a model for total quality healthcare. *Managing Service Quality: An International Journal*, *10*(2), 103-111.

82. Chiaramonte, D. (2008). Who's afraid of the empowered patient? *JAMA*, *300*(12), 1393-1394

83. Christianson, J. B., Warrick, L. H., & Wholey, D. R. (2005). Physicians' perceptions of managed care: a review of the literature. *Medical Care Research and Review*, *62*(6), 635-675.

84. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol 2009, 5(7):374-81.

85. Cimellaro G. P., Malavisi M., Mahin S. (2018). Factor analysis to evaluate hospital resilience. *ASCE-ASME Journal of Risk and Uncertainty in Engineering Systems, Part A: Civil Engineering,. 2018 Jan 16;4*(1), :04018002.

86. Cimellaro G. P., Renschler C., Reinhorn A. M., Arendt L. (2016). PEOPLES: a framework for evaluating resilience. *Journal of Structural Engineering, . 2016 Apr 15;142*(10), :04016063.

87. Cimellaro, G. P., Reinhorn, A. M., & Bruneau, M. (2006, April). Quantification of seismic resilience. In *Proceedings of the 8th US National conference on Earthquake Engineering* (pp. 18-22).

88. Cioffi, G., Faggiano, P., Vizzardi, E., Tarantini, L., Cramariuc, D., Gerdts, E., & de Simone, G. (2011). Prognostic effect of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. *Heart*, *97*(4), 301-307.

89. Collins F. S., Varmus H. (2015). A new initiative on precision medicine. *New England Journal of Medicine, 2015 Feb 26;372*(9), :793-5.

90. Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *New England Journal of Medicine*, *372*(9), 793-795.

91. Committee on the Quality of Health Care in America. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: National Academy Press; 2001.

92. Conrad, P., & Bury, M. (1997). Anselm Strauss and the sociological study of chronic illness: a reflection and appreciation. *Sociology of Health & Illness*, *19*(3), 373-376.

93. Corbin J., & Strauss A. A nursing model for chronic illness management based upon the trajectory framework. *Scholarly Inquiry for Nursing Practice: An International Journal. Vol 5*, 3, 1991, 155-174.

94. Corbin J, Strauss A. Comeback: Overcoming disability. In: A. Albrecht (Ed.) *Readings on disability*. Greenwich, Ct. IAI Press. 1991.

95. Corbin J. The Corbin-Strauss chronic illness trajectory model: An update. *Scholarly Inquiry for Nursing Practice: An International Journal.* Vol 12, 1, 1998, 33-41.

96. Costella, M. F., Saurin, T. A., & de Macedo Guimarães, L. B. (2009). A method for assessing health and safety management systems from the resilience engineering perspective. *Safety Science*, *47*(8), 1056-1067.

97. Cretin, S., Farley, D. O., Dolter, K. J., & Nicholas, W. (2001). Evaluating an integrated approach to clinical quality improvement: clinical guidelines, quality measurement, and supportive system design. *Medical Care*, II70-II84.

98. Cruse, H., Winiarek, M., Marshburn, J., Clark, O., & Djulbegovic, B. (2002). Quality and methods of developing practice guidelines. *BMC health services research*, *2*(1), 1.

99. Cutler D. M. (2009). The next wave of corporate medicine—How we all might benefit. *New England Journal of Medicine,6;361*(6), :549-51.

100. Dans, P. E. (1994). Credibility, cookbook medicine, and common sense: guidelines and the college. *Annals of Internal Medicine*, *120*(11), 966-968.

101. Davis, D. A., & Taylor-Vaisey, A. (1997). Translating guidelines into practice: a systematic review of theoretic concepts, practical experience and research evidence in the adoption of clinical practice guidelines. *Canadian Medical Association Journal*, *157*(4), 408-416.

102. De Backer, J., Renard, M., Campens, L., Muino Mosquera, L., De Paepe, A., Coucke, P., ... & von Kodolitsch, Y. (2015). Marfan syndrome and related heritable thoracic aortic aneurysms and dissections. *Current Pharmaceutical Design*, *21*(28), 4061-4075.

103. Denaxas, S. C., & Morley, K. I. (2015). Big biomedical data and cardiovascular disease research: opportunities and challenges. *European Heart Journal–Quality of Care and Clinical Outcomes*, *1*(1), 9-16.

104. Dessavre, D. G., Ramirez-Marquez, J. E., and Barker, K. (2016). Multidimensional approach to complex system resilience analysis. *Reliab. Eng. Syst. Saf.*, 149, 34–43

105. Dickson, B. C. (2004). Virchow's triad? *Southern medical journal*, *97*(9), 915-917.

106. Di Donato, M., Frigiola, A., Menicanti, L., Boghdabi, A., Badia, T., Neagu & Ranucci, M. (2003). Moderate ischemic mitral regurgitation and coronary artery bypass surgery: effect of mitral repair on clinical outcome. *The Journal of Heart Valve Disease*, *12*(3), 272-279.

107. Digby A. (1994) Making a Medical Living: Doctors and Patients in the English Market for Medicine, 1720-1911. Cambridge University Press.

108. DiStefano III, J. (2015). Dynamic systems biology modeling and simulation. Chapter 1, pp. 3-10. Academic Press.

109. Dimick, J. B., & Ryan, A. M. (2014). Methods for evaluating changes in health care policy: the difference-in-differences approach. *Jama*, *312*(22), 2401-2402.

110. Duijnhoven et al. (2017, June). Critical infrastructure resilience: Bridging the gap between measuring and governance. 7th Resilience Engineering International Symposium. Liège (Luik) (Belgium), 26 – 29 June 2017.

111. Eden, C., Ackermann, F., & Cropper, S. (1992). The analysis of cause maps. *Journal of management Studies*, *29*(3), 309-324.

112. Eddy, D. M., Adler, J., Patterson, B., Lucas, D., Smith, K. A., & Morris, M. (2011). Individualized guidelines: the potential for increasing quality and reducing costs. *Annals of Internal Medicine*, *154*(9), 627-634.

113. Elixhauser, A., Pancholi, M., & Clancy, C. M. (2005). Using the AHRQ quality indicators to improve health care quality. *Joint Commission journal on quality and patient safety*, *31*(9), 533-538.

114. Enger, T. B., Philipp, A., Videm, V., Lubnow, M., Wahba, A., Fischer, M., ... & Müller, T. (2014). Prediction of mortality in adult patients with severe acute lung failure receiving veno-venous extracorporeal membrane oxygenation: a prospective observational study. *Critical Care*, *18*(2), R67.

115. Emanuel R. N. (2017). Resilience and stakeholder need. In: Reliability and Maintainability Symposium (RAMS).2017 Annual 2017 Jan 23 (pp. 1-6). IEEE. Orlando, FL.

116. Epstein A. E., DiMarco J. P., Ellenbogen K. A., Estes N. M., Freedman R. A., Gettes L. S., Gillinov A. M., Gregoratos G., Hammill S. C., Hayes D. L., Hlatky M.A. (2008). ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *Heart Rhythm, 2008 Jun 1;5*(6):e1-62.

117. Fairbanks R. J., Wears R. L., Woods D. D., Hollnagel E., Plsek P., Cook R.I. (2014). Resilience and resilience engineering in health care. *Joint Commission Journal on Quality and Patient Safety, 40*(8), 376-83.

118. Feldman, R. P., & Goodrich, J. T. (1999). The edwin smith surgical papyrus. *Child's Nervous System*, *15*(6-7), 281-284.

119. Field, M. J., & Lohr, K. N. (1990). Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Clinical practice guidelines: directions for a new program.

120. Fierz, W. (2004). Challenge of personalized health care: to what extent is medicine already individualized and what are the future trends? *Medical Science Monitor*, *10*(5), RA111-RA123.

121. Finkbohner, R., Johnston, D., Crawford, E. S., Coselli, J., & Milewicz, D. M. (1995). Marfan syndrome. *Circulation*, *91*(3), 728-733.

122. Flynn S. (2017) Resilient Critical Infrastructures. The 10th Resilience Week. Wilmington, DE.

123. Flynn, S. E. (2015). Bolstering critical infrastructure resilience after Superstorm Sandy: Lessons for New York and the nation. *Boston, MA: Center for Resilience Studies.* Available at: http://www.northeastern.edu/resilience/programs/sloan-foundation. Last accessed May 5th, 2018.

124. Franchin, P., & Cavalieri, F. (2015). Probabilistic assessment of civil infrastructure resilience to earthquakes. *Computer-Aided Civil and Infrastructure Engineering*, *30*(7), 583–600. 10.1111/mice.2015.30.issue-7

125. Francis R., Bekera B. (2014). A metric and frameworks for resilience analysis of engineered and infrastructure systems. *Reliability Engineering & System Safety*, *121*, 90-103.

126. Frangopol, D. M., & Soliman, M. (2016). Life-cycle of structural systems: recent achievements and future directions. *Structure and infrastructure engineering*, *12*(1), 1-20.

127. Freeth, T., Bitsakis, Y., Moussas, X., Seiradakis, J. H., Tselikas, A., Mangou, H. & Allen, M. (2006). Decoding the ancient Greek astronomical calculator known as the Antikythera Mechanism. *Nature*, *444*(7119), 587.

128. Frické, M. (2009). The knowledge pyramid: a critique of the DIKW hierarchy. *Journal of information science*, *35*(2), 131-142

129. Fullerton, D. A., & Sundt, T. M. (2014). Process versus outcome: The sugar window. *The Journal of Thoracic and Cardiovascular Surgery*, *148*(6), 2458-2460.

130. Ganin, A. A., Massaro, E., Gutfraind, A., Steen, N., Keisler, J. M., Kott, A.& Linkov, I. (2016). Operational resilience: concepts, design and analysis. *Scientific reports*, *6*, 19540.

