Digital Twin Meets Digital Cousin

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True knowledge exists in knowing that you know nothing. [Socrates]

Digital Twin Meets Digital Cousin
From Paradox to Paradigm or a Paradoxical Paradigm?

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DEDICATION

This chapter is dedicated to Ève Curie Labouisse (December 6, 1904 - October 22, 2007), author of "Madame Curie" (Doubleday, Doran, 1937[1]) and "Journey Among Warriors" (Doubleday, Doran, 1943). "Madame Curie" may be the best known biography[2] in the past 85 years (since its first publication in 1937). There are 565 translations/versions[3] of "Madame Curie" by Ève Curie. Ève Curie was the daughter of Marie Salomea Skłodowska Curie (1867-1934) and Pierre Curie (1859-1906) and younger sister of Irène Joliot-Curie (1897-1956).

Ève Denise Curie Labouisse (left) at her home (One Sutton Place, New York, NY 10022) when this photograph was taken during March, 1997. Hélène Langevin Joliot-Curie (right) is the niece of Ève Curie and daughter of Irène Joliot-Curie and Frédéric Joliot-Curie. In the background, a copy of each of the translated versions/editions of the biography "Madame Curie" by Ève Curie. Photograph by Shoumen Datta (March 1997, New York). This is a personal (SD) photograph.

True knowledge exists in knowing that you know nothing. [Socrates]

DEDICATION

Sir Clive William John Granger

4 September 1934 – 27 May 2009

Mathematician, Statistician, Economist, Statesman, Scholar, Humanist, and Friend

Clive Granger. 9th September 2008 in Sammy's Restaurant on Inch Beach, County Kerry, Ireland (Clive's last birthday. Personal photo from S. Datta).

The global discussion of causality in the past half century can be traced to Granger Causality[4]. None of the countries of the world can escape from the profound impact of Granger causality on financial econometrics, finance and economics. Clive Granger shared the 2003 Nobel Prize in Economics with Robert Engle (Engle and Granger, 2003). The discussion of causality extends into every nook and cranny of logic and reason for any rational and analytical thought. The emphasis of causality in this article was directly influenced by Clive Granger and his association with the corresponding author (S. Datta) as well as the joint paper on forecasting accuracy (Datta and Granger, 2006).

True knowledge exists in knowing that you know nothing. [Socrates]

ABSTRACT

Laissez-faire interpretation of what constitutes a digital twin may catalyze a broader diffusion of the principles (ideas) and perhaps even accelerate adoption of digital representations of physical entities, albeit in select parts of the affluent world (where citizens have a significant amount of disposable income). The limits of efficiency and efficacy of digital proxies will affect the value of actionable information which may be extracted/shared/exchanged from data and analytics (contextually connected causal relationships, Figure 33). Applications are easier in the mechanical context (manufacturing, automotive, buildings). Digital duplicates of natural systems (environment, health, agriculture) are beguiling. Representation in the form of "twins" suggests exact/identical *twining* (of data) which is difficult to duplicate because the medium is different (physical versus digital). Hence, *digital cousins* of tiny sub-segments of systems may be useful if we can grasp the science of the data and shun the hand-waving hype about cognition or cognitive processes (by definition, cognition refers to mental action or process of acquiring knowledge and understanding through thought, experience, and the senses). If parameters are well understood (e.g., causality), if the acquired data is rigorous, mathematically robust (e.g., proportionality, rate, ratio) and abundantly informative (e.g., blood glucose levels and type II diabetes mellitus), then digital cousins may be less irrational as an aspirational goal on a future wish-list.

At the ***core*** of almost any system with a popular label or "buzz" word (digital twins, internet of things, cyberphysical systems, cloud, machine learning, "big data", "DL", "AI", "Industry X.O") we treat (mis-treat?) ***data*** to extract meaningful information of value. The sense of "meaning" is rooted in measurements and metrics. The sense of value is usually related to "performance" depending on the context (environment). The underlying glue that permeates the fabric of continuum between meaning and value is causality (what causes what we observe and what we record, as change, as data). Almost every "thing" (made of atoms) or processes or systems we dissect, deconstruct and reconstruct (solve? solution?) is more significant when they associate with data (bits). *The continuum of meaning and value is in dynamic interaction with the continuum between atoms to bits.* The key elements of this multi-string, multi-dimensional continuum are connectivity, data, analytics and context (ACDC). It is this "electricity" which powers the engines of decision science and data-informed systems. Directly or indirectly, knowingly or unknowingly, in astronomical events or in infinitesimal instances, almost all tools and techniques arising from "technology" converges to catalyze our need to be data-informed.

Economics of technology could make or break any product and reliable digital representation may remain prohibitive for decades, if not *centuries*, in resource constrained communities (i.e., greater than 80% of the global population). An abundance of caution (for example, about understanding of the nature and representation of causality in systems) and strenuous reservations (for example, about claims relative to cognition in systems) in this discussion has the potential to disintegrate or prove to be myopic or become incorrect due to future advances in science, in the next few years or centuries. Cybersecurity of digital twins are as quintessential as ethical applications.

BACKGROUND

Astronautics, space exploration and NASA have been using mechanical twins followed by digital representations of electro-mechanical systems since 1950's[5] and other attempts may reach as far back as the dawn of the 20th century. Basic *twining* was essential to space programs where physical duplicates on ground had to match system performance in space. Physical and digital duplicates (cyberphysical systems[6], virtual twins, digital twins) were key to NASA's finest hour[7] in accurately assessing and precisely simulating conditions on Apollo 13.

The safe return of the Apollo 13 astronauts unequivocally sealed the power of the idea of virtual proxies and digital copies/duplicates as a "sandbox" for monitoring, testing and analysis. Digital twins, therefore, is a digital by design metaphor, not a technology. Marketing of the term "digital twins" was not an epiphany[8] or invention or a pioneering flash of clarity, it was rational progress of reason. This progression[9] of insight was carefully packaged by for-profit corporate publicity machines to amplify sensationalism in the 21st century (outlined in[10] "history of digital twin technology"). The diffusion of digital twins and its adoption in our vernacular is due to centuries of scientific exploration[11] and foresight which empowered scientists and engineers to extract insight from experimental duplication of conditions and work with alternate forms of representation, to capture data and/or observe events/instances depending on the context.

Digital twins are an alternate (cyber, virtual) form of representation of mechanical (physical) objects or systems. Digital twins, therefore, are cyberphysical systems[12] (CPS) which are expected to inform operational behavior in order to enable humans and/or other decision systems to better optimize system performance. The latter may be loosely analogous to studying prions, viruses and single-cell bacteria to better understand molecular complementarity as the underlying mechanism of structure and function which may be extrapolated to test models of biological processes in multi-cellular eukaryotes, including plants, animals and humans.

In a previous essay on the emergence of digital twins[13] we discussed far-ranging issues, albeit unfocused, which are likely to remain unaddressed, unanswered and unexplored, for quite a while. Why?

The *first* answer is digital twin is not a technology, it is an idea, a design metaphor using the cyber ***medium*** to connect a physical entity with its digital representation as a mechanism to facilitate transparency between data of systems in the ***context*** of the networked physical world. To the chagrin of scientists, marketing gurus exacerbated the problems of digital transformation by leaning into fake veneers and exaggerated the hype to float their bloated hyperbole[14]. Hence, digital twins are now a part of the frenzied public relations campaigns where the principles of digital representation and transformation are "*a hammer searching for a nail"* catalyzed by tawdry, shallow, short-term gains which may not lead to profitability, after all. The latter are driven by delusional greed, besotted by the grand illusion of billions in market capitalization projected by unscrupulous[15] *drive-by-night* market "research" misfits and outfits.

The *second* reason is that science and engineering principles in the implementation of digital twins suffers from an abundance of unknown unknowns when transforming vision into reality. Patchwork of systems integration varies dramatically and influences the outcome.

The *third* reason is the sluggish pace of change and adoption as well as resistance to new tools to remove barriers created by conventional wisdom and the dead weight of old technology (see **APPENDIX**). The efficiency and efficacy of digital representations are still being debated in many "brown-field" industries. The lack of enthusiasm to invest in the process is partly due to deep mistrust fueled by dismal facts how conniving consulting firms swindled trillions[16] in the name of "billable hours" for digital transformation. *After-the-fact* pundits then pontificated tooth-less platitudes how digital transformation is not about technology[17] but continues to agressively peddle prosperity[18] by disguising non-existent demand for unproven technologies[19].

The *fourth* reason is the lack of standards[20], interoperability between standards, inability to merge/distribute data and lack of incisive logic in expert systems to make sense of data. The proliferation of shoddy and second grade software analytical tools further aggravates the already difficult task of extracting actionable information. Value (Datta *et al*, 2003) of information[21] is a complicated metric yet it may be the only highly relevant KPI for ROI (return on investment).

Digital duplicates, digital proxies, digital twins, digital cousins may be useful depending on the context of the application. The terms are synonymous and semantic differences may be significant but scenario-specificity and data-centricity are equally important. Digital twin is an umbrella term within the universal set of digital transformation where "twining" is a quagmire of amorphous metaphors applicable at various levels of sophistication (see Figures 1a, 1b and 1c).

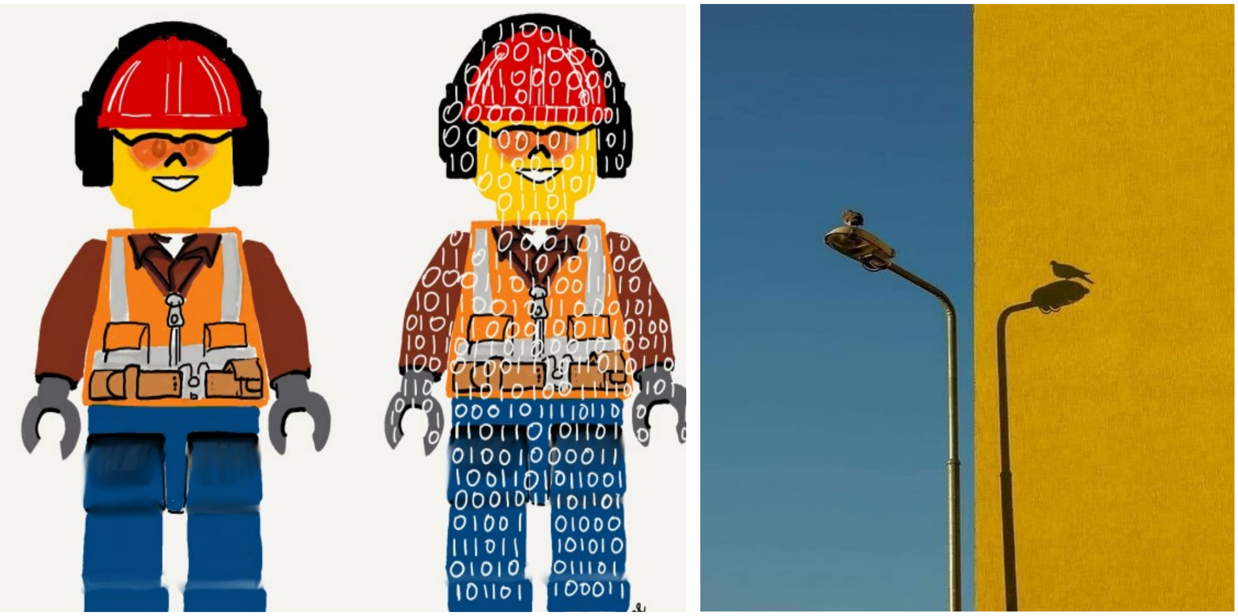


Figure 1a: Ideas and degrees of "twining" may vary but by reducing conceptual barriers we may be able to accelerate the adoption cycle, at least in principle. Both cartoons are "twins" of some sort but cartoon on the left[22] illustrates the canonical idea of digital twins. The cartoon on the right[23] highlights the pain inflicted due to unethical globalization, aggression and war crimes.

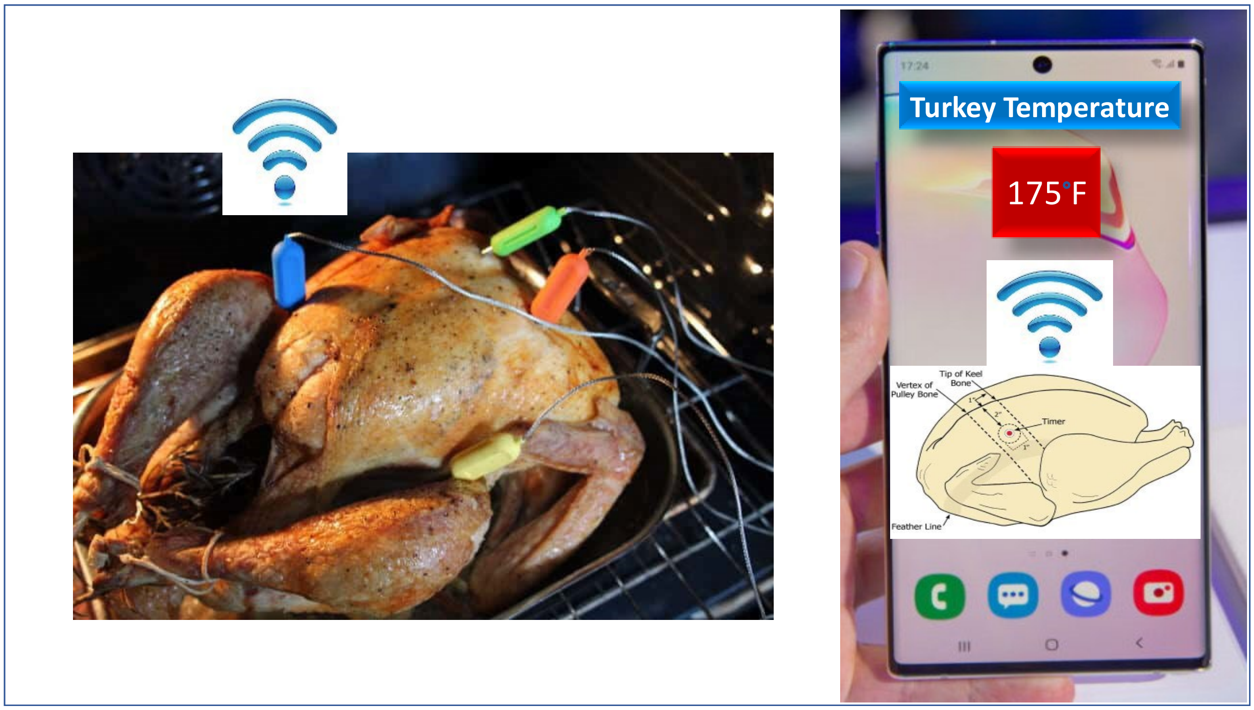


Figure 1b: In some instances it may appear that certain practices are loosely based on the idea or principle of digital twins but without the moniker. The "digital" representation of the turkey in the oven is delivering the on-demand functionality, i.e., the temperature of the turkey in the oven.

Figure 1c: Real vs virtual representation[24] of the train is devoid of new technology. It is a GUI illustrating the wireframe of an actual object to display data from hardware, using software.

INTRODUCTION

Enhanced diffusion of the digital-by-design metaphor may lift many boats including that of digital twins, cyberphysical systems[25] (CPS) and internet of things (IoT) in the networked[26] physical world system. These terms have evolved asynchronoulsy when engineering excellence spawned new ideas. On closer analysis[27] common grounds, relationships and interdependencies were identified between these systems (terms). What appears to get lost is the fact that these and other related ideas are "new improvizations" based on a bedrock of just a few core elements.

The foundation for all these systems and categories of systems are built on the pillars of *connectivity, data,* and *analytics*. Irrespective of how we view the organization of the cyber and physical components, all of these systems and sub-systems are inextricably linked with network of bridges built on a trinity of pillars (connectivity, data, analytics). The quintessential glue that binds these elements is made of ***context*** and ***causality***[28]. Without context of causal relationship these pillars and bridges will collapse because dependencies (*not correlations*) are salient to making sense from (uncorrupted) data. Semantics is germane to extracting information from data and it is at the core of *analytics* even if and even *when things start to think*[29].

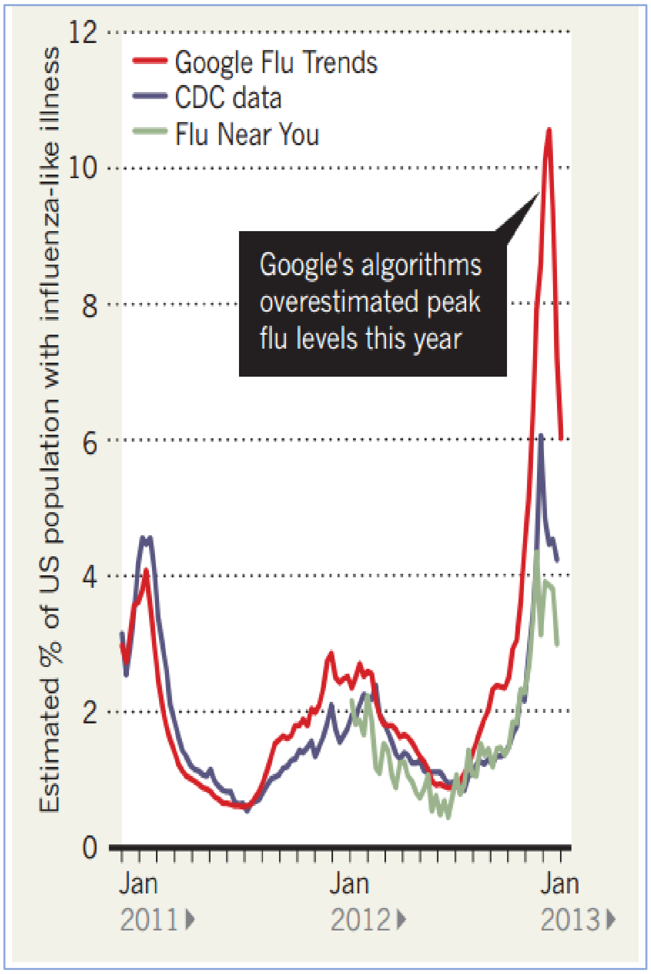
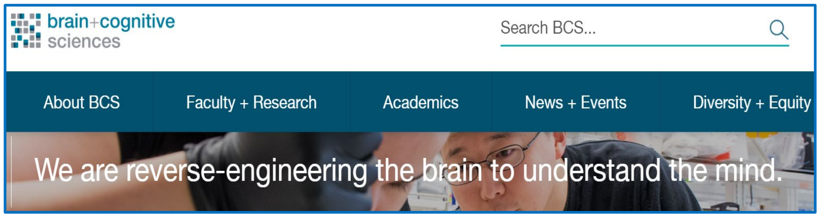


Figure 2: Corporate arrogance, lack of analytical domain insight and the hubris of so-called "big data" both were flogged in the hands of context/relevance. Google got flu wrong[30] was not a single event in 2013. Google Flu Trend (GFT) was quite consistently wrong since 2008-2009[31] but wasn't corrected due to vanity, conceit & ego. Small data, good data[32], contextual data are crucibles for credible outcomes. Corrupting or amplifying data using any callous tool[33] *without understanding the context* appears to generate papers, tenure and conference keynotes. In reality these tools and techniques could compromise patient safety[34], morbidity and mortality. Very slight changes in data due to data selection and data sampling errors may have cumulative effects (time series data) when aggregated (corrupted?) data is used at a different point/instance of use to generate incorrect decision or improper diagnosis (please see Figures 28 and 29).



We are reverse-engineering the brain to understand the mind.

Figure 3a: Causality: Photo[35] featuring Annie Boots (*Felis catus*[36]) implying correlation is not causation (lack of correlation need not imply lack of causality[37]). Chest-thumping academics, “billable hour” consultants and willy-nilly proponents have failed to assimilate the central role of causality with respect to data. In the clamor to embrace fake “artificial intelligence” in so-called AI (lacks intelligence[38]) the marketing forces buried the fact that programming is devoid of causality[39] and cognition[40]. Exploring[41] thoughts[42] and ideas[43] about cognition is essential. But, cheap irrational exuberance (“reverse” engineer[44] “the brain to understand the mind”) is blasphemous and and fuels degrading sensationalism which manifests as fake news, disinformation and foments the insidious underbelly of society. Artificial intelligence models, especially AI language models are *notorious*[45] *bullshitters*[46] (*quote*, Heikkilä, 2023) presenting falsehoods as facts. They are excellent at predicting the next word in a sentence because they use nearest neighbor search (which dates back to the 11th Century[47]). AI models have no knowledge of what the sentence actually means (semantics). The failure[48] to launch the semantic web[49] shows how difficult it is to represent semantics through programming languages because knowledge representation[50] with ontologies is a profound challenge which remains sorely[51] unaccomplished[52] due to the fact that real entities (as used by humans) resists mapping onto mathematically-sound hierarchies[53] for binary systems which run computation. AI code[54] and AI models are devoid of causality, cognition, and semantics - hence - incredibly feeble even as a toy, and too dangerous to trust as a tool, to be combined with logic and search - where it is crucial to obtain the unvarnished facts straight, e.g., point-of-care emergency nurse or doctor or a mission critical operator (for power generation infrastructure or energy distribution). AI is weirdly[55] entertaining if browsing with an AI-fueled search engine what not to watch on Netflix, while gorging on buckets of KFC.

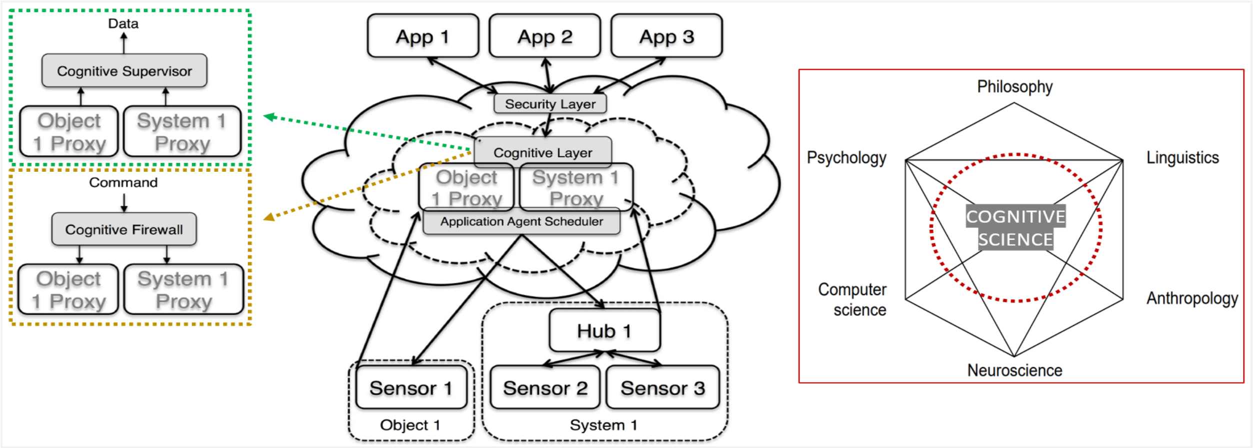


Figure 3b: Cognition: Is the cognitive[56] layer in the cartoon (center) representative of cognition, in its scientific perspective? Amorphous convergence of six august[57] disciplines[58] (right) may be involved in *cognitive science*. Cognitive patterns in the mind[59] are difficult to distill in discrete units for cognitive engines in any tool, software or agent based system, at the current level of our knowledge. Cognition in our vernacular oozes out of marketing[60] where brand imagery[61] (for all visual thinkers), allusion and possession are goals set by the sales department. Cognition in any tool is just akin to instructions but simple words are an anathema for glib marketing. Cognition conveys a far-reaching mystic aura, tangential to science but with an opulence of allure. It may be similar to marketing "intelligence" in AI (artificial intelligence) which bears little semblance to what constitutes the *scientific* nature of intelligence (a real enigma). DNA is an acronym which make scientists squirm with agony when it is used savagely by ignorant peddlers[62] for marketing (unrelated to the *science* of DNA). Every mention of timeless[63] beauty, time travel[64] and *time*[65] *frozen on the ladder of life* are decorative social expressions for advertisement and Hallmark greetings card but has nothing to do with physics or science of time. Albert Einstein was sitting up in his grave with the heretic publication (unfit even for slimy tabloids) claiming that a certain corporation reversed time[66] (***no***, they did not[67]). Capturing cognition in a few logic layers with values and ranges using "if this, then that" type of reasoning is as far as the *practice* of cognition may proceed, as a veneer. Tools based on the *science of cognition* are aspirational.

SOURCE OF DATA

The digital twin umbrella (CPS[68], IoT[69], industrial IoT[70], interplanetary IoT[71]) and other emerging proxy systems are scientific/engineetring manifestations of case-specific contextual interpretations aspiring to understand/unleash/reveal the meaning/value of operational data[72] [59a-59d]. The latter guides connectivity (what must be connected), identity of data nodes or sources and what information of value (i.e., actionable) can be extracted from data analytics (either alone or combining different results e.g. data fusion informed by causality, not cognition). Connectivity, data and analytics with respect to context are primordial layers for almost any decision science. A fitting analogy may be the geology of the base layer[73] of the Grand Canyon referred to as *Brahma, Vishnu and Rama schist*[74] (mythological creators of the world).

Almost all aspects of being digital[75] and the digital by design metaphor is governed by connectivity, data, analytics and context (ACDC). The contextual/causal digital thread runs through the fabric of digital transformation, as data, from various events/instances in/of the networked physical world. Relational semantics between data and information is still far from formulation but context is not optional in transforming data into information. The processes are human designed, human coded, human implemented, with no room for artificial intelligence[76].

Acquisition of data or percepts (**P**) from systems, environments (**E**) and operations are possible, if connected. Sources of data include a plethora of monitoring tools e.g., sensors (**S**). Making sense of data and extracting information of value from data (***if*** there is information in the data) is the performance driver for the "response" phase which includes information-informed (or data-informed) decision support (for humans-in-the-loop) or may involve autonomous and/or semi-autonomous actuation (**A**). Data from the post-actuation cycle (i.e., "feedback"[77] or "feed-forward"[78] controls[79]) may be pivotal for dynamic systems seeking to re-inform, re-optimize and re-evaluate the nature/quality/timing of the next response (albeit in an "ideal" scenario).

PEAS[80] is a mnemonic borrowed from agent-based systems which aims to address systems performance through convergence of percepts, environment, actuators, sensors. It may share common grounds with the OODA[81] loop (observe, orient, decide, act). PEAS and OODA contribute to advance DIKW (data, information, knowledge, wisdom), which begins with the core elements (connectivity, data, analytics) and includes data fusion[82] if contextually relevant.

Taken together, connectivity, data, and analytics plus versions of *case-specific* PEAS and OODA appears to be a smörgåsbord of interlocking and/or shared principles which when titrated may better inform the common practice of constrained optimization (but not always).

Optimization may influence the outcome or performance or prediction of anticipated performance. Productivity may depend on performance. Economies depend on productivity. Pursuit of globalization and development depends on the economy. By association, it follows that ethical progress of civilization may be ultimately guided by connected data (i.e., ACDC).

The causal significance of the trinity of connectivity, data and analytics (ACDC) may be compared with the philosophical trinity represented by *Brahma, Vishnu and Rama schists* at the base of the Grand Canyon. This mythological[83] analogy of *fundamentals* are quintessential layers relevant to *any context* of digital transformation including digital twins. (But, it is unnecessary to understand this analogy in order to grasp the significance of ACDC with respect to causality.)

Published literature (Jones, D. *et al,* 2020) and a review of various types of digital twins[84] [71a-71i] reveal a set of existing tools and technologies, integrated, re-configured and labelled as digital twins. Most models (are wrong but a few may be useful) of "digital twin technologies" are in engineering textbooks without any new "technology" that is distinct for digital twins (Table 1). These approaches face problems due to lack of standards or non-compliance with standards and challenges due to lack of interoperability between data and data distribution as well as information (databases) in multi-dimensional decision systems (service automation).

Table 1: Parameters that define the operation of digital twins are central to its design in terms of data acquisition (connectivity), integrity of the data and analytics performed on the data to obtain information. Publications appear to focus on models and architectures, which may be useful for development of standards. Systems integration is the commercial thrust. What is lacking from the discussion is the nature of the parameters (measurable factors) and the science of causality with respect to data. Data acquisition tools for systems integration are dumb as door-knobs but if the logic layer lacks the causal rational then how can we trust the value of information?

Digital Twins – focus, characteristics, approaches, tools and use of common technologies
Data-centricity[85]
Knowledge representation[86]
Physics-based system modelling and distributed real-time process data to generate a digital design of the system at the pre-production phase (engineering analysis capabilities)[87]
Standards[88]
Reference models[89]
Architecture[90]
Architecture (reference model for cloud-based cyber-physical systems)[91]
Architecture (data and simulation model for digital town)[92]
Architecture (Industry 4.0 services)[93]
Architecture (6-layer production system[94], 5-level CPS architecture[95] & L6 for simulation)
Sensing-as-a-Service[96]
Data architecture (for logistics[97] system)
Integrate real-time data processing (for logistics[98] system). Three component architecture: data acquisition, data processing, data visualization. Data acquisition: sensors, micro-controller, beacons (WLAN integrated with data processing). Data processing: SMACK (Spark, Mesos, Akka, Cassandra, Kafka) for distributed streaming big data. MQTT data broker Mosquitto and Java Spring Boot Framework for backend support. Components communicate with backend via representational state transfer (REST) API. Data visualization: KPIs & digital descriptions of physical objects on frontend e.g. Angular (component-based UI)

Deployment of digital twins ignores science and pursues existing systems integration tools and technologies based on established engineering principles. IoT and CPS are "A2B" (atoms[99] to bits[100]) design metaphors connecting atoms and/or bits with other atoms and/or bits. Implementation of IoT is no longer a scientific endeavor but connectivity in context of causality should ask the ***correct questions*** (a difficult task) to guide data acquisition (data of objects, data from processes). Actionable information from data analytics may strive to answer the questions.

The business of digital twins is deeply rooted in monetization of data where analytics is key. Creative analytics or innovative tools may make this space more valuable, if the analytical platform can make better sense of data and provide information in the semantic context of the use case (in real-time or near real-time before the value of the data/information perishes).

The context of deploying digital twins may be the nexus where science can also inform strategy rather than performance, alone. It is obvious but bears emphasis that science is necessary at every step since engineering is science-informed and technology is engineering-informed. By extension, almost every endeavor is based on or linked to science. However, most businesses suffer from myopia and makes every effort to prevent science from infecting their strategy and even may go as far as shunning scientists who may pollute their strategic management retreats.

Scientists on the other hand may make digital twins sound pompous to justify high-brow academic exercises by introducing complex models[101] with respect to performance optimization and predictive analytics. Enterprises are often averse to science infiltrating their mundane daily dose of traditional business packages, for example, manufacturing executions systems (MES), product lifecycle management (PLM), and supply chain management (SCM).

The push-pull between principles and practice may be better served with some degree of porosity between the two almost immiscible cultures. Creating industry-university partnerships (public private partnerships, PPP) are occasionally productive by informing scientists about the pragmatic needs of the corporate world and informing practitioners about science / engineering principles which may be amenable for pragmatic adoption in the business milieu.

Despite polarized perspectives, there is little doubt that uncorrupted contextual data from causal relationship is the most important lowest common denominator at the heart of any digital transformation, including digital twins, IoT, CPS. Acquisition of data is the central driver of the digital thread that runs through and connects almost all forms of digital transformation.

What types of data (parameters) are a part of the design for pragmatic applications of digital twins? What is the source of the data or the nature of causality between data sources?