131. Gardner, M. T., Cheng, Y., May, R., Beard, C., Sterbenz, J., & Medhi, D. (2016, March). Creating network resilience against disasters using service level agreements. In *Design of Reliable Communication Networks (DRCN), 2016 12th International Conference on the* (pp. 62-70). IEEE.

132. Garoupa, N. (April 2004). Regulation of professions in the US and Europe: A comparative analysis. Proceedings of the American Law and Economic Association Meetings. The Berkeley Electronic Press. Available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.483.1524&rep=rep1&type=pdf Last accessed May 10th, 2018.

133. Ghalioungui P. (1987). *The Ebers papyrus: A new English translation, commentaries and glossaries.* Academy of Scientific Research & Technology.

134. Glaser, B. G., & Strauss, A. L. (1975). *Chronic illness and the Quality of Life*. Sociology Press.

135. Grando, A., Peleg, M., & Glasspool, D. (2010). A goal-oriented framework for specifying clinical guidelines and handling medical errors. *Journal of Biomedical Informatics*, *43*(2), 287-299.

136. Grando, M. A., Schonenberg, M. H., & van der Aalst, W. (2011, January). Semantic-based conformance checking of computer interpretable medical guidelines. In *International Joint Conference on Biomedical Engineering Systems and Technologies* (pp. 285-300). Springer, Berlin, Heidelberg.

137. Graves K., Simmons D., & Galley M. D. (2010) Cause-and-effect mapping of critical events. *Crit Care Nurs Clin North Am. 2010 Jun*;22(2):243-51. doi: 10.1016/j.ccell.2010.03.012. Epub 2010 May 14.

138. Grilli, R., Magrini, N., Penna, A., Mura, G., & Liberati, A. (2000). Practice guidelines developed by specialty societies: the need for a critical appraisal. *The Lancet*, *355*(9198), 103-106.

139. Grimshaw, J. M., & Russell, I. T. (1993). Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *The Lancet*, *342*(8883), 1317-1322.

140. Grimshaw, J., Freemantle, N., Wallace, S., Russell, I., Hurwitz, B., Watt, I., ... & Sheldon, T. (1995). Developing and implementing clinical practice guidelines. *Quality in Health care*, *4*(1), 55.

141. Grol, R., & Grimshaw, J. (2003). From best evidence to best practice: effective implementation of change in patients' care. *The lancet*, *362*(9391), 1225-1230.

142. Gunderson, L. H., & Pritchard, L. (Eds.). (2012). *Resilience and the Behavior of Large-scale Systems* (Vol. 60). Island Press, Washington, D. C.

143. Hadley E. C., Kuchel G. A., Newman A. B. (2017). Report: NIA workshop on measures of physiologic resiliencies in human aging. *The Journals of Gerontology: Series A, 72*(7), 980-90.

144. Hajar R. The Air of History Part III: The Golden Age in Arab Islamic Medicine. An Introduction. *Heart Views*. 2013 Jan;14(1):43-6. doi: 10.4103/1995-705X.107125.

145. Hall, M. A., & Schneider, C. E. (2007). Patients as consumers: courts, contracts, and the new medical marketplace. *Mich. L. Rev.*, *106*, 643.

146. Hambleton, M. (2005). Applying root cause analysis and failure mode and effect analysis to our compliance programs. *Journal of Health Care Compliance*, *7*(2), 5-12.

147. Harteloh PPM. The meaning of quality in health care: a conceptual analysis. *Health Care Analysis*. 2003;11(3):259–67.

148. Harteloh, P. P. (2003). Quality systems in health care: a sociotechnical approach. *Health Policy*, *64*(3), 391-398.

149. Hashimoto, T., Stedinger, J. R., & Loucks, D. P. (1982). Reliability, resiliency, and vulnerability criteria for water resource system performance evaluation. *Water resources research*, *18*(1), 14-20.

150. Hawkins, D. M. (2004). The problem of overfitting. *Journal of chemical information and computer sciences*, *44*(1), 1-12.

151. Hayes B. Computer vision and computer hallucinations. *American Scientist* (Nov.-Dec. 2015) volume 103, number 6.

152. Henry, D., & Ramirez-Marquez, J. E. (2012). Generic metrics and quantitative approaches for system resilience as a function of time. *Reliability Engineering & System Safety*, *99*, 114-122.

153. Hey, J. (2004). The data, information, knowledge, wisdom chain: the metaphorical link. *Intergovernmental Oceanographic Commission*, *26*, 1-18.

154. Hiratzka, L. F., Bakris, G. L., Beckman, J. A., Bersin, R. M., Carr, V. F., Casey, D. E., ... & Kouchoukos, N. T. (2010). 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the

diagnosis and management of patients with thoracic aortic disease. *Circulation*, *121*(13), e266-e369.

155. Holland-Barkis, P., Forjuoh, S. N., Couchman, G. R., Capen, C., Rascoe, T. G., & Reis, M. D. (2006). Primary care physicians' awareness and adherence to cervical cancer screening guidelines in Texas. *Preventive Medicine*, *42*(2), 140-145.

156. Holling, C. S., & Gunderson, L. H. (Eds.). (2002). Panarchy: Understanding Transformations in Human and Natural Systems. Island Press.

157. Hollnagel, E. (2017). Resilience: the challenge of the unstable. In *Resilience engineering* (pp. 21-30). CRC Press, Boca Raton, FL.

158. Hollnagel E. (2016). The four cornerstones of resilience engineering. In Resilience Engineering Perspectives, Volume 2 2016 Dec 5 (pp. 139-156). CRC Press, Boca Raton, FL.

159. Hollnagel E., Nemeth C. P., Dekker S., editors. (Eds.). (2008). *Resilience engineering perspectives: remaining sensitive to the possibility of failure*. Surrey, UK: Ashgate Publishing, Ltd.; 2008.

160. Hollnagel E., Wears R. L., Braithwaite J. (2015). From Safety-I to Safety-II: A white paper. The resilient health care net: published simultaneously by the University of Southern Denmark, University of Florida, USA, and Macquarie University, Australia. 2015.

161. Holmes D. R., Mack M. J., Kaul S., Agnihotri A., Alexander K. P., Bailey S. R., Calhoon J. H., Carabello B. A., Desai M Y., Edwards F. H., Francis G. S. (2012). 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement: Developed in collaboration with the American heart association, American society of echocardiography, European association for cardio-thoracic surgery, heart failure society of America, mended hearts, society of cardiovascular anesthesiologists, society of cardiovascular computed tomography, and society for cardiovascular magnetic resonance. *The Journal of Thoracic and Cardiovascular Surgery*, *144*(3), e29-84.

162. Hosseini S., Barker K., Ramirez-Marquez J. E. (2016). A review of definitions and measures of system resilience. *Reliability Engineering & System Safety*, *145*, 47-61.

163. Horstkotte, D., & Loogen, F. (1988). The natural history of aortic valve stenosis. *European Heart Journal*, *9* (suppl_E), 57-64.

164. Hunt, D. L., Haynes, R. B., Hanna, S. E., & Smith, K. (1998). Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. *Jama*, *280*(15), 1339-1346.

165. Hutchinson, A., McIntosh, A., Anderson, J., Gilbert, C., & Field, R. (2003). Developing primary care review criteria from evidence-based guidelines: coronary heart disease as a model. *Br J Gen Pract*, *53*(494), 690-696.

166. Hutchison, B. G., Abelson, J., Woodward, C. A., & Norman, G. (1996). Preventive care and barriers to effective prevention. How do family physicians see it? *Canadian Family Physician*, *42*, 1693.

167. International Study Group. (1990). In-hospital mortality and clinical course of 20 891 patients with suspected acute myocardial infarction randomised between alteplase and streptokinase with or without heparin. *The Lancet*, *336*(8707), 71-75.

168. Iturra S. A., Suri R. M., Greason K. L., Stulak J. M., Burkhart H. M., Dearani J. A., Schaff H.V. (2014). Outcomes of surgical aortic valve replacement in moderate risk patients: implications for determination of equipoise in the transcatheter era. *The Journal of Thoracic and Cardiovascular Surgery*, *147*(1), 127-32.

169. Jameson J. L., Longo D. L. (2015). Precision medicine—personalized, problematic, and promising. *Obstetrical & Gynecological Survey*,*70*(10), 612-4.

170. Jankowski, M. D., Henry, C. S., Broadbelt, L. J., & Hatzimanikatis, V. (2008). Group contribution method for thermodynamic analysis of complex metabolic networks. *Biophysical journal*, *95*(3), 1487-1499.

171. Jensen A., Moseley P., Opera T., et al. Temporal disease trajectories condensed from population-wide registry data covering 6.2 million patients. *Nature Communications* **5**, Article number: 4022.

172. Jeong, G., Wicaksono, A., & Kang, D. (2017). Revisiting the resilience index for water distribution networks. *Journal of Water Resources Planning and Management*, *143*(8), 04017035.

173. Jia, G., & Gardoni, P. (2018). State-dependent stochastic models: A general stochastic framework for modeling deteriorating engineering systems considering multiple deterioration processes and their interactions. *Structural Safety*, *72*, 99-110.

174. Jifa, G., & Lingling, Z. (2014). Data, DIKW, Big data and Data science. *Procedia computer science*, *31*, 814-821.

175. Joint Commission on Accreditation of Healthcare Organizations. (1990). *Primer on indicator development and application: measuring quality in health care*. Joint Commission on.

176. Joint Commission on Accreditation of Healthcare Organizations. (1997). *National library of healthcare indicators*. Joint Commission on.

177. Kelavkar, U. P. (2006). Human Genome Project. eLS. Kelavkar UP. Human Genome Project. eLS. 2006.

178. Kenett, R. S. (2014). Cause-and-Effect Diagrams. Wiley StatsRef: Statistics Reference Online.

179. Kerwin, K. E., & Madison, J. (2002). The role of the internet in improving healthcare quality. *Journal of Healthcare Management*, *47*(4), 225.