Sensors are data sources for sensing changes (time series) in environments (temperature, vibration, lumens). In addition, data is acquired from automatic identification tools (for example, radio frequency identification, RFID) and positioning systems (local positioning systems, LPS and global positioning systems, GPS). From an engineering perspective, the field of sensors[102] in general and biosensors[103], in particular, include: electrochemical[104], thermal, piezoelectric, fiber optic, magnetic, pressure sensors, etc. Sensor engineering is focused on tools to capture and transmit the signal. Signal capture depends on material science, i.e., material medium of the sensor which reacts to or senses the stimuli and generates the signal for transduction.

SCIENCE BEHIND THE DATA (***not*** *data science*)

From a science perspective these different sensors are based on distinct fundamental units of activity and set of basic behaviors which are indicators of or "signals" the actions/reactions. If sensor data is deconstructed into its elemental form or sufficiently reduced, we observe patterns in signals based on units or models. Combinations of these models/units/patterns/elements can generate an almost unlimited variety of system behaviors (what we aim to sense and the signal we attempt to capture and then acquire in the form of sensor data from signal transduction).

In scientific terms, the observed manifestations are due to a few or a relatively small group of fundamental or universal 'truths' which are referred to as models, units, rules, logic, patterns, elements or behaviors (see Figure 2 in Datta *et al*, 2021[105]). These "truths" are not random behaviors whose entropy fluctuates with the degree of chaos. In physical sciences[106], large scale system behaviors can be reduced and mapped to simple models[107]. Combination of simple models, with widely different microscopic details, applies to, and generates, large set of possible system behaviors[108]. The perception of non-deterministic behavior (chaos) in human scales[109] may be explained by deterministic patterns of behavior in universal scales[110].

Sensor data in run-of-the-mill digital twins are often generated from waveform data (continuous streaming data) which are "sampled" as discrete data by human-specified time intervals in middleware (Figures 28 and 29). Continuous waveform data (raw data) may be computationally expensive to transmit (energy constraints, power consumption), collect, store and analyze. Streaming raw data may be plagued by errors introduced due to lack of suitable bandwidth, latency and jitter (inherent in telecommunications). Hence, continuous waveform data is converted to discrete data "points" and transmitted. The latter is the data "source" for the bulk of digital transformation scenarios which continues to evolve[111] as in-network[112] processing functions proceed from traditional (power, query, logic optimization[113]) to virtual machines[114].

The granularity of this time series data is adjusted by industry and businesses based on business logic and often without regard for science and engineering. However, this level of data acquisition is commonly acceptable for business applications where accuracy and precision are often viewed as "relative" terms and science, often, conjures images of a distant blackhole.

The physics of the waveform data make sensors amenable for continuous sensing or monitoring. This is crucial from an engineering perspective due to data flow, life cycle of the data stream and the physics of hysteresis[115] in devices (for example, thermostats for digital twins of buildings) where sensor reusability is key to performance optimization (for example, a digital twin for energy conservation). Waveforms are part of the natural radio frequency spectrum which are harnessed for applications by humans. The interruption, change (frequency, amplitude, phase), reflection, refraction in the radio frequency can be captured by a detector as a "variation from normal" due to "sensing" the phenomena we are trying to monitor (for example, *reflected* radio frequency[116] to monitor heart rhythm or respiration). The captured waveform[117] (raw) data may be compressed[118] as a discrete data[119] point for data analytics tools.

Digital twins which are able to source continuous waveform data are perhaps more reliable in terms of the digital representation of the parameter at the ground zero level of granularity. For example, temperature, pressure, light sensors detect waveforms and the primary data is in terms of waveform changes. The ***medium of the data*** is true waveform.

But for electrochemical sensors, as the name implies, the waveform medium is an ***indirect engineering tool*** created to capture and report the *data from a different medium* which is the primary trigger. In this case a chemical medium may be the source of the data. Changes triggered in the chemical medium where the primary activity occurs[120] induces a secondary change in the electrical circuit (conductance, capacitance, admittance) which is the waveform data capture by an electrochemical sensor (e.g., electrical impedance spectroscopy).

Electrochemistry may be viewed as a bridge between physics where ***waves*** are ubiquitous for transmission (radio frequency) vs biology (life) where ***molecules*** (***particles***) may be the dominant signal transducer (think de Broglie wave-particle duality[121] of the electron).

If digital twins can capture and represent this bridge between waves and molecules in terms of data, then, the field of digital transformation may be shaken and stirred. Is the key to that quantum leap rooted in sensing and sensors? In anything that is biological (living) ***binding*** of molecules act as a trigger and that data is vital to understanding status in biological systems. Once bound, molecules often are reluctant to dissociate. Lack of dissociation, or a very reduced dissociation rate, makes the sensor unusable for continuous monitoring purposes (opposite to that of motion sensors). Most sensors in this category may be single-use unless there is a scheme to regenerate the sensor (material / molecule for binding) and re-establish ground state (baseline).

The difficulty in capturing that binding is rooted in the definition of binding. When two molecules bind, it is a natural law that the binding is sufficiently stable for a time period, t, for an action/reaction to occur, as a part of the reaction kinetics. We need to ***identify molecular*** binding events with ***precision***, ***specificity*** and duration (that is, ***kinetics***, in biochemical terms). Identity, precision, specificity and kinetics must be measured. The “measure” of the molecular parameters must be ***transmitted***. Without data transmission (signal transduction) there cannot be any digital representation. The latter makes ***waves*** pivotal for acquisition of data from ***molecules***. Interaction between molecules (between ***atoms***) generates data (***bits***) as a record of that event. Cumulative data over time provides ***rate*** of reactions. Metric for kinetics as time series data is crucial to detect ***pattern(s) as signatures*** of change which we aim to detect (sense).

Connecting atoms to bits[122] is not a frivolous public relations vignette but the essence of *Being Digital* (Negroponte, 1999) and the Holy Grail of digital transformation, manufacturing[123] and digital twins. Connecting atoms to bits is not the end game, making sense of data is key to ***understanding the meaning*** of change. The value lies in analytics. Delivery of value to the end user in the form of actionable information is of paramount importance in order to profit from data (e.g., information as a service). Digital twins/cousins must embrace the rigor of science necessary to extract data from interactions at the nexus of physics, chemistry, biology and medicine which underlies/determines planetary[124] health, one health[125] and global safety.

DATA-DEFORMING STATISTICAL TOOLS EMBEDDED IN DIGITAL TWINS?

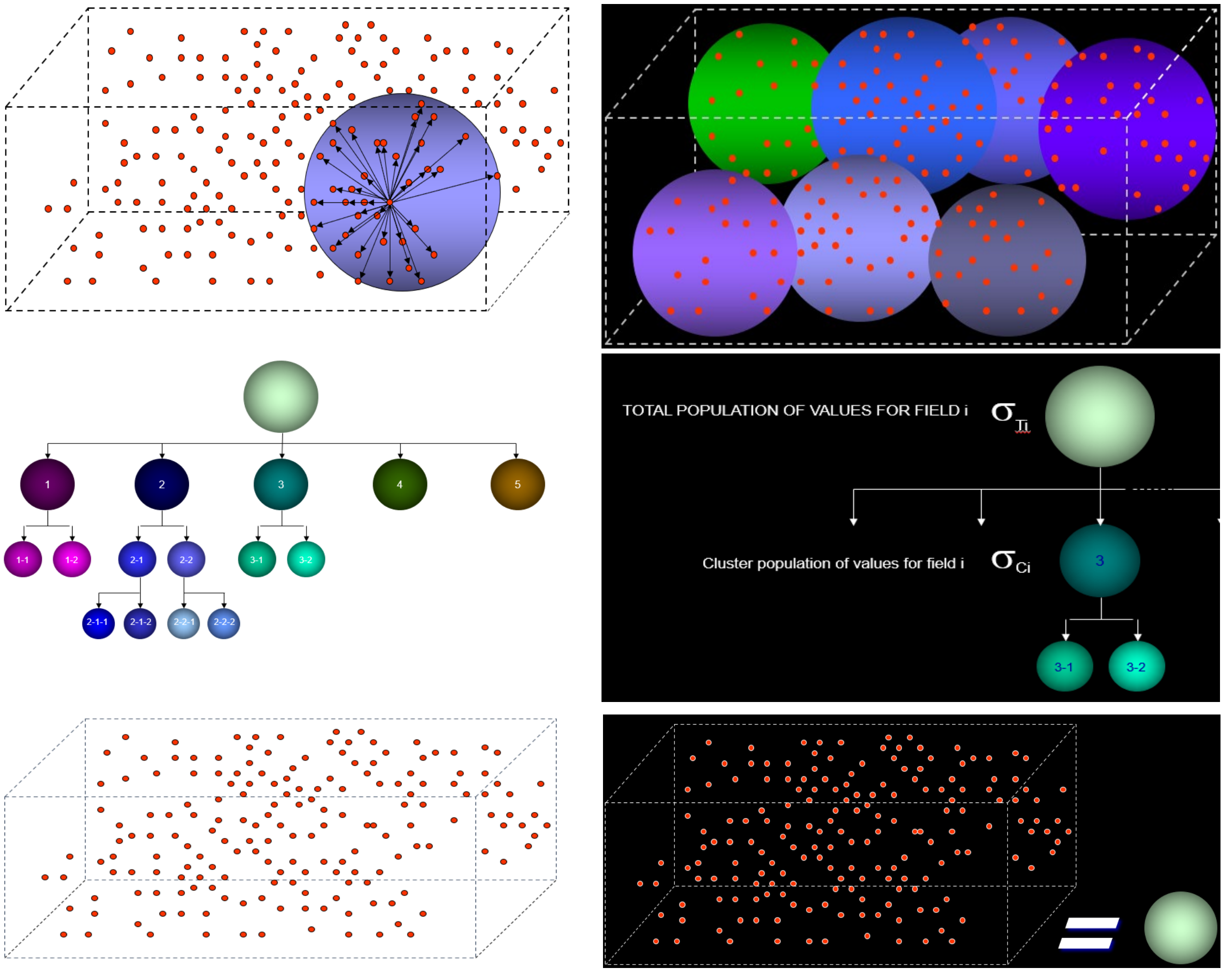
If connected data is the bedrock for advancing civilization, then the treatment of data and analysis must refrain from using techniques which tampers with the meaning and value of data. It is reasonable to assume that responsible and ethical scientists and data enthusiasts are unlikely to indulge in deliberate data manipulation using specific statistical tools to change, obfuscate, mask or modify the meaning of the data or subject it to statistical treatment in order to selectively "fit" pre-conceived models ("all models are approximations, and no model form can ever represent the truth absolutely"[126]) or *a priori* interpretations which are biased or conceals bias. Assumption of good faith may be patently incorrect if data is ingested by and subjected to machine learning tools where opaque "black box" operations are as much as a mystery as are cosmic blackholes. Even more damaging are the assumptions made by machine learning (ML) itself and the bias these assumptions may introduce. Perhaps the most debilitating of all assumptions is the one which assumes that all data (each data point) is an independent value (outcome). It may be partially true for some mechanical systems (fossil fuel source for power generation[127] versus composition of greenhouse gas emissions[128]) but ***almost always false*** for any biological system (where proportionality, dependencies and inter-relationships between events are the norm).

Uncompromising transparency about the treatment of raw data must be forthcoming from every nook and cranny (of the data network). Statistical tools are often implicated in "lying with statistics" (Huff, 1954) and over-fitting to models are often blamed (Box & Jenkins, 1970). But, this discussion should not be viewed as a criticism or denigration of statistics, rather a clarion call for informed judgement, ample caution and to seek wisdom (untainted by corporate greed) when perusing data, if one or more data-deforming statistical tools are implicated in the analysis.

The immense value[129] of statistics in data analysis[130] and statistical interpretations[131] cannot be over-emphasized. In the context of data science, the milestones over the past 50 years starts with Box-Jenkins ARMA/ARIMA (Box and Jenkins, 1970), fitting time-series model to lagged values of a time series. It is a perfect segue to 1970's Granger-Engle's ARCH/GARCH[132] error-correction applied to econometrics[133] (but not limited to econometrics[134]). 1970's also witnessed Stonebraker's insightful[135] INGRES[136] and later the post-INGRES (POSTGRES[137]). The trinity of ARMA/ARIMA, ARCH/GARCH, and relational INGRES/POSTGRES forms the foundational underpinning with respect to dealing with data[138]. (Hence, analysis of large volumes of data isn't "new" in the 21st century as implied by "big data" and other marketing gibberish. It was peddled by a few ephemeral pundits for self-aggrandizement and self-publicity[139]). Every tool is valuable in some context and possesses a statistically credible merit. For this discussion the usual suspects for potential data-deforming statistical techniques (some more, some less) include, but not limited to, the following few:

[i] Clustering
[ii] Bootstrapping (reinventing resampling to manufacture fake, synthetic data)
[iii] Winsorizing
[iv] Imputation
[v] Interpolation

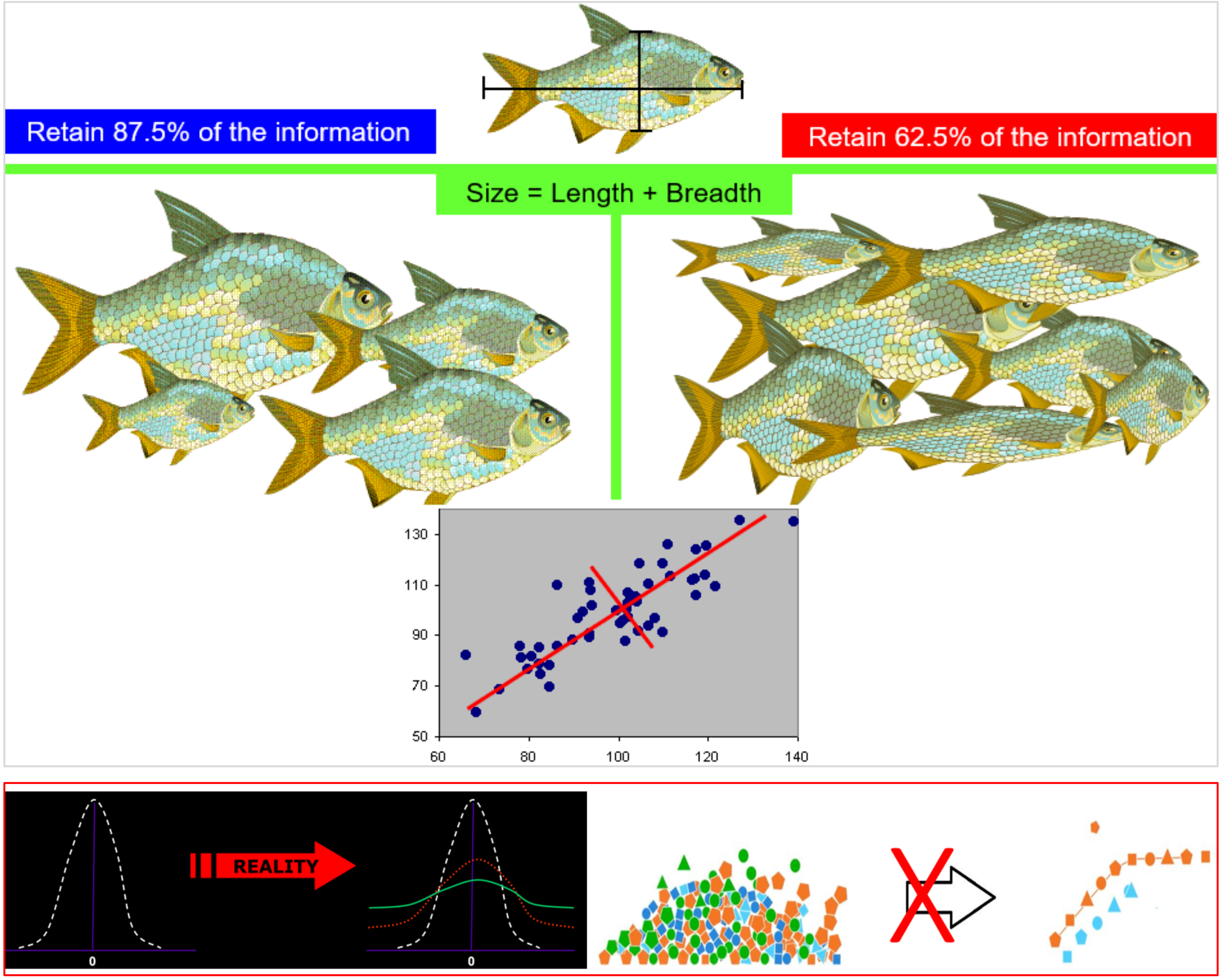
[i] Clustering



Cartoon 1a: Acquired raw data (bottom, L) is stripped of its characteristics, attributes, values and even meaning after clustering reduces it to a point value or field value (green circle; bottom, R).

Clustering is often mandatory for software packages ingesting high volume of raw data. Data or patterns of data are plotted in 'n' dimensional space. Each point in cartoon 1a (bottom, left panel) may represent multiple (n) pieces of information (data, patterns, dimensions, etc.). To begin the clustering process, distances are calculated to determine similarity (top, left panel). The choice of "distance" from a focal point may be entirely arbitrary. It follows that the cluster (top, left panel) is, therefore, an arbitrary grouping. The "family" of clusters (top, right) may contain a spread of data or data patterns, which loses its (individual) value due to this reductionist technique. The hierarchy of clustering (middle section, left panel) is an indication of granularity. The standard deviation ratio (calculated by dividing sigma C_i by sigma T_i) indicates how much a field (*i*) in a particular cluster varies in comparison to all clusters (middle section, right panel). If the standard deviation (sigma) ratio for a field is small (an arbitrary measure), the "field" value represents the cluster. The entire data set or pattern set may be denuded of its signal, significance and meaning by substituting the representative value for field "i" (green circle, bottom right) for the entire set.

True knowledge exists in knowing that you know nothing. [Socrates]

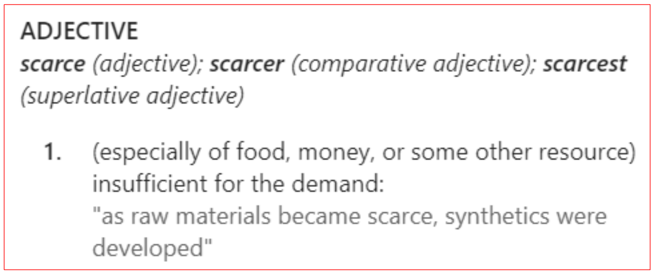


Cartoon 1b: Arbitrary measures in data software corrupts data, creates errors, generates artifacts. The trend is to bend data to fit normal distribution (bottom, left) but in reality it could be skewed with vastly different error terms and distribution of error (which may be farthest from "normal"). Data wrangling ignores/expunges subtle and not-so-subtle significance often cryptic in raw data to make data handling[140] easier (bottom, right) but may remain oblivious of potential "signature" points in occasional outliers which are often forerunners of events or antecedent instances.

There is no *one-size-fits-all* in reality but off-the-shelf data analytics software may often use simple templates (e.g., size = length + breadth) to deal with data deluge, irrespective of the features in the data. These processing steps erase information from data and ignore outliers. The latter may help to predict emerging or imminent change. Lost information significantly decreases the expected value from analytics, potentially may result in decreasing profitability and may be dangerous if the data is linked to or indirectly feeds mission-critical decision systems. Traditional homoscedastic data distribution may be far from reality, where heteroscedasticity is the norm.

[ii] Bootstrapping – Reinventing Resampling to Manufacturing Fake, Synthetic Data

“As raw materials became scarce, synthetics were developed” is *scarce* - by definition. When data was scarce (low volume), bootstrapping was created as a resampling[141] tool which copied segments of data and then replicated the copies (similar to block printing) to generate the illusion of high volume data (by repeating the process 1,000 or 10,000 times). Resampling was reinvented to manufacture fake data which is euphemistically marketed as “synthetic” data. The latter appears to have originated, most fittingly, from the financial sector (derivatives pricing[142]).



ADJECTIVE

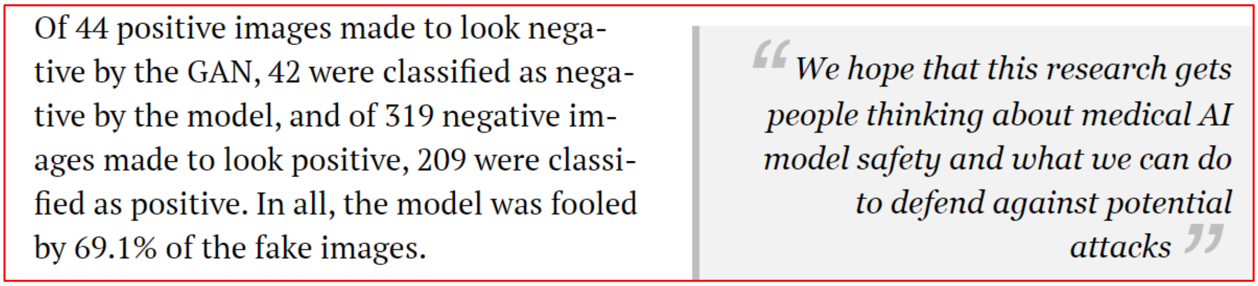
scarce *(adjective);* ***scarcer*** *(comparative adjective);* ***scarcest*** *(superlative adjective)*

1. (especially of food, money, or some other resource) insufficient for the demand:
   "as raw materials became scarce, synthetics were developed"

Bootstrapped fake synthetic data are copies (not real) of data where the two ***cardinal*** assumptions are that the data is independent and identically distributed (IID). What happens when we analyze data over time? Data collected over time, that is, time series data, is serially correlated and ***is not (cannot be) independent and identically distributed*** due to its very nature. The bootstrappers alternative to making “fakes” for time series data adds insult to injury by creating moving block bootstrap (MBB) and circular block bootstrap (CBB) tools to further advance fake data synthesis which aims to hide the process through obfuscation.

Fake synthetic data is used to train models, e.g., machine learning (ML) models, so-called artificial intelligence models (using artificial neural networks [ANN], convolutional neural networks [CNN], recurrent neural networks [RNN], very shallow deep learning [DL] models).

Imagine the outcome/performance of testing these models? When using a subset of the fake training data as a test or challenge, the performance/outcome, of course, is absolutely stellar. In the real world, the performance of bootstrapped synthetic data trained systems cannot be trusted except for trivial tasks, for example, returning the correct amount of change in a grocery store (if stores accept cash and if customers are using cash). In the face of complex challenges or cyber-attacks the “deep fake” systems are likely to perish. GAN (general adversarial network) created images[143] (see below, from Zhou *et al*, 2021) will fool the models trained on synthetic data.



Of 44 positive images made to look negative by the GAN, 42 were classified as negative by the model, and of 319 negative images made to look positive, 209 were classified as positive. In all, the model was fooled by 69.1% of the fake images.

> *“We hope that this research gets people thinking about medical AI model safety and what we can do to defend against potential attacks”*

[iii] Winsorizing

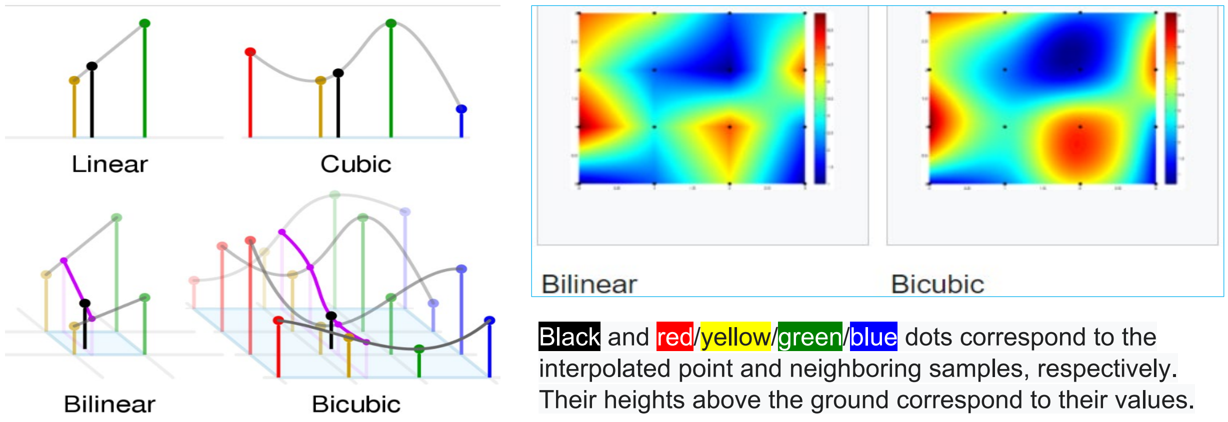
Censoring data by limiting extreme values or outliers (winsorization[144]) has a role in statistical treatment in certain fields but probably not in others, for example, healthcare. In the latter, outliers are often potential signals for prognosis. A winsorized estimator could be a source of error because extreme values are replaced by certain percentiles (unintentional introduction of artifacts and/or bias). Even worse is trimming or truncation, where extreme values are discarded.

[iv] Imputation

Replacing missing data[145] with substituted values[146] invites errors and data selection bias. Yet it appears to be in robust use[147] in different[148] domains with interesting outcomes[149] despite usual concerns about integrity of data.

[v] Interpolation

It is a type of estimation or approximation (replete with mathematical rigor[150] which dates back to the 7th century[151]). Interpolation aims to find new data (points) based on the range of a discrete set of known data points (finding data points outside the range of known data points is known as extrapolation, which is error prone and is often *art* rather than science or statistics).



Black and red/yellow/green/blue dots correspond to the interpolated point and neighboring samples, respectively. Their heights above the ground correspond to their values.

Cartoon 2: Multivariate Interpolation[152] of Waveform Data (for example, electrocardiography): Is it a concern? If digital filtering techniques are applied to waveform data during digital signal processing (DSP), could it involve bilinear and/or bicubic interpolation? Are the apparent differences between the bilinear and bicubic representations (right panel) in any shape or form influence the sampled data? Can it affect interpretation of the electrocardiograph waveform data?

Data from gun violence in the US[153] suggests that *living is a dying art*, especially without any penal consequences for the perpetrators and their protagonists. In the anti-parallel world of corporate sponsored ChatGPT[154], data fabrication makes *lying a living art* but with preventable consequences ("if we knew ahead of time, we could have tried to prevent it from happening"[155]).

SCIENCE OF CAUSALITY ERODED BY THE TSUNAMI OF DATA

Ubiquity of sensors (among other things) is increasing data volume but what about information in the data? Is it boosting productivity? A plethora of sensor types[156] (not only electrochemical sensors) and sensor engineering based on specificity of the context (application environment) may offer insight and/or novel perspectives and opportunities. It is also fraught with major challenges, for example, when analytics ignored causal relationships, but remained unresolved during the design phase of process engineering with respect to data acquisition.

Transmitting data from sensors (wired or wireless) may depend on telecommunication protocols, global standards, software and hardware already in commercial use. But just because sensors are available and/or data can be transmitted does not mean that data or digital twins are a panacea[157] or that it can be used for anything and everything including sensationalism[158].

In the 20th century the design of data acquisition and analysis commenced by asking the "correct" questions, first. Brainstorming sessions reviewed the questions and deconstructed-reconstructed the analysis as a series of questions. Then teams debated the data necessary (to be collected or acquired or sourced) to prove/disprove the *content* of the questions based on *causal relationships* in context of the primary problem(s). Data design was rationally informed by contributing mathematicians and statisticians operating within scientific principles of causality. Data analysis was mathematically rigorous but also used statistical techniques[159] followed by visualization[160]. Design of data acquisition paid attention to veracity and integrity of data.

In the 21st century with the advent of mass media "data" we now collect/store/source even polluted, corrupted as well as irrational and often worthless data in the name of "big data" in data lakes, swamps and dumps. Making sense of the khichuri (by "data scientists") does not start with questions (forget the concept of "correct" questions, first) but how to fit the data to models or "cook-up" models from data for monetization (review Figure 2) to amplify sales of artificial[161] stupidity[162]. In "data science" correct questions may be just an after-thought.

Stupidity in science and research is valuable[163] but can it be extended to data science? The few good ideas in digital twins must not be lost in this quagmire or in our attempt to provide definitions or create taxonomies. Digital twins will benefit from thoughtful granularity of data design embracing causality but on the other hand it may also flourish as a laissez-faire term for digital representations of physical entities. It may remain agnostic of how much more[164] or less[165] sophisticated it is as long as it delivers quantifiable value to facilitate viewing/observing events in near-real time for digital users. Caution may be prudent (see Figure 3) in interpretation of data and analysis based on context and causality. For example, in some form or the other primordial versions of digital dashboards for building management and energy efficiency came into existence since SCADA[166] appeared in practice and gained popularity over the past 25 years. Attempts to extrapolate these experiences to urban planning and indulging in the ill-conceived amorphous notion of "smart cities" is disquieting[167] but perhaps better than other types of indulgences[168]. Science and its application[169] to human dignity[170] and social values "must always form the chief interest of all technical endeavors," we should never forget this in the midst of our debate, dissent, disagreement, comments, criticisms, "diagrams and equations."

DIGITAL TWINS FOR DIABETES: BLOOD GLUCOSE DATA VIEWED THROUGH THE LENS OF CAUSALITY

Causality in mechanical systems can be established by independence of data and data points but not readily in living systems. In other parallel worlds, data mining and/or pattern recognition (without formal causality) may reveal facts and/or artefacts of value. For example, non-obvious relationship awareness (NORA) evolved from risk[171] analysis, it was applied to vulnerable systems[172] and proved to be useful as a methodological framework for scenario tracking and intelligence collection for counter-terrorism[173] and analysis of terrorist networks[174].

Causality in biological systems cannot guarantee independence of data and/or data points. Living systems are system of systems which are inextricably intertwined, share dependencies and is a complex pattern of multi-level inter-relationships. The heart of this multi-dimensional push-pull balance is germane to the conscious and subconscious maintenance of homeostasis. Isolating an independent variable and an independent data point is reasonably impossible.

With this context, we begin our discussion on diabetes and its economic[175] as well as productivity impact from the global epidemic of type II diabetes mellitus[176]. The mortality and morbidity from undiagnosed type II diabetes mellitus (T2DM) is unknown but it includes 277,000 premature deaths attributed to diabetes in 2017 in US (cost of diagnosed diabetes was US$327 billion in 2017 in the US, alone). Hence, it may be worth exploring whether digital monitoring (individuals at risk due to diabetes) may help to improve quality of life and reduce healthcare costs. In other words, architecting a digital twin equivalent for monitoring diabetes.

The biotech industry reports executed by paid agents and for-profit consultants (carefully disguised as "scientific" papers) ooze with malfeasance, if probed beyond the title and if the list of authors and their affiliations are compared. These reports claim one commercial blood glucose monitoring system at a cost of EUR 50,000 to be "cost-effective" (in France[177], UK[178] and Australia[179]). This is an action comparable to the US sugar industry offering bribes[180] to Harvard scientists to publish lies about the risks of sugar consumption on heart disease[181].

To be worthy of our consideration, the digital monitoring digital twin equivalent for diabetes (may include type I and type II) must be feasible for home use in Asia and Africa, for example, in India and Nigeria[182]. The US-centric view of health digital twins is a definitive path to bankruptcy (62.1% of all US bankruptcies in 2007 were due to medical expenses[183]).

Science reveals that blood glucose concentration (milligrams per deciliter, mg/dl) is generally a good indicator of the status of diabetes (type I and II). The causal relationship between blood glucose level and the "status of diabetes" is historically[184] documented. Elevated levels of blood glucose levels may be recorded after intake of sugar/carbohydrate-rich food but levels should return to 80-120 mg/dl for non-diabetic adults within two hours. The persistence of blood glucose values above this range (hyperglycemia) is viewed as diabetes. The status of diabetes (*not the **etiology** of diabetes*), therefore, may be extrapolated with confidence from the data obtained by monitoring blood glucose concentration. This data is based on robust causal relationship. The use of this data in a digital twin for diabetes (or any other form of digital representation) offers value for healthcare and precision treatment to improve quality of life.