180. Kessler, R. C., & Mroczek, D. K. (1996). Some methodological issues in the development of quality of life measures for the evaluation of medical interventions. *Journal of evaluation in clinical practice*, *2*(3), 181-191.

181. Kimberly, J. R., & Minvielle, E. (Eds.). (2000). *The quality imperative: Measurement and management of quality in healthcare*. World Scientific Publishing Company.

182. Klein, W. W. (2002). Current and future relevance of guidelines. *Heart, 87*(6), 497–500.

183. Kline Leidy, N. (1989). A physiologic analysis of stress and chronic illness. *Journal of Advanced Nursing*, *14*(10), 868-876.

184. Knebel, E., & Greiner, A. C. (Eds.). (2003). *Health professions education: A bridge to quality*. National Academies Press, Washington, D. C.

185. Koliou, M., van de Lindt, J. W., McAllister, T. P., Ellingwood, B. R., Dillard, M., & Cutler, H. (2017). State of the research in community resilience: progress and challenges. *Sustainable and Resilient Infrastructure*, 1-21.

186. Koliou, M., van de Lindt, J., Ellingwood, B., Dillard, M. K., Cutler, H., & McAllister, T. P. (2018). *A Critical Appraisal of Community Resilience Studies: Progress and Challenges* (No. Sustainable and Resilient Infrastructure).

187. Koller, D., & Friedman, N. (2009). Probabilistic Graphical Models: Principles and Techniques. MIT Press.

188. Krishnaswamy P., Ramasamy S., Al-Dujaili A., Sridharan S., Goh G., Tong S. C., Aung K. C., Toh G. L., Madonald M. R., Guang S. L., Cao Y. (2018) A Predictive Analytics Methodology to Assess and Optimize Readmission Risk in Heart Failure Patients. Proceedings of AAAI-18: Thirty-second AAAI conference on artificial intelligence. American association for the advancement of artificial intelligence. Available online at: http://oar.a-star.edu.sg/jspui/bitstream/123456789/2338/1/17078-72944-1-SM.pdf Last accessed May 15th, 2018.

189. Krumholz H. M., Wang Y., Mattera J. A., Wang Y., Han L. F., Ingber M. J., Roman S., Normand S. L. (2006). An administrative claims model suitable for profiling hospital performance based on 30-day mortality rates among patients with heart failure. *Circulation, 113*(13), 1693-701.

190. Laine, C., Taichman, D. B., & Mulrow, C. (2011). Trustworthy clinical guidelines. *Annals of Internal Medicine, 154*(11), 774-775.

191. Lancellotti P., Rosenhek R., Pibarot P., Iung B., Otto C. M., Tornos P., Donal E., Prendergast B., Magne J., La Canna G., Piérard L. (2013). A. ESC Working Group on Valvular Heart Disease position paper—heart valve clinics: organization, structure, and experiences. *European Heart Journal, 34*(21), 1597-606.

192. Latoszek-Berendsen, A., Tange, H., Van Den Herik, H. J., & Hasman, A. (2010). From clinical practice guidelines to computer-interpretable guidelines. *Methods of information in medicine, 49*(6), 550-570.

193. Lauritzen, S. L. (1996). *Graphical models* (Vol. 17). Clarendon Press.

194. Lay E., Branlat M., Woods Z. (2015). A practitioner's experiences operationalizing resilience engineering. *Reliability Engineering & System Safety, 141*, 63-73.

195. Lemor A., Setareh-Shenas S., Alvarado A., Gowda R. N., Gowda R. M. (2017). Etiologies for 30-day readmission in patients admitted with congestive heart failure that were discharged to a nursing home or facility. *European Heart Journal, 38*(suppl_1).

196. Leape, L., Berwick, D., Clancy, C., Conway, J., Gluck, P., Guest & Pinakiewicz, D. (2009). Transforming healthcare: a safety imperative. *BMJ Quality & Safety, 18*(6), 424-428.

197. Lebel, L., Anderies, J., Campbell, B., Folke, C., Hatfield-Dodds, S., Hughes, T., & Wilson, J. (2006). Governance and the capacity to manage resilience in regional social-ecological systems. *Ecology and Society*, *11*(1).

198. Li, Y., & Lence, B. J. (2007). Estimating resilience for water resources systems. *Water Resources Research*, *43*(7).

199. Lindman, B. R., Alexander, K. P., O'Gara, P. T., & Afilalo, J. (2014). Futility, benefit, and transcatheter aortic valve replacement. *JACC: Cardiovascular Interventions*, *7*(7), 707-716.

200. Linkov, I., & Palma-Oliveira, J. M. (Eds.). (2017). *Resilience and risk.* Amsterdam: Springer.

201. Linkov, I., Trump, B., & Keisler, J. (2018). Correspondence: Risk and resilience must be individually managed. *Nature*, *555*(7694), 30. doi: 10.1038/d41586-018-02567-0

202. Lohr, K. N., & Field, M. J. (Eds.). (1990). *Clinical practice guidelines: directions for a new program* (Vol. 90, No. 8). National Academies PressField, M. J., & Lohr, K. N. (1990). Institute of Medicine Committee to Advise the Public Health Service on Clinical Practice Guidelines. Clinical practice guidelines: directions for a new program.

203. Lugtenberg, M., Burgers, J. S., & Westert, G. P. (2009). Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. *BMJ Quality & Safety*, *18*(5), 385-392.

204. Madni, A. M., & Jackson, S. (2009). Towards a conceptual framework for resilience engineering. *IEEE Systems Journal*, *3*(2), 181-191.

205. Maureira, J. P., Vanhuyse, F., Lekehal, M., Hubert, T., Vigouroux, C., Mattei, M. F., ... & Villemot, J. P. (2012). Failure of Marfan anatomic criteria to predict risk of aortic dissection in Turner syndrome: necessity of specific adjusted risk thresholds. *Interactive Cardiovascular and Thoracic Surgery*, *14*(5), 610-614.

206. Maks, J. A. H. and Philipsen, N. J., (2005), An Economic Analysis of the Regulation of Professions., In: Crals, E. & Vereeck, L. (Eds.) *Regulation of Architects* in Belgium and the Netherlands. Pages 12-16. Lannoo, the Netherlands.

207. Mansfield, C. D. (1995). Attitudes and behaviors towards clinical guidelines: the clinicians' perspective. *BMJ Quality & Safety*, *4*(4), 250-255.

208. Matney, S., Brewster, P. J., Sward, K. A., Cloyes, K. G., & Staggers, N. (2011). Philosophical approaches to the nursing informatics data-information-knowledge-wisdom framework. *Advances in Nursing Science*, *34*(1), 6-18.

209. McDaniels, T., Chang, S., Cole, D., Mikawoz, J., & Longstaff, H. (2008). Fostering resilience to extreme events within infrastructure systems: Characterizing decision contexts for mitigation and adaptation. *Global Environmental Change*, *18*(2), 310-318.

210. McEwen, B. S. (1998). Stress, adaptation, and disease: Allostasis and allostatic load. *Annals of the New York academy of sciences*, *840*(1), 33-44.

211. McEwen, B. S. (2000). Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology*, *22*(2), 108-124.

212. McEwen, B. S., & Wingfield, J. C. (2003). The concept of allostasis in biology and biomedicine. *Hormones and behavior*, *43*(1), 2-15.

213. McKenna, B., & Rooney, D. (2005, January). Wisdom management: Tensions between theory and practice in practice. In *KMAP 2005 Knowledge Management in Asia Pacific Conference: Building a Knowledge Society*. Victoria University, Wellington.

214. McKie, A., Baguley, F., Guthrie, C., Jackson, C., Kirkpatrick, P., Laing, A. & Wimpenny, P. (2012). Exploring clinical wisdom in nursing education. *Nursing ethics*, *19*(2), 252-267.

215. McNab D., Bowie P., Morrison J., Ross A. (2016). Understanding patient safety performance and educational needs using the 'Safety-II' approach for complex systems. *Education for Primary Care, 27*(6), 443-50.

216. McNeil, K., & Dunning, J. (2007). Chronic thromboembolic pulmonary hypertension (CTEPH). *Heart*, *93*(9), 1152-1158.

217. Mehrabi, S., Sohn, S., Li, D., Pankratz, J. J., Therneau, T., Sauver, J. L. S. & Palakal, M. (2015, October). Temporal pattern and association discovery of diagnosis codes using deep learning. In *Healthcare Informatics (ICHI), 2015 International Conference on* (pp. 408-416). IEEE.

218. Melé, D. (2010). Practical wisdom in managerial decision making. *Journal of Management Development*, *29*(7/8), 637-645.

219. Metzelthin, S. F., Daniëls, R., van Rossum, E., Cox, K., Habets, H., de Witte, L. P., & Kempen, G. I. (2013). A nurse-led interdisciplinary primary care

approach to prevent disability among community-dwelling frail older people: a large-scale process evaluation. *International journal of nursing studies*, *50*(9), 1184-1196.

220. Mitchell, P. B., Goodwin, G. M., Johnson, G. F., & Hirschfeld, R. (2008). Diagnostic guidelines for bipolar depression: a probabilistic approach. *Bipolar Disorders*, *10*(1p2), 144-152.

221. Miles, S. H. (2005). *The Hippocratic oath and the ethics of medicine*. Oxford University Press.

222. Miller, J., & Petrie, J. (2000). Development of practice guidelines. *The Lancet*, *355*(9198), 82-83.

223. Molyneaux, L., Brown, C., Wagner, L., & Foster, J. (2016). Measuring resilience in energy systems: Insights from a range of disciplines. *Renewable and Sustainable Energy Reviews*, *59*, 1068-1079.

224. Monin, J. L., Lancellotti, P., Monchi, M., Lim, P., Weiss, E., Piérard, L., & Guéret, P. (2009). Risk score for predicting outcome in patients with asymptomatic aortic stenosis. *Circulation*, *120*(1), 69-75.