It is critical to recognize that data from blood glucose level may be linked to several different etiologies[185] but the ***outcome*** of most etiological conditions converge to increase or decrease[186] only ***one data*** parameter - blood glucose concentration. The change in the value of this data (range 80-120 mg/dl) is indicative of hypoglycemia (consistently <80 mg/dl) or hyperglycemia (consistently >120 mg/dl). Hence, this parameter (blood glucose concentration) has a ***defined causal relationship*** and the veracity of this data, if reliable, is of diagnostic value.

The idea of a digital twin for diabetes (DtD) is supported by the clarity of causality with respect to the data (acquired to inform the medical status of the individual). Diffusion of DtD may be a boon for society but may face political suppression by "big" pharma because it may reduce sales[187] of diabetes medication. Transparency from continuous monitoring of blood glucose concentration will expose the march of unreason[188] to justify over-medication. Sales of medication is the commercial[189] reason to lower[190] the range to ***"create"*** more "diabetic" (label) individuals. Physicians, legally, must prescribe medication based on blood tests (e.g., HbA1c[191]). Digital monitoring and digital representation may unleash the individual's *time series data* to enable precision medication, adjusted for individual need, to better alleviate health conditions.

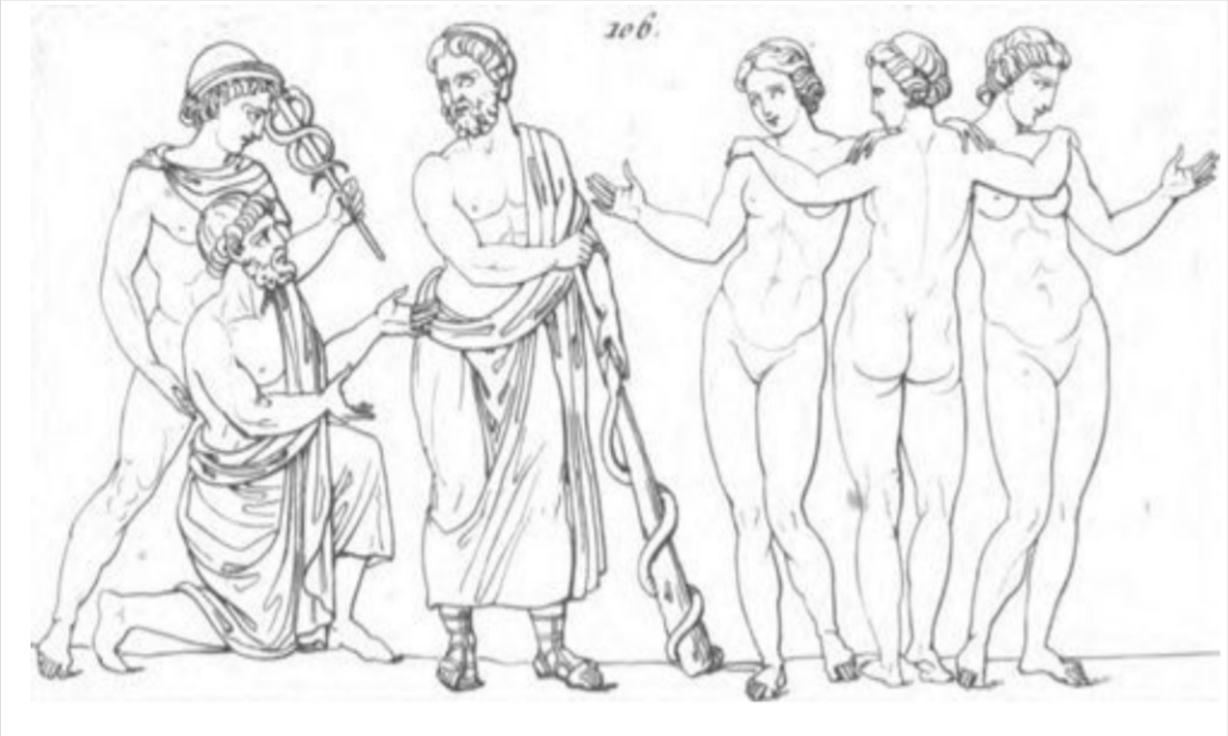


Figure 4: Asclepius, the god of healing and his three daughters, Meditrina (medicine), Hygieia (hygiene), and Panacea (healing). The staff and single snake of Asclepius should not be confused with the twin snakes and caduceus of Hermes, the deified trickster and god of commerce, who is viewed with disdain (Figure 1.1[192]). Plate from Aubin L. Millin, Galerie Mythologique (1811)[193]

The "diabetes pandemic" has moved ahead of the *silent epidemic*[194] phase and perhaps more catastrophic[195] in the long run compared to the social upheaval due to CoVID pandemic[196]. Estimating blood glucose concentration, over time (time series data) may be helpful in analysis of the pre-diabetic state in individuals and control of diabetes in patients, at home.

In the 21st century, there is nothing to crow about a digital representation in software (DtD) with non-invasive[197] blood glucose[198] data monitoring[199]. Health data collection profile may also include oxygenation (pulse oximetry SpO_2) and data from photoplethysmography[200] including hemoglobin[201] and blood pressure[202]. These few parameters along with body mass index (BMI) and other health history may suffice to offer individuals remote guidance, e.g., with respect to diabetes (without the cost incurred if visiting a clinic). This simplified scenario of mobile retail health is applicable to countries with national health systems and where health is not a wealth creation platform for salesmen, medical professionals and insurance behemoths. This suggestion (Figure 5) *in lieu of digital twins* may be useful worldwide but excludes USA[203] and India. The latter appears to be aggressively pursuing[204] for-profit healthcare business.

Figure 5: Palm[205] or finger[206] biometric photoplethysmography[207] in retail shops, grocery stores, shopping malls, petrol pumps, etc., can record blood glucose levels, SpO_2, hemoglobin, blood pressure, respiratory rate[208], heart rate[209] (pulse), body temperature and bone density[210] (with additional[211] tools) for a compendium of vital[212] signs (key physiological indicators, **KPI**). The biometric id and time stamped individualized time series data is sent to the user's mobile phone, designated physicians, hospitals and any authorized entity (family). Children in schools, students in universities, employees in work-places and customers in restaurants can choose to record their vital data agnostic of age. Instruments placed in community centers, primary care or convenience stores can serve citizens. Granular data over time is a digital treasure trove for personalized medicine, if needed. Anonymized data collected by health groups can map zip codes where help is necessary. Data-informed evidence-based policies can improve local and national governance. Data from sewers (wastewater, sanitation) may be integrated with crowd-sourced medical data to begin to build the epidemiologic tools to aid precision public health prevention and control.

DIGITAL TWINS FOR COMPLEX EVENTS: CARDIOVASCULAR DISEASES (CVD)

Cardiovascular disease (CVD) risk factors include hypertension, hypercholesterolemia[213], dyslipidemia, atherosclerosis, obesity, tobacco use, and elevated hemoglobin A1c (diabetes). Independently or in combination they contribute to stroke[214] and other CVD including[215] congestive heart failure (CHF[216]), myocardial infarction (MI), stroke, pulmonary embolism, cardiopulmonary arrest (cardiac arrest), peripheral artery disease (PAD), atrial fibrillation, and angina pectoris[217] (chest pain). Taken together, cardiovascular dysfunction is the number one cause of death (~18 million deaths in 2017, almost ***one-third of all deaths, globally***[218]).

After SARS-CoV-2[219] infection (CoVID-19 pandemic) patients (some with pre-existing CVD) experienced acute respiratory distress syndrome (ARDS), venous thromboembolism (VTE), acute myocardial infarction (AMI), and acute heart failure (AHF). In addition, with or without pre-existing co-morbidities, few patients also experienced SARS-CoV-2 induced[220] myocarditis[221] (inflammation of heart muscle) and pericarditis (inflammation of outer lining of the heart) which presented symptoms of (but not limited to) angina (chest pain), tachycardia and/or arrhythmia (heart palpitations) and dyspnea (shortness of breath).

If pursued, *stratified* molecular epidemiological analysis in the post-pandemic era of CoVID-19 may reveal an even greater share of global deaths directly or indirectly due to CVD or complications resulting from CVD (for example, chronic kidney disease and increased mortality due to ESRD, end-stage renal disease[222]). These multi-factorial complications will be further confounded by factors based on individual genetics, immunological functions, nutritional status and other known (drug use[223], contra-indications from prescribed medications, basal metabolic rate, body mass index[224], diet, stress, lifestyle[225]) or unknown or yet unidentified determinants.

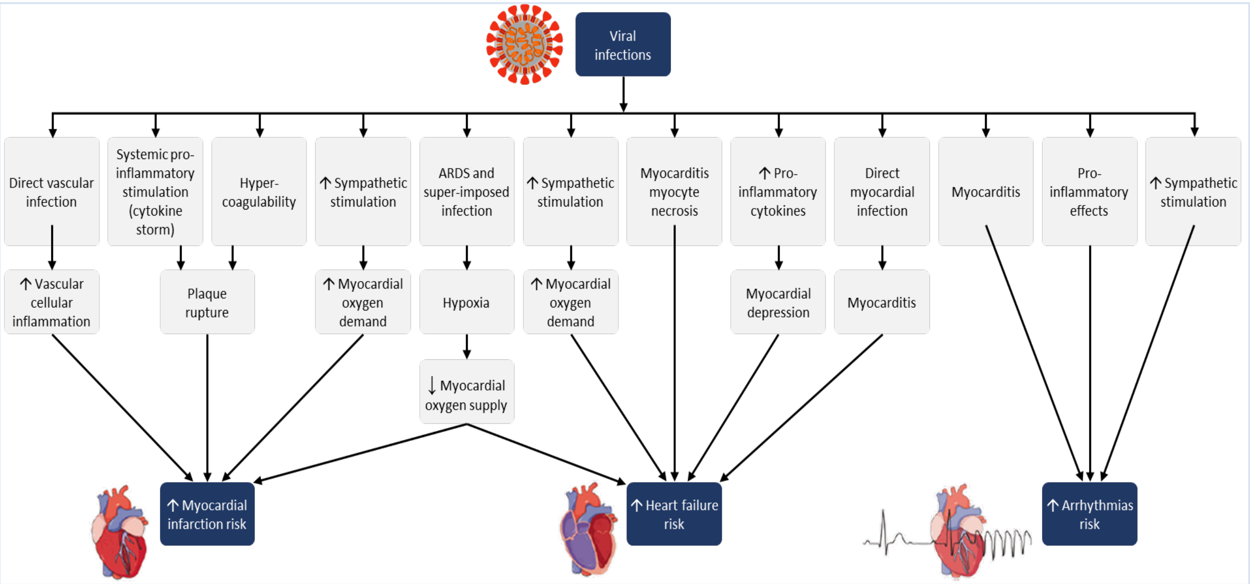


Figure 6: Post-pandemic incidents of CVD are increasing due to multi-factorial confounding[226] reasons which makes it difficult to make predictions of risk based on bio-markers. An estimated 3.39 billion[227] (of the 8 billion global population) were infected with SARS-CoV-2 (2020-2021).

There is a need for additional focus on CVD at a granular level to detect changes before they reach levels where it becomes an acute care or emergency medicine statistic. Figure 6 indicates the cross-linked complexity due to viral myocarditis without accounting for pre-existing co-morbidities or patient-specific genomic/metabolomic constitution or behaviors[228].

Even before the pandemic, groups were keen to propose digital twins for cardiovascular health (for example, very poor attempt at detection of stroke[229] due to silent ischemia). The urge to *model* ***precision*** *cardiology*[230] for digital twins using AI (applications of incredibly shallow artificial intelligence) decision support to solve precision human-specific problems may be an example of FOMO (*fear of missing out*[231]). In an ideal utopian world where data, information and knowledge about CVD is complete and computable, it could be worthwhile to consider designing a *sub-segment* of CVD using digital representation of data from electrophysiology and bio-markers for individual-specific CVD digital twins, under supervision (humans-in-the-loop).

Bio-markers	Pathophysiology (AMI, AHF, CHF)	Clinical Value
hs-cTn	Myocardial injury	P - D - RS - TG
BNP/NT-proBNP	Myocyte stretch Inflammation, Oxidative stress	P - D - RS - TG - TT
Copeptin	Inflammation, Oxidative Stress	P - D
CRP, sCD40L	Inflammation	P
IL-6	Inflammation, Hypertrophy/fibrosis	P - D - RS
Gal-3	Hypertrophy/fibrosis, Myocardial injury	P - TG
ESM-1	Endothelial dysfunction, Hypertrophy/fibrosis	P - RS
cMyC	Endothelial dysfunction	D
hFABP	Myocardial injury	D
ST-2	Myocardial injury	P - TG - RS
TREML, PAPP-A	Myocardial injury	P
miRNA	Oxidative stress	P - D
lncRNA	Inflammation	P
SIRT, GDF-15	Apoptosis	P
MPV, cys-C		P

Table 2: Acute MI and heart failure (CHF, AHF) bio-markers[232]: Prognostic [P]; Diagnostic [D]; Risk Stratification [RS]; Therapeutic Guidance [TG]; Therapeutic Target [TT]. BNP: B-type natriuretic peptide; cMyC: cardiac myosin-binding protein C; CRP: C-reactive protein; cys-C: cystatin C; ESM-1: endothelial cell-specific molecule 1; Gal-3: galectin-3; GDF-15: growth-differentiation factor-15; hFABP: heart-type fatty acid binding protein; hs-cTn: high-sensitivity troponin; IL-6: interleukin-6; lncRNA: long noncoding RNA; miRNA: microRNA; MPV: mean platelet volume; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAPP-A: pregnancy-associated plasma protein-A; sCD40L: soluble CD40 ligand; SIRT: sirtuin; ST-2: suppression of tumorigenicity 2; TREML: triggering receptor expressed on myeloid cells.

The array of known[233] biomarkers (Table 2) for only a couple (myocardial infarction and heart failure) of the many dysfunctions that constitute cardiovascular diseases should drive home the tortuous complexity of cardiac physiology and biochemistry in CVD. Establishing causality with clarity in the context of known dependencies between these bio-markers (and their networks of biological activities) may not be taken lightly. "Cardio digital twins" in the context of CVD may be comparable to a kindergarten science fair project (Martinez-Velazquez, 2019).

It may be decades to biochemically ascertain how the profile of these and other bio-markers may change in individuals infected by SARS-CoV-2. Massive epidemiological studies may be required given that half the global population[234] are infected (through November 2021).

For example, B-type natriuretic peptide (brain natriuretic peptide, BNP) in patients with acute myocardial infarction (Table 2) showed statistically[235] significant[236] ($p< 0.001$) elevation (elevated BNP of 462.875 picogram per milliliter) compared to controls (BNP concentration of 35.356 pg/ml). Because viral myocarditis can cause acute myocardial infarction and acute heart failure, we may re-think medical decision[237] making and re-establish diagnostic criteria[238] for levels of BNP (bio-marker concentration) in the post-CoVID population.

In terms of data for digital representation or digital twins, are we certain what levels of BNP bio-marker may be suitable for prognosticating? In terms of the data, are we clear about the ranges we should choose to indicate "normal" level? In terms of data, should we use the same range in our analysis of BNP data from individuals who were, versus, who were not, infected by SARS-CoV-2? In terms of data, what error correction may be necessary if the analytical tool for BNP data analysis is used for individuals from sub-Saharan Africa (highest infection rate of 79.3%, that is, 79·3 per 100 were infected with SARS-CoV-2) versus individuals from Asia (southeast Asia, east Asia, and Oceania had the lowest infection rate of 13%, that is, 13 per 100 population was infected with SARS-CoV-2)?