225. Monte I., Sicuso R., Bottari V. (2018). (Eds.). Aortic Stenosis: Diagnosis. In: *Percutaneous Treatment of Left Side Cardiac Valves. A practical guide for the interventional cardiologist*. Ussia, G. (Ed.) 2018 (pp. 253-275). Springer, Cham, Catania, Italy.

226. Motulsky, H. Intuitive Biostatistics: a Nonmathematical Guide to Statistical Thinking. 2010. Oxford University Press, New York, NY.

227. Müller-Mundt, G., Bleidorn, J., Geiger, K., Klindtworth, K., Pleschberger, S., Hummers-Pradier, E., & Schneider, N. (2013). End of life care for frail older patients in family practice (ELFOP)–protocol of a longitudinal qualitative study on needs, appropriateness and utilisation of services. *BMC Family Practice*, *14*(1), 52.

228. Munoz, A., and Dunbar, M., (2015). On the quantification of operational supply chain resilience. *Int. J. Prod. Res*., *53*(22), 6736–6751.

229. Murray, SA. and Sheikh, A. (2008). Care for all at the end of life. the three main trajectories of decline at the end of life. *British Medical Journal*, 336, 958-959.

230. Nadkarni, S., & Shenoy, P. P. (2004). A causal mapping approach to constructing Bayesian networks. *Decision Support Systems, 38*(2), 259-281.

231. Nan, C., and Sansavini, G. (2017). A quantitative method for assessing resilience of interdependent infrastructures. *Reliab. Eng. Syst. Saf., 157*, 35–53.

232. Nathan, P. E. (1998). Practice guidelines: Not yet ideal. *American Psychologist, 53*(3), 290.

233. Nemeth CP. (2016). *Resilience engineering perspectives, Volume 1: Remaining sensitive to the possibility of failur*e. CRC Press.

234. Nguyen, Ahn, Jason Yosinski, and Jeff Clune. 2015. Deep neural networks are easily fooled: High confidence predictions for unrecognizable images. In: *Computer Vision and Pattern Recognition 2015*.

235. Nishimura R. A., Otto C. M., Bonow R. O., Carabello B. A., Erwin J. P., Guyton R. A., O'Gara P. T., Ruiz C. E., Skubas N. J., Sorajja P., Sundt T. M. (2014). AHA/ACC guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *The Journal of Thoracic and Cardiovascular Surgery, 148*(1), e1-32.

236. Nolte, E., & McKee, M. (Eds.). (2008). Caring for people with chronic conditions: a health system perspective. McGraw-Hill Education (UK).

237. O'Connor, P. J. (2005). Adding value to evidence-based clinical guidelines. *JAMA, 294*(6), 741-743.

238. Ogunnaike B. A. (2009). *Random phenomena: fundamentals of probability and statistics for engineers.* CRC Press, Boca Raton, FL; 2009 Sep 21. Pages 293-295.

239. Ogus, A. (1993)., Regulation of the legal profession in England and Wales., In: *Regulation of Professions: A Law and economics approach to the regulation of attorneys and physicians in the US, Belgium, the Netherlands, Germany and the UK*. Antwerpen, Maklu.Faure, M., Fisinger, J, Siegers, J and Van den Bergh, R. (Eds.)

240. Olesen, F., & Lauritzen, T. (1997). Do general practitioners want guidelines? Attitudes toward a county-based and a national college-based approach. *Scandinavian journal of primary health care, 15*(3), 141-145.

241. Oravecz, Z., Huentelman, M., & Vandekerckhove, J. (2016). Sequential Bayesian updating for big data. *Big Data in Cognitive Science*, 13.

242. O'Rourke, T. D. (2007). Critical infrastructure, interdependencies, and resilience. *BRIDGE-Washington-National Academy of Engineering-*, *37*(1), 22.

243. Orwin, K. H., & Wardle, D. A. (2004). New indices for quantifying the resistance and resilience of soil biota to exogenous disturbances. *Soil Biology and Biochemistry*, *36*(11), 1907-1912.

244. Otto C. M., Burwash I. G., Legget M. E., Munt B. I., Fujioka M., Healy N. L., Kraft C. D., Miyake-Hull C. Y., Schwaegler R. G. (1997). Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation, 95*(9), 2262-70.

245. Ouyang, M., Dueñas-Osorio, L., and Min, X. (2012). A three-stage resilience analysis framework for urban infrastructure systems. *Struct. Saf., 36*, 23–31.

246. Pai, R. G., Kapoor, N., Bansal, R. C., & Varadarajan, P. (2006). Malignant natural history of asymptomatic severe aortic stenosis: benefit of aortic valve replacement. *The Annals of Thoracic Surgery*, *82*(6), 2116-2122.

247. Papageorgiou, E. I., De Roo, J., Huszka, C., & Colaert, D. (2012). Formalization of treatment guidelines using Fuzzy Cognitive Maps and semantic web tools. *Journal of biomedical informatics*, *45*(1), 45-60.

248. Pappalardo, F., Pieri, M., Greco, T., Patroniti, N., Pesenti, A., Arcadipane, A., ... & Beutel, G. (2013). Predicting mortality risk in patients undergoing venovenous ECMO for ARDS due to influenza A (H1N1) pneumonia: the ECMOnet score. *Intensive Care Medicine*, *39*(2), 275-281.

249. Patterson M., Deutsch E. S. (2015). Safety-I, safety-II and resilience engineering. *Current Problems in Pediatric and Adolescent Health Care.*, *45*(12), 382-9.

250. Pearl, J. (2009). *Causality*. Cambridge University Press.

251. Peleg, M. (2013). Computer-interpretable clinical guidelines: a methodological review. *Journal of biomedical informatics*, *46*(4), 744-763.

252. Pellikka P. A., Sarano M. E., Nishimura R. A., Malouf J. F., Bailey K. R., Scott C. G., Barnes M. E., Tajik A. J. (2005). Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation, 111*(24), 3290-5.

253. Pelling M. Unofficial and Unorthodox Medicine in Western Medicine: An Illustrated History (London/Irvine: Oxford University Press, 1997)

254. Pérez, B., & Porres, I. (2010). Authoring and verification of clinical guidelines: A model driven approach. *Journal of Biomedical Informatics*, *43*(4), 520-536.

255. Pepke-Zaba, J., Delcroix, M., Lang, I., Mayer, E., Jansa, P., Ambroz, D. & Bresser, P. (2011). Chronic Thromboembolic Pulmonary Hypertension (CTEPH) Clinical Perspective: Results From an International Prospective Registry. *Circulation*, *124*(18), 1973-1981.

256. Phillips K. A. (2017). assessing the value and implications of personalized/precision medicine and the" lessons learned" for emerging technologies: an introduction. *Value in Health: the Journal of the International Society for Pharmacoeconomics and Outcomes Research, 20*(1), 30.

257. Piazza, G., Hohlfelder, B., & Goldhaber, S. Z. (2015). Pathophysiology of Deep Vein Thrombosis and Pulmonary Embolism: Beyond Virchow's Triad. In *Handbook for Venous Thromboembolism* (pp. 15-20). Springer International Publishing.

258. Popper, K. R. (1963). Conjectures and refutations. *Routledgc and Kegan Paul, London*.

259. Porter, M. E. (2010). What is value in health care? *New England Journal of Medicine, 363*(26), 2477-2481.

260. Posner, R. A., (1975). The social costs of monopoly and regulation., *Journal of Political Economy, 83*, 807-827.

261. Prandoni, P., Lensing, A. W., Cogo, A., Cuppini, S., Villalta, S., Carta, M. & Prins, M. H. (1996). The long-term clinical course of acute deep venous thrombosis. *Annals of Internal Medicine*, *125*(1), 1-7.

262. Pronovost, P. J. (2013). Enhancing physicians' use of clinical guidelines. *Jama*, *310*(23), 2501-2502.

263. Raach, J. H. (1944). English medical licensing in the early seventeenth century. *The Yale Journal of Biology and Medicine, 16*(4), 267–288.

264. Reach, G. (2014). Clinical inertia, uncertainty and individualized guidelines. *Diabetes & Metabolism*, *40*(4), 241-245.

265. Reardon M. J., Van Mieghem N. M., Popma J. J., Kleiman N. S., Søndergaard L., Mumtaz M., Adams D. H., Deeb G. M., Maini B., Gada H., Chetcuti S. (2017). Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. *New England Journal of Medicine, 376*(14), 1321-31.

266. Reason J. T., Carthey J., De Leval M. R. (2001). Diagnosing "vulnerable system syndrome": An essential prerequisite to effective risk management. *BMJ Quality & Safety, 10*(suppl 2), ii21-5.

267. Reed, E., & Corner, J. (2013). Defining the illness trajectory of metastatic breast cancer. *BMJ Supportive & Palliative Care*, bmjspcare-2012.

268. Rich, E. L., & Romero, L. M. (2005). Exposure to chronic stress downregulates corticosterone responses to acute stressors. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 288*(6), R1628-R1636.

269. Risse G. Imhotep and medicine –a reevaluation. *West J Med*. 1986 May; 144(5): 622–624.

270. Rizzo, J. A., Chen, J., Fang, H., Ziganshin, B. A., & Elefteriades, J. A. (2014). Statistical challenges in identifying risk factors for aortic disease. *Aorta, 2*(2), 45.

271. Robinson J. O. (1984). The barber-surgeons of London. *Archives of Surgery, 119*(10), 1171-5.

272. Robinson, L. A., Catherine Bevil EdD, R. N., Virginia Arcangelo Ph.D., R. N., JoAnne Reifsnyder MSN, R. N., & Nancy Rothman EdD, R. N. (1993). Operationalizing the Corbin & Strauss trajectory model for elderly clients with chronic illness. *Research and Theory for Nursing Practice, 7*(4), 253.

273. Romaszkiewicz, R., Lewczuk, J., Piszko, P., Lenartowska, L., Jagas, J., Konieczny, A., & Cisowska, M. (2011). Clinical course of unoperated mild chronic thromboembolic pulmonary hypertension. *Kardiologia Polska (Polish Heart Journal), 69*(5), 438-443.