More than 30 years after the discovery of BNP[239] and recognition of the significance of this vasoactive peptide (32 amino acids) in myocardial infarction (MI), only recently[240] we have started creating sensors[241] for hBNP-32. BNP is an excellent indicator as a bio-marker for MI because it is produced[242] in response to pressure overload in ventricles and increased stress on ventricular walls (the main etiology of myocardial infarction is a lack of oxygen supply causing acute ischemia of cardiac tissue). BNP under 100pg/ml is "normal" for all ages but >450pg/ml, >900pg/ml and >1800pg/ml indicates acute heart failure for 50 years and older, 50-75 years and over 75 years, respectively. Detection and sensing is clouded by the short circulation time of BNP (about 20 minutes). Rapid release and diffusion of hBNP-32 from injured cardiac tissue to blood increases the signature bio-marker level (but rarely exceeds 2ng/ml during acute heart failure). Pre-pro-BNP (108 amino acids) undergoes proteolytic cleavage to generate human BNP32 (77-108 residues, 32 amino acid vasoactive peptide[243]) and the amino terminal fragment NT-pro-BNP (residues 1-76 amino acids, lacks biological activity). NT-pro-BNP circulation time is ~1-2 hours and serves as the target for most clinical tests. NT-pro-BNP levels <125 pg/mL (under 74 years) and <450 pg/mL (over 75 years) are normal. NT-pro-BNP >450 pg/mL (under 50 years) and >900 pg/mL (over 50 years) indicates serious cardiac problems.

In terms of causality, hBNP-32 and NT-pro-BNP data is closely aligned with myocardial infarction (without other confounding factors, according to published reports). The narrow time windows makes "after the fact" data useless (highly perishable value of data). The detection level of pg/ml makes it a difficult metric for traditional sensors (LoD, limit of detection).

In response to stretch, atrial cardiocytes also synthesize and release (secreted from the right atrium) atrial natriuretic peptide (ANP[244]) but this 28 amino acid vasoactive hormone with a half-life of 2-5 minutes is not regarded as a general bio-marker in MI, CHF or other CVD. ANP has vasodilating properties[245] both in arteries and veins which improves hemodynamics in heart failure and alleviates hypertension. Non-competitive immunoradiometric assay (IRMA) or competitive immunoradiometric assay (radiometric immunoassay, RIA) are usual laboratory[246] procedures to estimate plasma levels of ANP (16.1 +/- 8.6 ng/l, 5.2 +/- 2.8 pmol/l) and BNP (8.6 +/- 8.2 ng/l, 2.5 +/- 2.4 pmol/l) to better inform clinical treatment of patients with MI/CHF/CVD.

Table 2 row 1 refers to high-sensitivity troponin[247] (hs-cTn) i.e., cardiac troponin I (cTnI inhibits interaction with myosin heads in the absence of sufficient calcium ions) and cardiac troponin T (cTnT attaches the troponin complex to the actin filament) are two of three proteins that form the troponin complex (ITC includes troponin C which acts as the calcium binding site and involved in regulation of contraction of skeletal muscles but also synthesized by cardiac muscles). Cardiac-specific isoform troponins I and T (produced only by cardiac muscles with a plasma half-life of ~2 hours) are established bio-markers of cardiomyocyte injury. Data from cTnI and cTnT must be included in any CVD clinical profile, must be analyzed to inform treatment, both in reality and virtually (e.g., for aspirational "cardio" flavored digital twins).

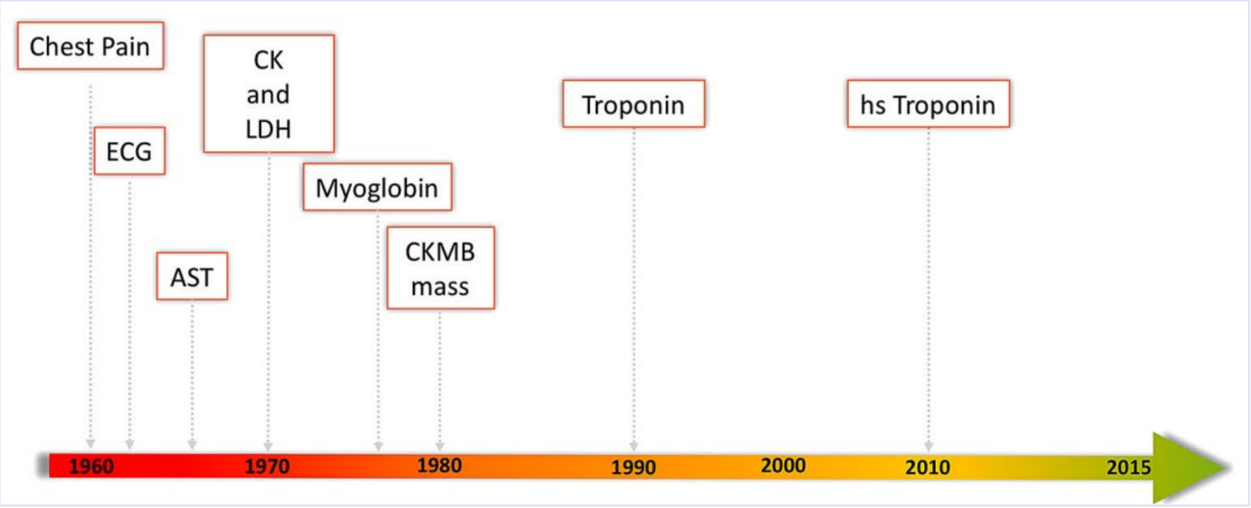
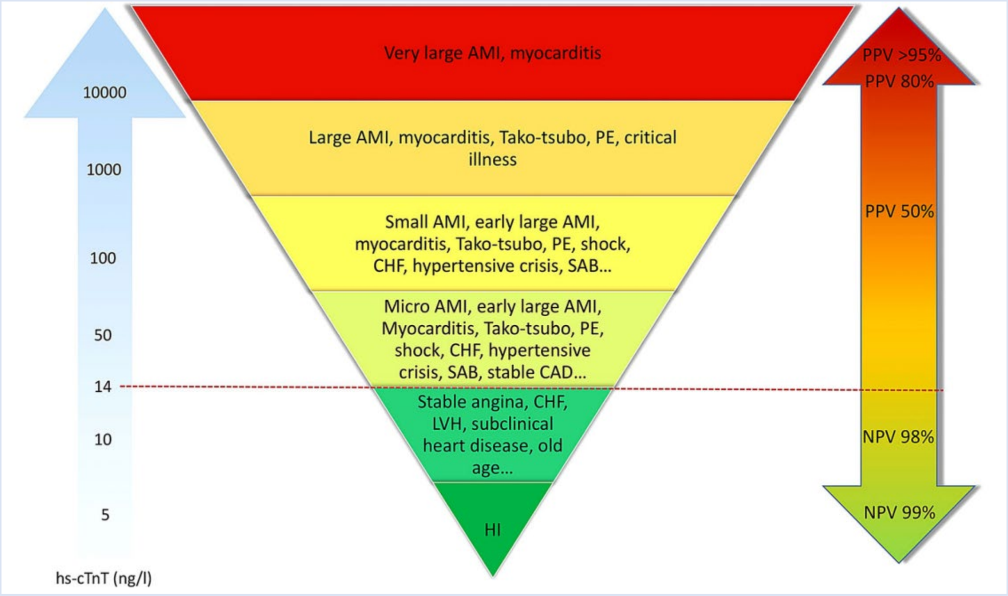
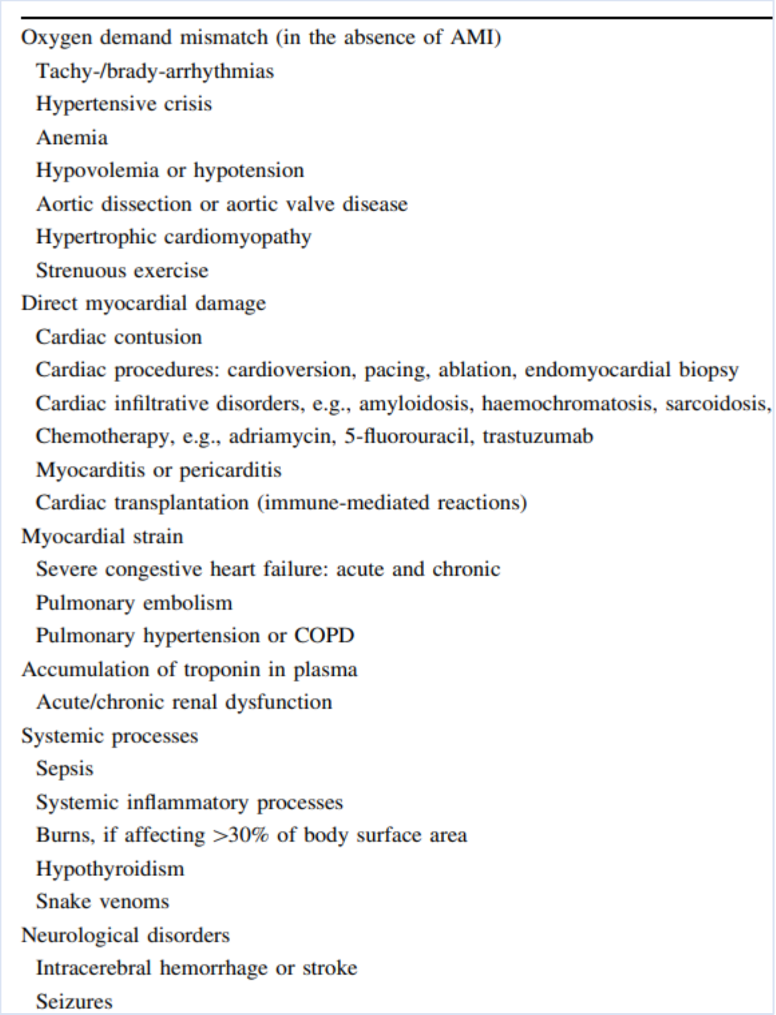


Figure 7A: Is there anything new[248]? Timeline of Troponin as a cardiac bio-marker for acute myocardial infarction[249]. ECG – ElectroCardioGram; AST – Aspartate Transaminase; CK – Creatine Kinase; LDH – Lactate DeHydrogenase; CKMB[250] – Creatine Kinase Myocardial Band; hs – high sensitivity.





Oxygen demand mismatch (in the absence of AMI)
- Tachy-/brady-arrhythmias
- Hypertensive crisis
- Anemia
- Hypovolemia or hypotension
- Aortic dissection or aortic valve disease
- Hypertrophic cardiomyopathy
- Strenuous exercise

Direct myocardial damage
- Cardiac contusion
- Cardiac procedures: cardioversion, pacing, ablation, endomyocardial biopsy
- Cardiac infiltrative disorders, e.g., amyloidosis, haemochromatosis, sarcoidosis,
- Chemotherapy, e.g., adriamycin, 5-fluorouracil, trastuzumab
- Myocarditis or pericarditis
- Cardiac transplantation (immune-mediated reactions)

Myocardial strain
- Severe congestive heart failure: acute and chronic
- Pulmonary embolism
- Pulmonary hypertension or COPD

Accumulation of troponin in plasma
- Acute/chronic renal dysfunction

Systemic processes
- Sepsis
- Systemic inflammatory processes
- Burns, if affecting >30% of body surface area
- Hypothyroidism
- Snake venoms

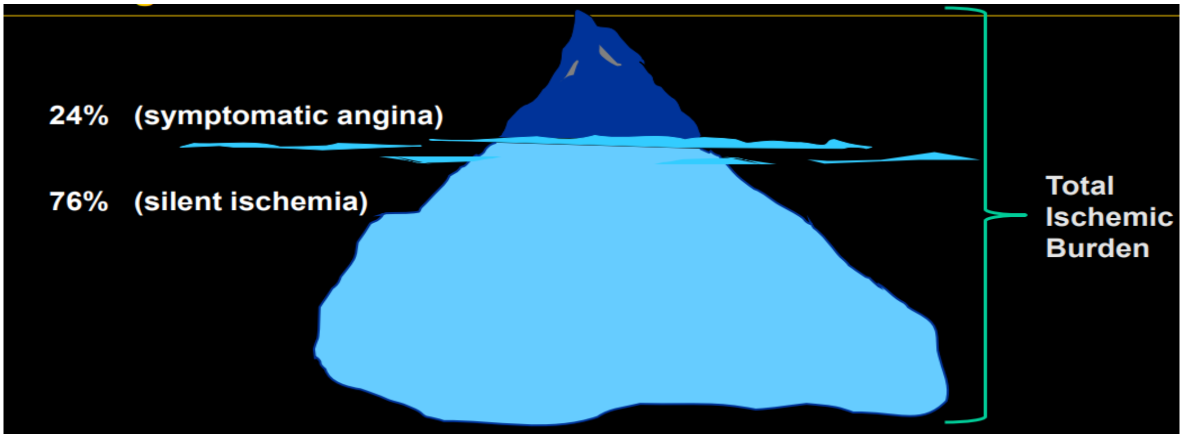
Neurological disorders
- Intracerebral hemorrhage or stroke
- Seizures

Figure 7B: Is high-sensitivity cardiac troponin a reliable quantitative marker for AMI? (**TOP**) AMI acute myocardial infarction, CAD coronary artery disease, CHF congestive heart failure, HI healthy individual, LVH left ventricular hypertrophy, PE pulmonary embolus, SAB Staphylococcus aureus bacteremia. The lower the level of hs-cTn, the higher the negative predictive value (NPV) for the presence of AMI. The higher the level of hs-cTn, the higher the PPV (positive predictive value) for the presence of AMI. Levels just above the 99th percentile have a low PPV for AMI. (**TABLE**) Panel on the right indicates other causes of troponin elevation in addition to myocardial necrosis.

The table in Figure 7B begs to ask whether elevated levels of hs-cTn necessarily reflect heart failure or acute myocardial infarction, by definition? (Myocardial[251] infarction defines acute myocardial infarction (AMI) as evidence of myocardial necrosis in a patient with the clinical features of acute myocardial ischemia). Elevation of cTn may indicate myocardial injury but there are myriad of diseases, inflammation, systemic dysfunctions (table in Figure 7B) and infections[252] which releases troponin. Hence, elevated cTn data is not exclusively causal for AMI and calls for differential diagnosis[253], correlation with BNP[254] and non-ischemic[255] cases[256].

How does the *science of **causality** with respect to the data* resonate with the design of "cardio" (Corral-Acero *et al,* 2020) digital twins? CVD signatures may not rely exclusively on electrical signals (***waves***) because the cardiovascular system (most physiological systems) is an electro-chemical juggernaut where signals (waves) are influenced by molecules (***particles***) and rarely mutually exclusive without dependencies between *networks and circuits* of affiliated functions. Physiology is an inextricably linked system of systems which has evolved through synergistic integration of innumerable sub-systems acted on and guided by homeostasis[257].

If compared with even a tiny sub-system in physiology or medicine, the most advanced mechanical systems of today (e.g., Mars Rover[258]) may be akin to motion pictures in the late 19th century or TV[259] in the 1930's: goofy, grainy, snowy and a drizzly experience in entertainment. The silver lining in the latter is what makes mechanical systems more suitable for digital twins. However, digital representation to monitor (diabetes-linked[260]) silent[261] myocardial ischemia[262] may save lives. Hence, it may be a worthy effort for cardio digital cousins, *no matter how crude.*



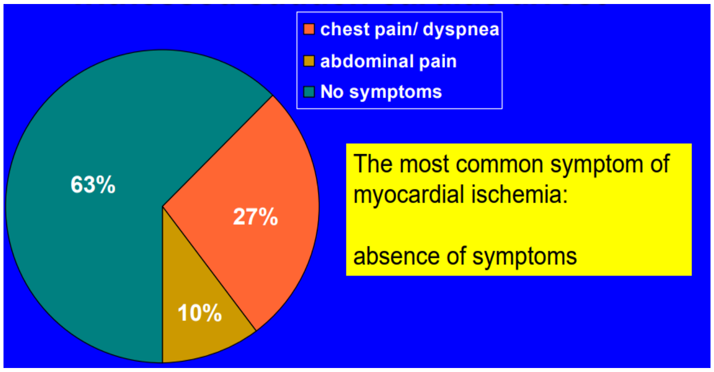


Figure 8: Symptomatic Angina: Tip of the Ischemic Iceberg[263]. Can NT-pro-BNP and other bio-markers predict MI, stroke, CHF? Perhaps. Will it feature in any "cardio" digital twins? A 27-protein model may predict a 4-year likelihood[264] of MI, stroke, CHF, or death due to CVD.