274. Runciman, W. B., Hunt, T. D., Hannaford, N. A., Hibbert, P. D., Westbrook, J. I., Coiera, E. W., ... & Braithwaite, J. (2012). CareTrack: assessing the appropriateness of health care delivery in Australia. *Medical Journal of Australia, 197*(2), 100.

275. Root cause analysis in healthcare Tools and techniques. R. J. Croteau, Ed. Fourth edition. Joint Commission Resources. 2010. Washington, D.C.

Available at: http://www.jcrinc.com/assets/1/14/rca09_sample_pages.pdf Last accessed May 15th, 2018.

276. Rosa L. V., Haddad A. N., de Carvalho P. V. (2015). Assessing risk in sustainable construction using the Functional Resonance Analysis Method (FRAM). *Cognition, Technology & Work, 17*(4), 559-73.

277. Rose, A., & Krausmann, E. (2013). An economic framework for the development of a resilience index for business recovery. *International Journal of Disaster Risk Reduction*, *5*, 73-83.

278. Rosenfeld, R. M., Shiffman, R. N., & Robertson, P. (2013). Clinical practice guideline development manual: a quality-driven approach for translating evidence into action. *Otolaryngology—Head and Neck Surgery*, *148*(1_suppl), S1-S55.

279. Rosenhek R., Klaar U., Schemper M., Scholten C., Heger M., Gabriel H., Binder T., Maurer G., Baumgartner H. (2004). Mild and moderate aortic stenosis: natural history and risk stratification by echocardiography. *European Heart Journal*, *25*(3), 199-205.

280. Rosenhek R., Zilberszac R., Schemper M., Czerny M., Mundigler G., Graf S., Bergler-Klein J., Grimm M., Gabriel H., Maurer G. (2010). Natural history of very severe aortic stenosis. *Circulation, 121*(1), 151-6.

281. Rothman, D. J. (2017). Strangers at the bedside: A history of how law and bioethics transformed medical decision making. Routledge.

282. Rowley, J. (2006). Where is the wisdom that we have lost in knowledge? *Journal of Documentation*, *62*(2), 251-270.

283. Rowley, J. (2007). The wisdom hierarchy: representations of the DIKW hierarchy. *Journal of information science*, *33*(2), 163-180.

284. Rowley, J. E. (2007). The wisdom hierarchy: representations of the DIKW hierarchy. Journal of information science.pp.1-18.

285. S. Nadkarni, & P. P. Shenoy, A Bayesian network approach to making inferences in causal maps. *European Journal of Operational Research, 128*, No. 3 (2001).

286. Salem-Schatz, S. R., Gottlieb, L. K., Karp, M. A., & Feingold, L. (1997). Attitudes about clinical practice guidelines in a mixed model HMO: the

influence of physician and organizational characteristics. *HMO practice*, *11*(3), 111-117.

287. Sawicki M. P., Samara G., Hurwitz M., Passaro E. (1993). Human genome project. *The American Journal of Surgery*, *165*(2), 258-64.

288. Schaller, R. R. (1997). Moore's law: past, present and future. *IEEE spectrum*, *34*(6), 52-59.

289. Schmidt, M., Bailey, M., Sheldrake, J., Hodgson, C., Aubron, C., Rycus, P. T. & Combes, A. (2014). Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. *American Journal of Respiratory and Critical Care Medicine*, *189*(11), 1374-1382.

290. Schmidt, M., Burrell, A., Roberts, L., Bailey, M., Sheldrake, J., Rycus, P. T. & Brodie, D. (2015). Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score. *European Heart Journal*, *36*(33), 2246-2256.

291. Schmidt, M., Zogheib, E., Rozé, H., Repesse, X., Lebreton, G., Luyt, C. E. & Ouattara, A. (2013). The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *Intensive Care Medicine*, *39*(10), 1704-1713.

292. Seligman, M. E. (1996). Science as an ally of practice. *American Psychologist*, *51*(10), 1072.

293. Séroussi, B., Bouaud, J., Chatellier, G., & Venot, A. (2004). Development of computerized guidelines for the management of chronic diseases allowing to position any patient within recommended therapeutic strategies. In *Medinfo* (pp. 154-158).

294. Sharma, N., Tabandeh, A., & Gardoni, P. (2018). Resilience analysis: a mathematical formulation to model resilience of engineering systems. *Sustainable and Resilient Infrastructure*, *3*(2), 49-67.

295. Shekelle, P., Eccles, M. P., Grimshaw, J. M., & Woolf, S. H. (2001). When should clinical guidelines be updated? *BMJ: British Medical Journal*, *323*(7305), 155.

296. Sherif H. M. F. (2001). Design and construction of a computer-based logical system for medical diagnosis. In J. D. Westwood et al. (Eds.), *Studies in Health Technology and Informatics*, vol. 81. IOS Press, the Netherlands.

297. Sherif HMF. Dissecting the dissection: Toward more comprehensive decision making methodology for thoracic aortic disease. *Aorta (Stamford)* 2015, June 3(3):108-117.

298. Sherif H. M. F. (2006). Is practicing medicine virtually impossible? *Healthcare Informatics, 23*(8), 54-5.

299. Sherif HMF, et al. (2009). Recovery after resuscitation from cardiac arrest in ST elevation myocardial infarction: A computer-based decision support tool. In J. D. Westwood, et al, (Eds.). *Studies in Healthcare and Informatics*, vol. 142 (310-312). IOS Press, the Netherlands.

300. Sherif H. M. F. (August 2017). Scripts and scriptures: Evolving from personality-based practice to evidence based practice. *Bulletin of the Society for Cardiothoracic Surgery in Great Britain and Ireland*, (2), 54-55. London, UK.

301. Sherif H. M. F. (2014). The role of bioinformatics in developing clinical practice guidelines: principles and opportunities. Journal of *Biomedical Graphics and Computing, 4*(4) 54-62.

302. Sherif H. M. F. (July 2014). Developing a true cardiothoracic surgeon: Professionalism, regulation and the normalization of deviance. *Bulletin of the Society for Cardiothoracic Surgery in Great Britain and Ireland*, (2), 18-20. London, UK.

303. Sherif H. M. (2016). Turner syndrome and guidelines for management of thoracic aortic disease: Appropriateness and utility. *Artery Research, 15*, 21-9.

304. Shroyer A. L., Coombs L. P., Peterson E. D., Eiken M. C., DeLong E. R., Chen A., Ferguson T. B., Grover F. L., Edwards F. H. (2003). The Society of Thoracic Surgeons: 30-day operative mortality and morbidity risk models. *The Annals of Thoracic Surgery, 75*(6), 1856-65.

305. Soley-Bori, M. (2013). Dealing with missing data: Key assumptions and methods for applied analysis. *Boston University*.

306. Smith, C. M. (2005). Origin and uses of primum non nocere—above all, do no harm! *The Journal of Clinical Pharmacology*, *45*(4), 371-377.

307. Smith, J., Dixon, R. A., & Baltes, P. B. (1989). Expertise in life planning: A new research approach to investigating aspects of wisdom.

308. Smith, R. D. (1980). Avicenna and the Canon of Medicine: a millennial tribute. *Western Journal of Medicine*, *133*(4), 367.

309. Spath, P., & Spath, P. L. (2009). *Introduction to healthcare quality management* (Vol. 2). Chicago, IL: Health Administration Press.

310. Stamatis, D. H. (2003). Failure mode and effect analysis: FMEA from theory to execution. ASQ Quality Press.

311. Steen R., Aven T. (2011). A risk perspective suitable for resilience engineering. *Safety Science*, 49(2), 292-7.

312. Steinberg, E., Greenfield, S., Wolman, D. M., Mancher, M., & Graham, R. (Eds.). (2011). *Clinical practice guidelines we can trust*. National Academies Press.

313. Studdert, D. M., Mello, M. M., Sage, W. M., DesRoches, C. M., Peugh, J., Zapert, K., & Brennan, T. A. (2005). Defensive medicine among high-risk specialist physicians in a volatile malpractice environment. *Jama*, *293*(21), 2609-2617.

314. Sullivan, G. M. (2011). Getting off the "gold standard": randomized controlled trials and education research. *Journal of graduate medical education*, *3*(3), 285-289.

315. Taylor, M. J., McNicholas, C., Nicolay, C., Darzi, A., Bell, D., & Reed, J. E. (2013). Systematic review of the application of the plan–do–study–act method to improve quality in healthcare. *BMJ Qual Saf*, bmjqs-2013.

316. Terenziani, P., Montani, S., Bottrighi, A., Torchio, M., Molino, G., & Correndo, G. (2004). A context-adaptable approach to clinical guidelines. In *Medinfo* (pp. 169-173).

317. Titler M. G. (2008). The evidence for evidence-based practice implementation. In: Hughes R. G. (, ed.). Patient Safety and Quality: An Evidence-Based Handbook for Nurses (chapter 7). Rockville (MD): Agency for Healthcare Research and Quality (US). Available at: https://www.ncbi.nlm.nih.gov/books/NBK2659/ Last accessed May 15th, 2018.

318. Todman L. C., Fraser F. C., Corstanje R., Deeks L. K., Harris J. A., Pawlett M., Ritz K., Whitmore A. P. (2016). Defining and quantifying the resilience of

responses to disturbance: A conceptual and modelling approach from soil science. *Scientific Reports*, *6*, 28426.

319. Toman, C., Harrison, M. B., & Logan, J. (2001). Clinical practice guidelines: Necessary but not sufficient for evidence-based patient education and counseling. *Patient Education and Counseling*, *42*(3), 279-287.

320. Towle, A., & Godolphin, W. (1999). Framework for teaching and learning informed shared decision making. *BMJ: British Medical Journal*, *319*(7212), 766.

321. Tsigos C, Kyrou I, Kassi E, et al. Stress, Endocrine Physiology and Pathophysiology. [Updated 2016 Mar 10]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK278995/ Last accessed May 5th, 2018.

322. Van de Bovenkamp, H. M., & Trappenburg, M. J. (2009). Reconsidering patient participation in guideline development. *Health Care Analysis*, *17*(3), 198-216.

323. Vahanian, A., Alfieri, O., Andreotti, F., Antunes, M. J., Barón-Esquivias, G., Baumgartner, H., ... & Falk, V. (2012). Joint task force on the management of valvular heart disease of the European society of cardiology (ESC); European association for cardio-thoracic surgery (EACTS). guidelines on the management of valvular heart disease (version 2012). *Eur Heart J*, *33*(19), 2451-96.

324. Varadarajan, P., Kapoor, N., Bansal, R. C., & Pai, R. G. (2006). Clinical profile and natural history of 453 nonsurgically managed patients with severe aortic stenosis. *The Annals of thoracic surgery*, *82*(6), 2111-2115.

325. Vincent, C. A. (2004). Analysis of clinical incidents: a window on the system not a search for root causes.

326. Vugrin, E. D., Turnquist, M. A., & Brown, N. J. (2014). Optimal recovery sequencing for enhanced resilience and service restoration in transportation networks. *International Journal of Critical Infrastructures*, *10*(3-4), 218-246.

327. Wagner, E. H. (2000). The role of patient care teams in chronic disease management. *Bmj*, *320*(7234), 569-572.

328. Walker, B., Holling, C. S., Carpenter, S., & Kinzig, A. (2004). Resilience, adaptability and transformability in social–ecological systems. *Ecology and Society*, *9*(2).

329. Wang, D., Peleg, M., Tu, S. W., Boxwala, A. A., Greenes, R. A., Patel, V. L., & Shortliffe, E. H. (2002). Representation primitives, process models and patient data in computer-interpretable clinical practice guidelines: A literature review of guideline representation models. *International journal of medical informatics*, *68*(1-3), 59-70.

330. Weiss K. (1982). Corporate medicine. What's the bottom line for physicians and patients? *The New Physician*, *31*(9), 19-25.

331. Whitson H. E., Cohen H. J., Schmader K. E., Morey M. C., Kuchel G., Colon-Emeric C. S. (2018). Physical resilience: Not simply the opposite of frailty. Editorial. *Journal of the American Geriatrics Society*. 2018 March 25. Doi: 10.1111/jgs.15233. (Epub ahead of print]

332. Whitson H. E., Duan-Porter W., Schmader K. E., Morey M. C., Cohen H. J., Colón-Emeric C. S. (2015). Physical resilience in older adults: systematic review and development of an emerging construct. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 71*(4), 489-95.

333. Woods, D. D. (2006). Essential characteristics of resilience. *Resilience Engineering: Concepts and Precepts*, 21-34.

334. Woods, D. D., & Hollnagel, E. (2006). Prologue: resilience engineering concepts. *Resilience Engineering. Concepts and Precepts*, 1-16.

335. Woods D. D. (2015). Four concepts for resilience and the implications for the future of resilience engineering. *Reliability Engineering & System Safety, 141*, 5-9.

336. Woolf, S. H. (2000). Evidence-based medicine and practice guidelines: an overview. *Cancer Control*, *7*(4), 362-367.

337. Wright, C. J. (1979). Academics and their aims: English and Scottish approaches to university education in the nineteenth century. *History of Education*, *8*(2), 91-97.

338. Yodo N., Wang P. (2016). Resilience modeling and quantification for engineered systems using Bayesian networks. *Journal of Mechanical Design, 138*(3), 031404.

339. Yu C and Ho Z. (May 2008) Resilience Degree – A new indicator of sustainable development to water resources system. In 2008 2nd International Conference on Bioinformatics and Biomedical Engineering, pages 3499-3502. IEEE. Orlando, FL.

340. Zangrillo, A., Biondi-Zoccai, G., Landoni, G., Frati, G., Patroniti, N., Pesenti, A., & Pappalardo, F. (2013). Extracorporeal membrane oxygenation (ECMO) in patients with H1N1 influenza infection: a systematic review and meta-analysis including 8 studies and 266 patients receiving ECMO. *Critical Care*, *17*(1), R30.

# Appendix A

# HUMAN SUBJECT PROTOCOL

HUMAN SUBJECTS PROTOCOL
University of Delaware

Protocol Title: A Novel Hybrid Model for Clinical Decision-Making. Corbin-Strauss Model and Resilience Engineering

Principal Investigator
Name: Hisham M.F. Sherif, MD
Department/Center: Biomedical Engineering
Contact Phone Number: (302) 836-4831
Email Address: hisham@udel.edu

Advisor (if student PI):
Name: Nii Attoh-Okine
Contact Phone Number: 302-831-4532
Email Address: okine@udel.edu

Other Investigators:

Investigator Assurance:

By submitting this protocol, I acknowledge that this project will be conducted in strict accordance with the procedures described. I will not make any modifications to this protocol without prior approval by the IRB. Should any unanticipated problems involving risk to subjects occur during this project, including breaches of guaranteed confidentiality or departures from any procedures specified in approved study documents, I will report such events to the Chair, Institutional Review Board immediately.

1. **Is this project externally funded?** ☐ YES ☐ NO

If so, please list the funding source:

**2. Research Site(s)**

☐ University of Delaware
☐ Other (please list external study sites)

Is UD the study lead? ☐ YES ☐ NO (If no, list the institution that is serving as the study lead)

3. **Project Staff**
Please list all personnel, including students, who will be working with human subjects on this protocol (insert additional rows as needed):

| NAME | ROLE | HS TRAINING COMPLETE? |
|---|---|---|
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

4. **Special Populations**
Does this project involve any of the following:

Research on Children? NO

Research with Prisoners? NO

If yes, complete the Prisoners in Research Form and upload to IRBNet as supporting documentation

Research with Pregnant Women? NO

Research with any other vulnerable population (e.g. cognitively impaired, economically disadvantaged, etc.)? please describe
NO

5. **RESEARCH ABSTRACT** Please provide a brief description in LAY language (understandable to an 8th grade student) of the aims of this project.

Collection of archived medical records data to be utilized in the construction and validation of a novel hybrid model for decision-making incorporating the Corbin-Strauss disease trajectory model and based on resilience engineering principles. Data is collected from the local Society of Thoracic Surgeons database for adult patients undergoing aortic valve replacement. Data variables include: Age, Gender, Location, Time between examination (diagnosis) and surgery and Survival status at 30-days after surgery. All private and confidential patient information is removed.

6. **PROCEDURES** Describe all procedures involving human subjects for this protocol. Include copies of all surveys and research measures.

Not Applicable.

7. **STUDY POPULATION AND RECRUITMENT**
Describe who and how many subjects will be invited to participate. Include age, gender and other pertinent information.

None applicable

Attach all recruitment fliers, letters, or other recruitment materials to be used. If verbal recruitment will be used, please attach a script.

None applicable

Describe what exclusionary criteria, if any will be applied.

Not applicable

Describe what (if any) conditions will result in PI termination of subject participation.
Not applicable

8. **RISKS AND BENEFITS**
List all potential physical, psychological, social, financial or legal risks to subjects (risks listed here should be included on the consent form).

Not applicable

In your opinion, are risks listed above minimal* or more than minimal? If more than minimal, please justify why risks are reasonable in relation to anticipated direct or future benefits.

*(*Minimal risk means the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the perfo rmance of routine physical or psychological examinations or tests)*

Not applicable

What steps will be taken to minimize risks?
NO interventions or interaction with subjects

Describe any potential direct benefits to participants.

Describe any potential future benefits to this class of participants, others, or society.

If there is a Data Monitoring Committee (DMC) in place for this project, please describe when and how often it meets.

9. **COMPENSATION**
Will participants be compensated for participation?
Not applicable

If so, please include details.

10. **DATA**
Will subjects be anonymous to the researcher?
YES

If subjects are identifiable, will their identities be kept confidential? (If yes, please specify how)
All identifying information removed

How will data be stored and kept secure (specify data storage plans for both paper and electronic files. For guidance see http://www.udel.edu/research/preparing/datastorage.html )
YES

How long will data be stored?
Secure digital storage

Will data be destroyed? ☐ YES ☐ NO (if yes, please specify how the data will be destroyed)
YES. All files will be deleted at the conclusion of the research

Will the data be shared with anyone outside of the research team? ☐ YES ☐ NO (if yes, please list the person(s), organization(s) and/or institution(s) and specify plans for secure data transfer)
NO

How will data be analyzed and reported?
Standard statistical analysis and novel resilience engineering model

11. **CONFIDENTIALITY**
Will participants be audiotaped, photographed or videotaped during this study?
NO

How will subject identity be protected?
NO identifying information collected

Is there a Certificate of Confidentiality in place for this project? (If so, please provide a copy).

12. **CONFLICT OF INTEREST**
(For information on disclosure reporting see: http://www.udel.edu/research/preparing/conflict.html )

Do you have a current conflict of interest disclosure form on file through UD Web forms?
NO

Does this project involve a potential conflict of interest*?
NO
* As defined in the University of Delaware's Policies and Procedures ,a potential conflict of interest (COI) occurs when there is a divergence between an individual's private interests and his or her professional obligations, such that an independent observer might reasonably question whether the individual's professional judgment, commitment, actions, or decisions could be influenced by considerations of personal gain, financial or otherwise.

If yes, please describe the nature of the interest:

13. **CONSENT and ASSENT**

____ Consent forms will be used and are attached for review (see Consent Template under Forms and Templates in IRBNet)
Not Applicable

____ Additionally, child assent forms will be used and are attached.

Not Applicable
____ Waiver of Documentation of Consent (attach a consent script/information sheet with the signature block removed).
Not Applicable

____ Waiver of Consent (Justify request for waiver)
Not applicable

14. **Other IRB Approval**
Has this protocol been submitted to any other IRBs?