CAN DIGITAL TWINS COPE WITH COMPLEXITY? CANCER? AGRICULTURE?

In the very distant future, science and sensor engineering inventions in health monitoring may help the idea of digital twins for patients with respect to patient-specific metabolomic data, if there is verifiable causality to use the data. In our current approach, KPI (Figure 5) may be viewed as case-specific digital representations (individual, patient) by integrating waveform time series data with medical records and providing visualization (phones, tablets).

The example of CVD illustrates the value of continuously monitoring bio-markers to predict risk of disease. Currently in the *in utero* stage of digital twins, the ability to track and trace bio-markers or other metabolomic targets is possible at a substantial cost, in clinics/labs. Testing non-invasive[265] bio-markers[266] for certain types of cancer[267] may reveal clues[268] and/or predict treatment (prevention), even years (decades) before the appearance of clinical symptoms.

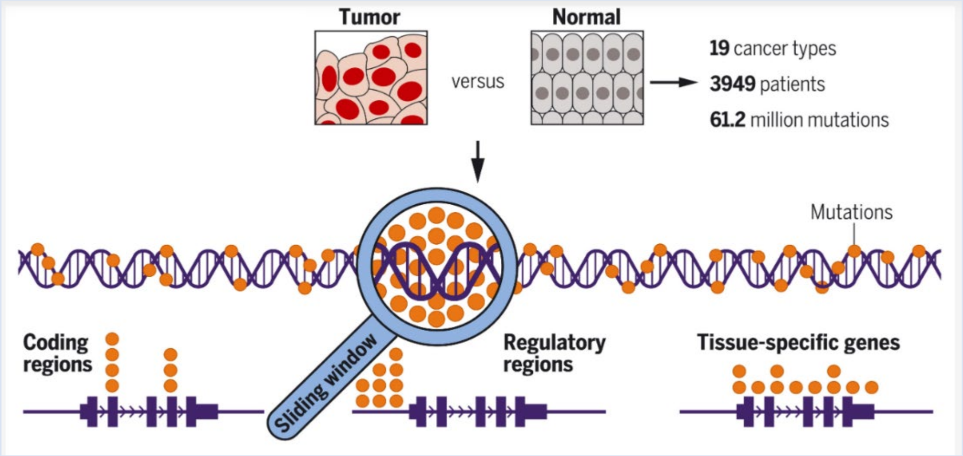


Figure 9: The futility of addressing (attempting) digital representations of complex biological issues may be appreciated by understanding the outline of the information packaged in this one cartoon[269]. Analysis of whole genomes[270] of 3,949 patients in 19 cancer types detected 61.2 ***million*** somatic mutations. An average of 7.5 events per cancer type were in protein-coding regions (meaning: these mutations can change the proteins synthesized by these genes). In the noncoding genome, 3.7 events per cancer type were detected proximal to certain genes in certain tissue types (meaning; we have very little clue as to how and why mutations in the noncoding region can/will affect gene expression, transcription or translation and/or how it may affect biological function/outcomes). In regulatory region of genes, 3.8 noncoding events per cancer type involved cancer-relevant genes (meaning: these mutations can up/down/stop expression of these genes). In a few centuries, we may shed some light on the functional role or significance of these 61.2 million somatic mutations. Long range interactions in genomes may share similarities with long range and allosteric[271] interactions[272] between proteins and between/within protein binding domains[273]. When can we expect this type of data to be a part of digital twins? More importantly, will it be necessary ***if*** prevention of cancer by vaccines[274] gains momentum?

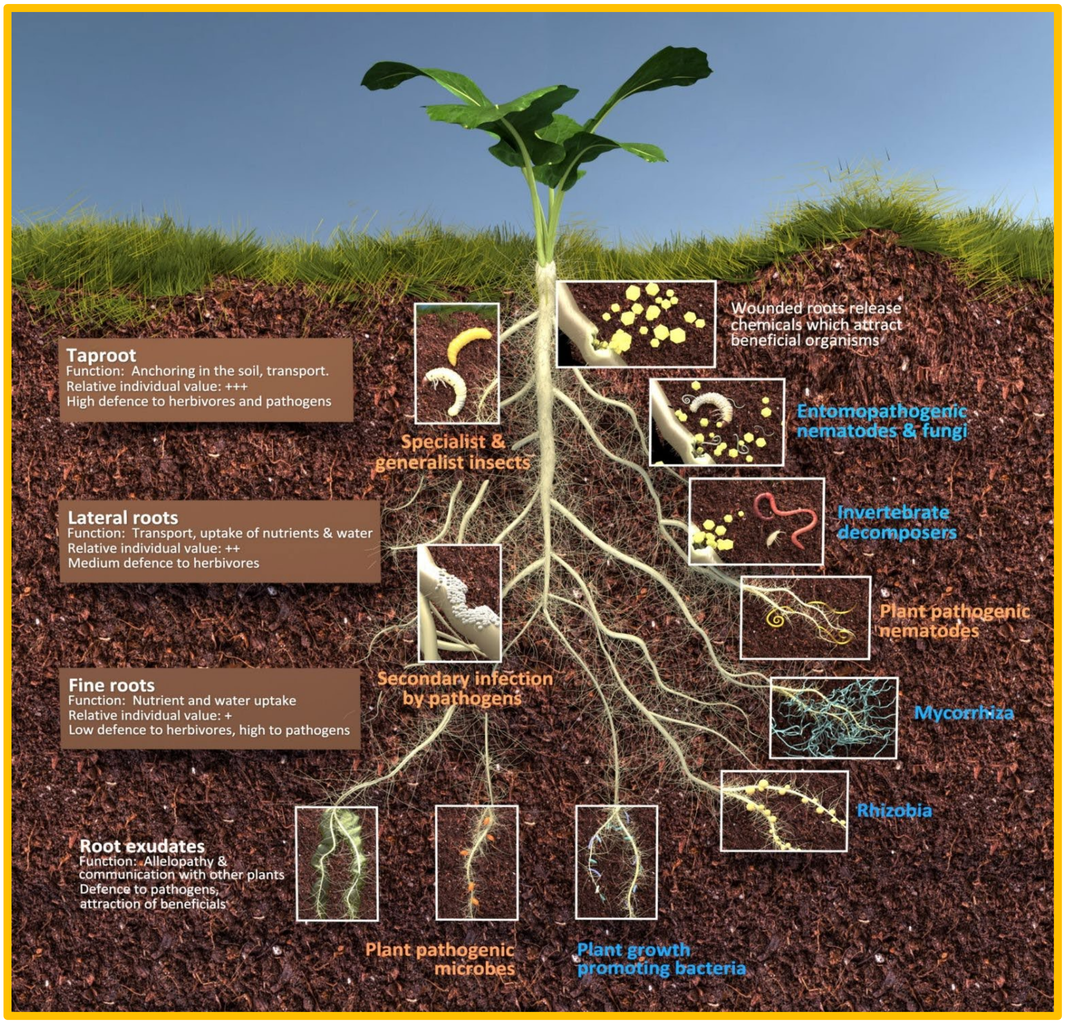


Figure 10: Interactions[275] of soil organisms (microbiome). Root chemicals (orange - antagonists against plants; blue - mutualists). The chemistry between soil organisms (symbionts, pathogens, herbivores) is differentiated over a vertical gradient in the rhizosphere. Interaction continuum between roots and soil biota are closely related to the gradient of root chemical traits. Most of the insect herbivores are present in the top horizon of soils and interact with taproots (defended by chemicals against herbivores and pathogens. Plant pathogenic nematodes and microbes generally infect fine roots (physically most vulnerable). Root exudates are actively released from root tips and contain various chemicals. Beneficial microbes, such as mycorrhizal fungi rhizobia, and plant growth-promoting bacteria, also interact mostly with fine roots (attracted by the released chemicals). Except for names of the microbiota and parts of the plants there is an almost total absence of molecular understanding of chemical, biochemical and growth processes. In the absence of relevant data how could we even begin to think in terms of digital twins for the plant or the soil or the microbiome? But, it appears science and science of data may be irrelevant for some proponents[276] of digital twins where the mantra of "publishing first" trumps credibility.

IS IT UP TO SCRATCH? DATA-INFORMED DIGITAL SERVICES (DIDS)

At the core of the trinity of connectivity, data and analytics in the context of causality, is the need for diffusion of data, which can inform decisions in a manner that *non-expert end-users* may have access to actionable information. For providers, value from digital twin translates to *profit.* Intuitive and user-friendly features are crucial for adoption of tools by the masses.

We will avoid business school[277] strategies and focus on debating data-informed digital services (DIDS) as an umbrella for digital representation to deliver services (see Figure 5 for resource constrained environments). DIDS may be an alternative digital *twin-esque* or cousin-esque approach for mission-critical applications and life-saving devices, such as the ventilator. This device is currently a part of the global vernacular due to its quintessential role in saving millions of lives at the peak of CoVID-19 pandemic (which is still in progress, in its 4th year).

We begin with an alphabet soup at the bottom of the pyramid in Figure 11(top). It begins with "atoms to bits" and adds connectivity to catalyze decision making, that is, ABCD (Atoms to Bits Connectivity in Decisions). ABCD is a data acquisition layer where sensors, tags, manual input and other sources feed raw data. The internet of things (IoT) is the canonical data layer for objects and things which feeds on the granularity of the common denominator (ABCD). CPS combines data from atoms (physical objects) with instructions (bits) from commands, processes and procedures which directs/determines actions/reactions in the networked physical world[278].

The user may benefit from the synthesis of these layers (blurred boundaries) through DIDS where distributed data may be curated for quality control, analyzed with mathematical model(s) and/or statistical technique(s), perhaps even fused with other internal or external data.

The outcome of this data processing is information which "informs" the user (humans in the loop) how to make better decisions. The "edge" interactions may be immobile contexts (control tower, office, factory[279]) or real-time dynamic interactions where outcomes (data, information) may influence the user, instantly (via mobile platforms, smartphone, tablets) or users may wish to subscribe to information updates (publish/subscribe) for decision support.

The mark of interrogation at the tip of the pyramid offers further room for imagination, invention, innovation and interpretation of the collective path, which data may take to arrive at information, which users can synergize/integrate to improve/profit from their decisions/actions. This ability in the [?] segment on top of the pyramid is suggestive of an "always on" real-time digital representation with DIDS-integrated decision support for systems (farm, factory, flying saucers), mission critical applications and even for life-saving ventilators or security devices.

This ability in the [?] segment on top of the pyramid (Figure 11) may be erroneously evangelized as "digital twins" to enhance the marketing panache of what may be, in some/many instances, simply a vanilla aggregation of data and analytics in a dumb digital duplicate, which may, in appropriate circumstances, provide useful data, information and collective system status.

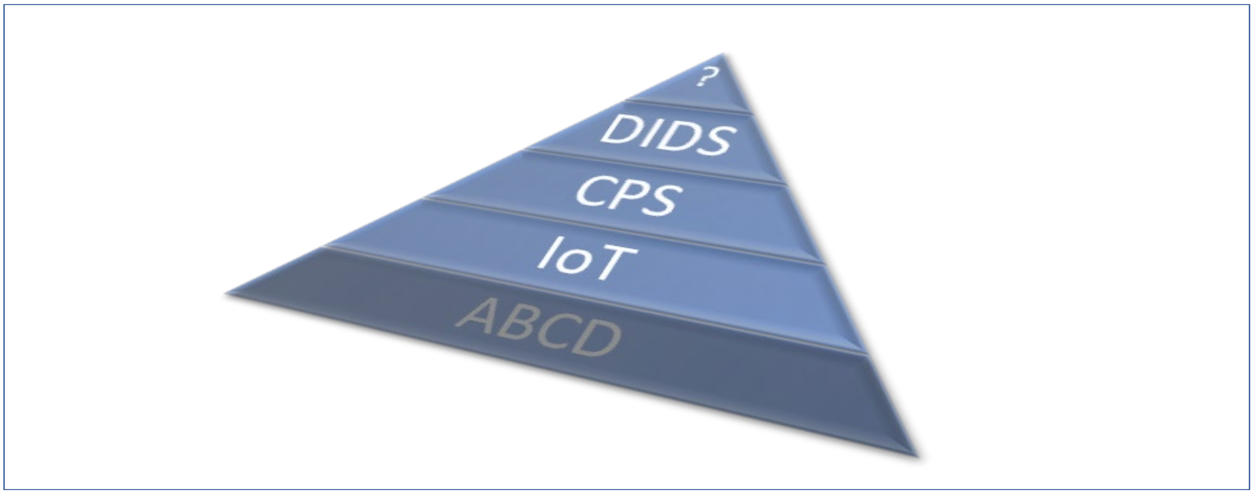


Figure 11: Pyramid (top) suggests the importance of integrated systems thinking to synergize the trinity of connectivity, data and analytics in the context of causality. An analogy is that of six (blind) men from Indostan[280] (India) touching parts of an elephant[281] and claiming the "elephant is a tree" (man who touched the leg), "it is like a rope" said the blind man who touched the tail. "Like a snake" (man who touched the trunk). "It is like a big hand fan" (man who touched the ear). "Like a huge wall" said the man who touched the belly of the elephant. "Like a spear" said the blind man who touched the tusk. By focusing on parts they missed the far greater value from the *sum of the parts*. Misguided by solely focusing on the part (sub-system? silo?) their data, understanding and decision was incorrect. As a consequence, their interpretation lacks actionable value in the context of the "whole" animal (system, system of systems, ecosystem).

Humans are ill-equipped, non-linear, irrational[282] systems and immersed in artefacts of complex systems. Most rational and natural actions are governed by a set of immutable scientific principles based on a few natural laws (mathematics, physics, chemistry, biology). The journey from individual molecule to individuality is a natural outcome. The former (molecules) may not behave unnaturally but the latter (individuals) are prone to irrational behaviors. Therefore, data from systems guided by natural laws (machines guided by physics and engineering) generally generate data from deterministic events. Humans-in-the-loop systems (e.g., manual healthcare data acquisition / entry; economic data) are sources of uncertainty, corrupt data, altered artefacts and data due to spurious events (fake big data[283]), uninformed models or biased frameworks.

Frameworks are workhorses for science. The over-arching importance of understanding, creating and implementing robust frameworks may be best exemplified by the theory of quantum mechanics[284]. The latter is less of a theory and more of a foundational framework[285] where physical theory fits or must be fitted (?). A lesser known but another highly relevant framework is the theory of quantum chromodynamics[286] (QCD) based on the discovery of quarks and gluons. Unlike the theory of quantum mechanics where physical theories "fit" (? nicely[287]) in case of QCD the "fit" is constrained due to lack of mathematical tools (open research topic).

The underlying mathematical infrastructure at the heart of frameworks is referred to as schema, a common conceptual feature in complex adaptive systems (e.g., epidemiology). The granularity of such schemas makes it possible for highly modular mathematical expressions (e.g., equations for rates/flows) to be "mixed and matched" (from repertoire of model schemas) to generate different sub-frameworks depending on the desired outcome (i.e., what the complex adaptive system expects to create, modify or represent). Modular mathematical expressions that constitute frameworks or schemas may be viewed as scaffolds for data. An equation for rate or flow in a complex adaptive system is alive when it acquires data or is involved in information arbitrage (e.g., data or information from environment or interaction with/within the environment of the system which is referred to as the "percept" from the "environment"). The source of data (data acquisition system) may be human or data harvesting tool, such as sensors. This (sensor) data represents actions in the real world which feeds schemas (rates, flows, weights) and the feedback (in a closed loop system) influences the schema(s) to change/modify actions/behaviors (actuate/automate) to improve/optimize system performance.