If so, please list along with protocol title, number, and expiration date.

15. **Supporting Documentation**
Please list all additional documents uploaded to IRBNet in support of this application.

## Appendix B

## PERMISSION REQUESTS FOR MODIFICATION OF FIGURES

1. Attoh-Okine, N. O., Cooper, A. T., & Mensah, S. A. (2009). Formulation of resilience index of urban infrastructure using belief functions. IEEE Systems Journal, 3(2), 147-153.

   The following message is provided by IEEE for thesis use:

   ***The IEEE does not require individuals working on a thesis to obtain a formal reuse license, however, you may print out this statement to be used as a permission grant:***

   *Requirements to be followed when using any portion (e.g., figure, graph, table, or textual material) of an IEEE copyrighted paper in a thesis:*

   *1) In the case of textual material (e.g., using short quotes or referring to the work within these papers) users must give full credit to the original source (author, paper, publication) followed by the IEEE copyright line © 2011 IEEE.*
   *2) In the case of illustrations or tabular material, we require that the copyright line © [Year of original publication] IEEE appear prominently with each reprinted figure and/or table.*
   *3) If a substantial portion of the original paper is to be used, and if you are not the senior author, also obtain the senior author's approval.*

   *Requirements to be followed when using an entire IEEE copyrighted paper in a thesis:*

   *1) The following IEEE copyright/ credit notice should be placed prominently in the references: © [year of original publication] IEEE. Reprinted, with permission, from [author names, paper title, IEEE publication title, and month/year of publication]*
   *2) Only the accepted version of an IEEE copyrighted paper can be used when posting the paper or your thesis on-line.*
   *3) In placing the thesis on the author's university website, please display the following message in a prominent place on the website: In reference to IEEE copyrighted material which is used with permission in this thesis, the IEEE does not endorse any of [university/educational entity's name goes here]'s products or services. Internal or personal use of this material is permitted. If interested in reprinting/republishing*

*IEEE copyrighted material for advertising or promotional purposes or for creating new collective works for resale or redistribution, please go to http://www.ieee.org/publications_standards/publications/rights/rights_link.html to learn how to obtain a License from RightsLink.*

*If applicable, University Microfilms and/or ProQuest Library, or the Archives of Canada may supply single copies of the dissertation.*

If you need to contact the publisher directly, please email pubs-permissions@ieee.org.

2. Sharma, N., Tabandeh, A., & Gardoni, P. (2018). Resilience analysis: a mathematical formulation to model resilience of engineering systems. Sustainable and Resilient Infrastructure, 3(2), 49-67.

   The following message is provided by Taylor & Francis for thesis use:

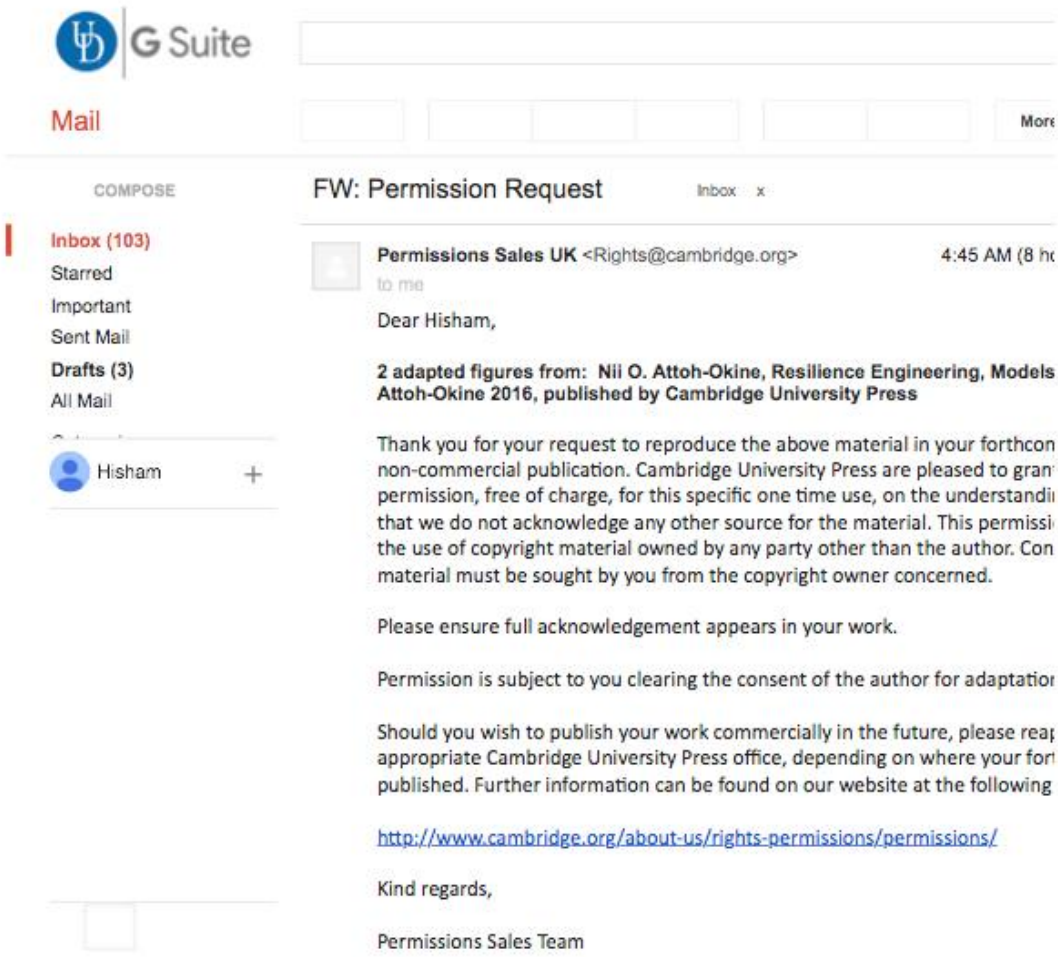
   *Taylor & Francis is pleased to offer reuses of its content for a thesis or dissertation free of charge contingent on resubmission of permission request if work is published.*

   If you need to contact the publisher, please email permissionrequest@tandf.co.uk.

3. Reed, E., & Corner, J. (2013). Defining the illness trajectory of metastatic breast cancer. BMJ Supportive & Palliative Care, bmjspcare-2012.

   The following message is provided by BMJ for this article:

   *This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:* http://creativecommons.org/licenses/by-nc/3.0/



G Suite

Mail

More

COMPOSE

Inbox (103)
Starred
Important
Sent Mail
Drafts (3)
All Mail

Hisham

FW: Permission Request Inbox x

**Permissions Sales UK** <Rights@cambridge.org> 4:45 AM (8 hc
to me

Dear Hisham,

**2 adapted figures from: Nii O. Attoh-Okine, Resilience Engineering, Models Attoh-Okine 2016, published by Cambridge University Press**

Thank you for your request to reproduce the above material in your forthcon non-commercial publication. Cambridge University Press are pleased to gran permission, free of charge, for this specific one time use, on the understandi that we do not acknowledge any other source for the material. This permissi the use of copyright material owned by any party other than the author. Con material must be sought by you from the copyright owner concerned.

Please ensure full acknowledgement appears in your work.

Permission is subject to you clearing the consent of the author for adaptatior

Should you wish to publish your work commercially in the future, please rea appropriate Cambridge University Press office, depending on where your for published. Further information can be found on our website at the following

http://www.cambridge.org/about-us/rights-permissions/permissions/

Kind regards,

Permissions Sales Team

**BMJ PUBLISHING GROUP LTD. LICENSE TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and BMJ Publishing Group Ltd. ("BMJ Publishing Group Ltd.") consists of your license details and the terms and conditions provided by BMJ Publishing Group Ltd. and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386210980152 |
| License date | Jul 11, 2018 |
| Licensed Content Publisher | BMJ Publishing Group Ltd. |
| Licensed Content Publication | The BMJ |
| Licensed Content Title | Care for all at the end of life |
| Licensed Content Author | Scott A Murray, Aziz Sheikh |
| Licensed Content Date | Apr 24, 2008 |
| Licensed Content Volume | 336 |
| Type of Use | Dissertation/Thesis |
| Requestor type | Individual |
| Format | Electronic |
| Portion | Figure/table/extract |
| Number of figure/table/extracts | 1 |
| Descriptionof figure/table/extracts | Figure 1 |
| Will you be translating? | No |
| Circulation/distribution | 1 |
| Title of your thesis / dissertation | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Expected completion date | Aug 2018 |
| Estimated size(pages) | 1 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Publisher Tax ID | GB674738491 |
| Billing Type | Invoice |
| Billing Address | Hisham MF Sherif<br>7 Vinca Drive |

| | |
|---|---|
| **Title:** | Journal of mechanical design |
| **Article ID:** | 1050-0472 |
| **Publication:** | Publication1 |
| **Publisher:** | CCC Republication |
| **Date:** | Jan 1, 1990 |





## Order Completed

Thank you for your order.

This Agreement between Hisham MF Sherif ("You") and American Society of Mechanical Engineers ASME ("American Society of Mechanical Engineers ASME") consists of your order details and the terms and conditions provided by American Society of Mechanical Engineers ASME and Copyright Clearance Center.

| | |
|---|---|
| License number | Reference confirmation email for license number |
| License date | Jul, 17 2018 |
| Licensed content publisher | American Society of Mechanical Engineers ASME |
| Licensed content title | Journal of mechanical design |
| Licensed content date | Jan 1, 1990 |
| Type of use | Thesis/Dissertation |
| Requestor type | Academic institution |
| Format | Electronic |
| Portion | chart/graph/table/figure |
| Number of charts/graphs/tables/figures | 6 |
| The requesting person/organization | Hisham M.F. Sherif |
| Title or numeric reference of the portion(s) | Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 8, Table 1 |
| Title of the article or chapter the portion is from | Engineering Resilience Quantification and System Design Implications: A Literature Survey |
| Editor of portion(s) | N/A |
| Author of portion(s) | Nita Yodo, Pingfeng Wang |
| Volume of serial or monograph | 138 |
| Issue, if republishing an article from a serial | 111 |
| Page range of portion | 111408-1 to 111408-8 |
| Publication date of portion | 2016 |
| Rights for | Main product |
| Duration of use | Current edition and up to 5 years |
| Creation of copies for the disabled | no |
| With minor editing privileges | no |
| For distribution to | Worldwide |
| In the following language(s) | Original language of publication |

| | |
|---|---|
| With incidental promotional use | no |
| Lifetime unit quantity of new product | Up to 499 |
| Title | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Instructor name | Hisham M.F. Sherif |
| Institution name | University of Delaware |
| Expected presentation date | Aug 2018 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Billing Type | Invoice |
| Billing address | Hisham MF Sherif<br>7 Vinca Drive<br><br>Newark, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Total (may include CCC user fee) | 0.00 USD |
| Total | 0.00 USD |

CLOSE WINDOW

**ELSEVIER LICENSE**
**TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386210864339 |
| License date | Jul 11, 2018 |
| Licensed Content Publisher | Elsevier |
| Licensed Content Publication | The Lancet |
| Licensed Content Title | Aortic stenosis |
| Licensed Content Author | Blase A Carabello,Walter J Paulus |
| Licensed Content Date | 14–20 March 2009 |
| Licensed Content Volume | 373 |
| Licensed Content Issue | 9667 |
| Licensed Content Pages | 11 |
| Start Page | 956 |
| End Page | 966 |
| Type of Use | reuse in a thesis/dissertation |
| Portion | figures/tables/illustrations |
| Number of figures/tables/illustrations | 1 |
| Format | electronic |
| Are you the author of this Elsevier article? | No |
| Will you be translating? | No |
| Original figure numbers | Figure 5 |
| Title of your thesis/dissertation | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Publisher of new work | University of Delaware |
| Author of new work | Hisham M.F. Sherif |
| Expected completion date | Aug 2018 |
| Estimated size (number of pages) | 1 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States |

**BMJ PUBLISHING GROUP LTD. LICENSE TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and BMJ Publishing Group Ltd. ("BMJ Publishing Group Ltd.") consists of your license details and the terms and conditions provided by BMJ Publishing Group Ltd. and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386210565431 |
| License date | Jul 11, 2018 |
| Licensed Content Publisher | BMJ Publishing Group Ltd. |
| Licensed Content Publication | The BMJ |
| Licensed Content Title | Care for all at the end of life |
| Licensed Content Author | Scott A Murray, Aziz Sheikh |
| Licensed Content Date | Apr 24, 2008 |
| Licensed Content Volume | 336 |
| Type of Use | Dissertation/Thesis |
| Requestor type | Individual |
| Format | Electronic |
| Portion | Figure/table/extract |
| Number of figure/table/extracts | 1 |
| Descriptionof figure/table/extracts | Figure 1 |
| Will you be translating? | No |
| Circulation/distribution | 1 |
| Title of your thesis / dissertation | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Expected completion date | Aug 2018 |
| Estimated size(pages) | 1 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Publisher Tax ID | GB674738491 |
| Billing Type | Invoice |
| Billing Address | Hisham MF Sherif<br>7 Vinca Drive |

**OXFORD UNIVERSITY PRESS LICENSE**
**TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386051402895 |
| License date | Jul 11, 2018 |
| Licensed content publisher | Oxford University Press |
| Licensed content publication | European Heart Journal |
| Licensed content title | Mild and moderate aortic stenosis: Natural history and risk stratification by echocardiography |
| Licensed content author | Rosenhek, Raphael; Klaar, Ursula |
| Licensed content date | Feb 1, 2004 |
| Type of Use | Thesis/Dissertation |
| Institution name | |
| Title of your work | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Publisher of your work | University of Delaware |
| Expected publication date | Aug 2018 |
| Permissions cost | 0.00 USD |
| Value added tax | 0.00 USD |
| Total | 0.00 USD |
| Title | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Instructor name | Hisham M.F. Sherif |
| Institution name | University of Delaware |
| Expected presentation date | Aug 2018 |
| Portions | Figure 1 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Publisher Tax ID | GB125506730 |
| Billing Type | Invoice |
| Billing Address | Hisham MF Sherif<br>7 Vinca Drive |

**OXFORD UNIVERSITY PRESS LICENSE**
**TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386051402895 |
| License date | Jul 11, 2018 |
| Licensed content publisher | Oxford University Press |
| Licensed content publication | European Heart Journal |
| Licensed content title | Mild and moderate aortic stenosis: Natural history and risk stratification by echocardiography |
| Licensed content author | Rosenhek, Raphael; Klaar, Ursula |
| Licensed content date | Feb 1, 2004 |
| Type of Use | Thesis/Dissertation |
| Institution name | |
| Title of your work | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Publisher of your work | University of Delaware |
| Expected publication date | Aug 2018 |
| Permissions cost | 0.00 USD |
| Value added tax | 0.00 USD |
| Total | 0.00 USD |
| Title | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Instructor name | Hisham M.F. Sherif |
| Institution name | University of Delaware |
| Expected presentation date | Aug 2018 |
| Portions | Figure 1 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Publisher Tax ID | GB125506730 |
| Billing Type | Invoice |
| Billing Address | Hisham MF Sherif<br>7 Vinca Drive |

**OXFORD UNIVERSITY PRESS LICENSE**
**TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and Oxford University Press ("Oxford University Press") consists of your license details and the terms and conditions provided by Oxford University Press and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386050528800 |
| License date | Jul 11, 2018 |
| Licensed content publisher | Oxford University Press |
| Licensed content publication | European Heart Journal |
| Licensed content title | Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE)-score |
| Licensed content author | Schmidt, Matthieu; Burrell, Aidan |
| Licensed content date | Jun 1, 2015 |
| Type of Use | Thesis/Dissertation |
| Institution name | |
| Title of your work | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Publisher of your work | University of Delaware |
| Expected publication date | Aug 2018 |
| Permissions cost | 0.00 USD |
| Value added tax | 0.00 USD |
| Total | 0.00 USD |
| Title | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Instructor name | Hisham M.F. Sherif |
| Institution name | University of Delaware |
| Expected presentation date | Aug 2018 |
| Portions | Figure 4 |
| Requestor Location | Hisham MF Sherif<br>7 Vinca Drive<br><br>NEWARK, DE 19702<br>United States<br>Attn: Hisham MF Sherif |
| Publisher Tax ID | GB125506730 |
| Billing Type | Invoice |
| Billing Address | Hisham MF Sherif<br>7 Vinca Drive |

**ELSEVIER LICENSE**
**TERMS AND CONDITIONS**

Jul 11, 2018

This Agreement between Hisham MF Sherif ("You") and Elsevier ("Elsevier") consists of your license details and the terms and conditions provided by Elsevier and Copyright Clearance Center.

| | |
|---|---|
| License Number | 4386041061983 |
| License date | Jul 11, 2018 |
| Licensed Content Publisher | Elsevier |
| Licensed Content Publication | Critical Care Nursing Clinics of North America |
| Licensed Content Title | Cause-and-effect Mapping of Critical Events |
| Licensed Content Author | Krisanne Graves,Debora Simmons,Mark D. Galley |
| Licensed Content Date | Jun 1, 2010 |
| Licensed Content Volume | 22 |
| Licensed Content Issue | 2 |
| Licensed Content Pages | 9 |
| Start Page | 243 |
| End Page | 251 |
| Type of Use | reuse in a thesis/dissertation |
| Portion | figures/tables/illustrations |
| Number of figures/tables/illustrations | 1 |
| Format | electronic |
| Are you the author of this Elsevier article? | No |
| Will you be translating? | No |
| Original figure numbers | Figure 1 |
| Title of your thesis/dissertation | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Publisher of new work | University of Delaware |
| Author of new work | Hisham M.F. Sherif |
| Expected completion date | Aug 2018 |
| Estimated size (number of pages) | 1 |
| Requestor Location | Hisham MF Sherif<br>4755 Ogletown-Stanton Road<br>Suitre 1E50<br><br>Newark, DE 19718<br>United States |

## AMERICAN SOCIETY OF MECHANICAL ENGINEERS ASME ORDER DETAILS

Jul 11, 2018

| | |
|---|---|
| Order Number | 501413698 |
| Order date | Jul 11, 2018 |
| Licensed content publisher | American Society of Mechanical Engineers ASME |
| Licensed content title | Journal of mechanical design |
| Licensed content date | Jan 1, 1990 |
| Type of Use | Thesis/Dissertation |
| Requestor type | Academic institution |
| Format | Electronic |
| Portion | chart/graph/table/figure |
| Number of charts/graphs/tables/figures | 6 |
| The requesting person/organization is: | Hisham M.F. Sherif |
| Title or numeric reference of the portion(s) | Figure 1, Figure 2, Figure 3, Figure 4, Figure 5, Figure 6, Figure 8, Table 1 |
| Title of the article or chapter the portion is from | Engineering Resilience Quantification and System Design Implications: A Literature Survey |
| Editor of portion(s) | N/A |
| Author of portion(s) | Nita Yodo, Pingfeng Wang |
| Volume of serial or monograph. | 138 |
| Issue, if republishing an article from a serial | 111 |
| Page range of the portion | 111408-1 to 111408-8 |
| Publication date of portion | 2016 |
| Rights for | Main product |
| Duration of use | Current edition and up to 5 years |
| Creation of copies for the disabled | no |
| With minor editing privileges | no |
| For distribution to | Worldwide |
| In the following language(s) | Original language of publication |
| With incidental promotional use | no |
| The lifetime unit quantity of new product | Up to 499 |
| Title | A novel hybrid model for clinical decision making. Corbin Strauss model and resilience engineering |
| Instructor name | Hisham M.F. Sherif |
| Institution name | University of Delaware |