Multiple arrays of schemas may have multiple data feeds (may switch between data feeds depending on tasks or desired systems-level outcome). Individual outcomes must be synthesized and/or synergized as a whole for the most relevant semantic interpretation which is of value for the whole or "performance" based on PEAS framework (percepts, environments, actuators and sensors, discussed earlier). DIDS offers clues as to how frameworks, performance and PEAS may influence decision support. Unbeknownst to solution providers in the real world, they are trying to create (?) systemic solutions and/or predictive[288] tools for "profitable problems" by using this rubric, translating these concepts for (pragmatic?) implementations, e.g., digital twins. Data, dependencies, relationships and ratios are granularities which influences and/or informs weights, rates, flows to enable contextual titration/optimization of system outcome/performance.

In an ideal situation data-informed feedback from humans in the loop may wish to use tools based on the concept of DIDS, PEAS, etc. Tuning or adapting outcomes to a desired level is often valuable for end-users and that triggers adoption of such tools (including digital twins). Pre-setting desired outcomes are common in certain systems e.g., fuel-dependent optimization of turbines to limit release of greenhouse gases (GHG) to a pre-specified level. The retrosynthetic[289] approach is a form of "backward planning and optimization" if system attributes are identifiable (parts, components, characteristics) and if each are associated with rigorous performance metrics.

What if we create mathematical models, frameworks or schemas for parts or components of the system? Each schema is then subjected to PEAS-like treatment and the components (think individual gears) are brought back together (inside a clock) to deliver the "whole" performance. But, complexity of complex adaptive systems may be rate-limiting for retrosynthesis because the ability to deconstruct the end point (performance) may be influenced by too many "synthons" (e.g., state space explosion in an optimization problem [lemma] with too many dependencies).

A crucial question is whether these schema or mathematical expressions can be created as modular entities which can be stored in a "library" or a repertoire of modular units (e.g., weights, rates, flows) which can be re-used as granular entity level models when probing other systems or optimizing performance? Simulated 3D concurrent engineering[290] workbenches[291] may be an analogy where functions and components may be sourced from a repertoire ("drag & drop" from a menu of choices) to modify/re-construct/re-configure engineering design for diverse objects.

A highly analytical, deeply incisive and very significant mathematical framework which embraces some of these ideas (discussed in the last eight paragraphs) was recently published[292] to highlight a brilliant convergence of epidemiology and economic factors from the perspective of disease modelling in plants. Perusal of this paper reveals the importance of parameters which could be equivalent to features (in our hypothetical model and a potential general mathematical framework) linked to data (data feeding the feature or the feature/parameter as a higher level data node). Murray-Watson *et al* effectively uses "switching terms" with values (0, 1) indicating portability of parameters in an equation based model (add or delete, depending on the context). This attribute lends itself to integrating EBM with agent based models (ABM) where inclusion or exclusion of the (software) agent (data tool) makes the framework modular, agile, adaptable and dynamic, to the address the specificity in queries (questions from non-expert end users, farmers).

Translating this mathematical structure of the infrastructure into frameworks (ASIM, application specific integrated models) and simulation tools may converge with the 30+ year old idea[293] of tangible user interface[294] (TUI[295]). Computationally illiterate non-expert users[296] may experiment (e.g., strategic planning) by changing values, parameters and variables to explore deterministic ***what-if*** scenarios (not only for managers or executives but a training tool for new entrants, workforce development, and high school vocational training). The next few paragraphs (and understanding the depth of Figure 12) may add further clarity to this "value added" thinking if non-experts are empowered to change/modify equation based models using "drag and drop" tools linked to a menu of features/parameters/variables with a sliding scale (e.g., values high to low) which the user can manipulate/control/command/limit/extend (on-demand, in real-time).

Convergence of epidemiology and economic factors in Murray-Watson *et al* is poised to add error correction (models are, naturally, error prone), e.g., generalized autoregressive conditional heteroskedasticity (GARCH; Datta and Granger, 2006). It is a representative error correction technique from financial econometrics, which is useful in view of volatility and veracity of high volume data, which introduces, amplifies and accumulates error in equation based models (GARCH models the variance of the error). A simulation tool or TUI which enables users to *change the error rate* will be immensely helpful to observe how errors may manifest in descriptive, prescriptive and predictive analytics. The latter may suggest acceptable boundaries (e.g., limits of data clustering) or if data curation must be even more rigorous and a pre-requisite for the data to be useful or if it is at all reliable for use in information arbitrage in decision support systems (also see Figures 13 and 14 for other related discussions).

Libraries of practical use-case models (mathematical frameworks) must contain examples of use cases in demand (domain specific). For example, water supply[297], water quality and water requirement[298] calculations[299] are central for crop production. Water use, water treatment and irrigation practices are under threat from climate change as well as limits on fresh water (versus brown water, etc). The gradient of the arable land, soil moisture determinants (type of soil, soil microbes, etc.) and chemicals (fertilizers, pesticides, herbicides) are a few of the parameters (vectors, vector spaces) generally taken into account (integrated with experience) by growers when making decisions to support their target goals (crops, produce, cattle). These parameters (features/vectors) are linked with tier-1, tier-2 or even tier-3, dependencies. The base of this "pyramid" (Figure 11) consists of events/instances which may generate time series data (scalar). Specific sensors (if deployed) can collect data to provide information (related to vectors and if there is information in the data) to better equip decision support systems to assist humans-in-the-loop (unable to mine/capture "experience" which can computationally substitute for a human).

A mathematical representation of this model, its network of dependencies and range of values (scalar) for each feature/sub-feature (vectors) may serve as an embedded logic engine behind an user interface. Non-expert users can benefit from such tools using drag and drop objects or changing levers or selecting tools to optimize their expectations of performance. Tools are less useful if data or information is unidirectional. In order to re-tune, re-set, re-calibrate system performance at the edge, the features[300] must be familiar to users. We must simplify[301] the "Lego Mindstorms" approach[302] by dragging and dropping icons and "joining" (the subject and the predicate, conjunction) to reflect the intended "meaning" (semantics) using (Boolean logic) embedded operators (designed as connections). At points of use, it serves as a mobile distributed *sense and response system* which may *actuate* (sense, analyze, respond, actuate, SARA[303]) with limited semi-autonomy for non-mission critical systems with high fault tolerance. The foundation of such a system, now available as SCRATCH[304] (was started 20 years ago by co-author[305]). MIT spin-off Thunkable[306] and Lego[307] Mindstorms[308] uses related ideas.

Scratch-esque tools for real-world edge applications/scenarios are the *bridge* to the next billion users in manufacturing, energy, logistics, agriculture, smart homes, healthcare, cybersecurity.

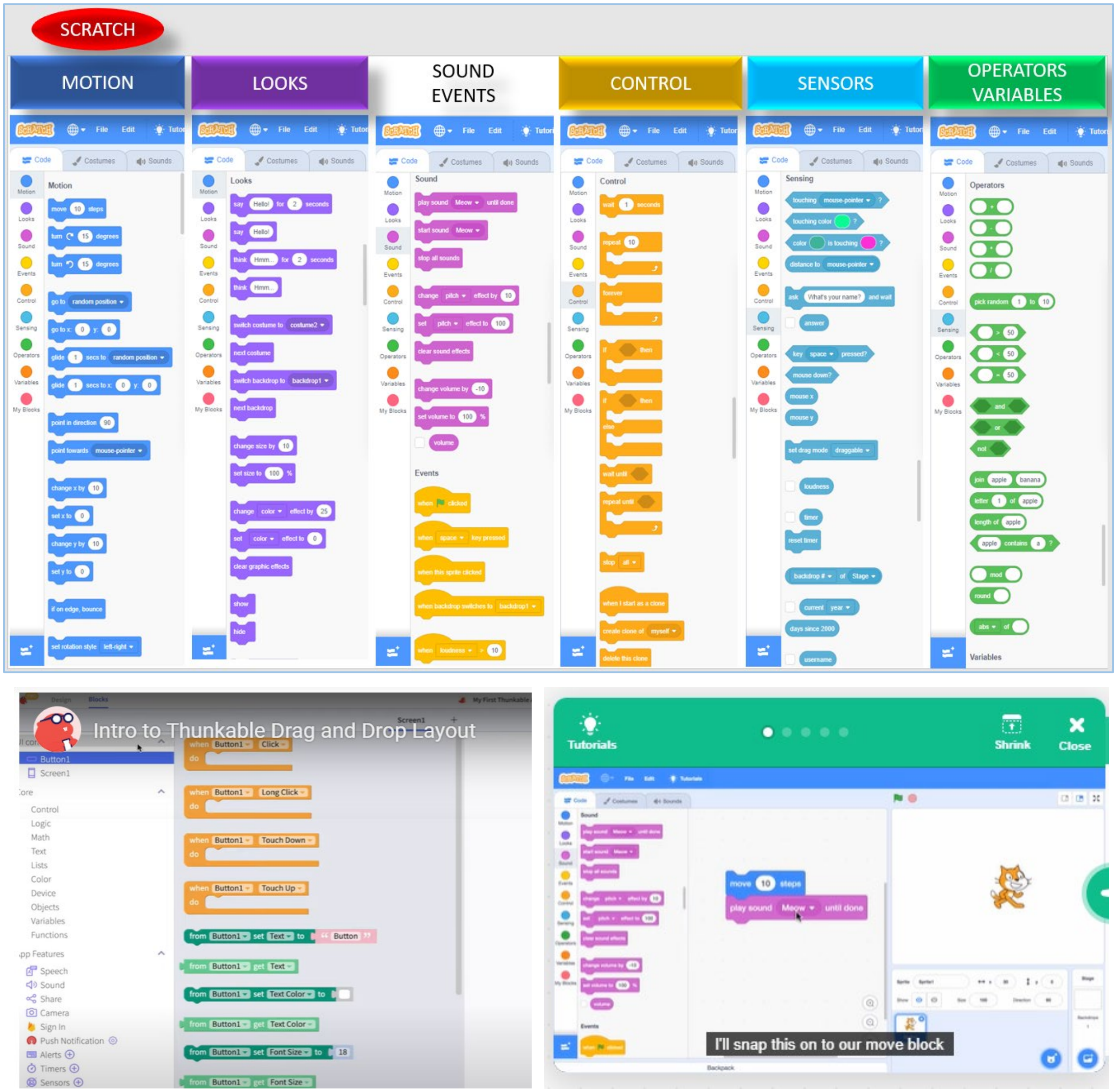


Figure 12a: Sylvan (2007) described “tools to build online communities” where almost any user capable of articulating the task in natural language (English) may create command sets to instruct computation without the need to “code” the syntax of the instruction in a programming language. “Drag & drop” icons (embedded code) deliver user’s task description to configure instructions. MIT “Scratch” (top) shows list of features/instructions which can be combined on a design board (bottom, right) to deliver an outcome that non-experts can construct. MIT spin-off “Thunkable” (bottom, left) appears to be a “digital twin” (for-profit commercial version) of MIT Scratch.

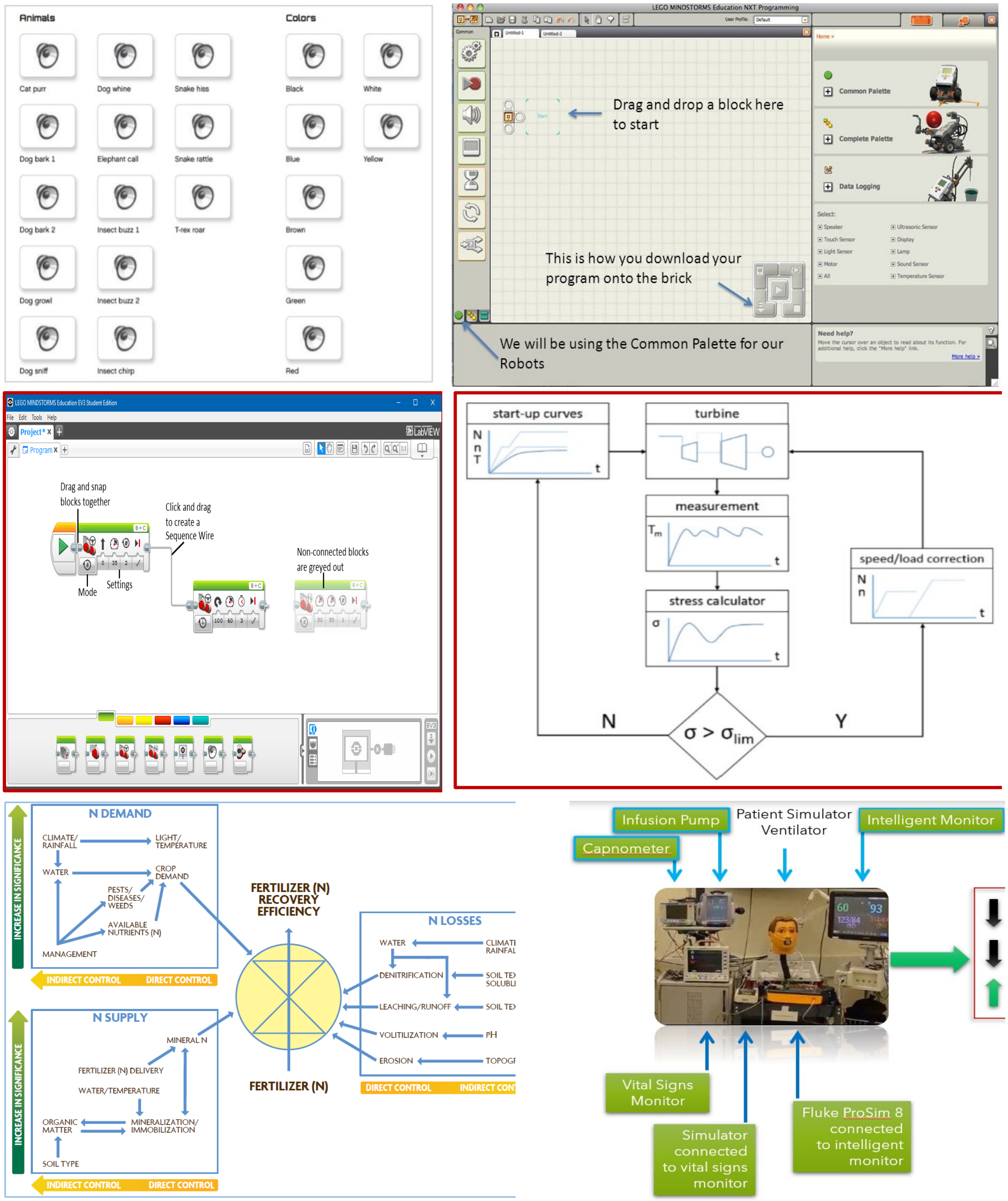


Figure 12b: Diffusion of ubiquitous computing at the edge may be transformed from vision to reality, partially, using tools with embedded code (Sylvan, 2007). Non-experts may create new tasks, or sense, analyze, respond and even actuate (SARA) to adapt or optimize key performance indicators based on need, events, feedback. Can we transform these principles into practice?

The common denominator emphasized in Figure 12 are tasks which can be performed by non-expert users without programming (each time, for each instance). If it is up to Scratch, can we use a common platform with a workbench[309] containing a palette of tools with embedded code? The tools must be application-specific but the principle of embedded code may be applied far and wide. Non-expert users can choose user interfaces optimized for mobile computing as long as scenario-specific tools are available and adequately addresses the user's need/purpose.

In the Lego Mindstorms palette of tools for animal calls/colors (Fig 12b, top, left), children may create "robo-dog" using an user interface on the workbench (Fig 12b, top, right). The "digital twin" robo-dog may look like a black and white spotted Dalmatian but may purr like a cat if the user inserts "cat purr" as the animal call instead of dog sound (whine, bark, etc). The middle panel (Fig 12b, burgundy outline) extends the idea (Lego workbench, left) to energy generation, specifically, turbine optimization[310] for energy plants (Fig 12b, middle, right). Non-technical users may program an optimization routine/step without knowledge of programming or code. Users choose icons with pre-determined functions/values and connects in a manner which produces a desired outcome. Users must understand functions related to turbine start parameters (domain knowledge) and the palette of tools must have embedded code in modules/connectors that is relevant to the scenario (in this example, turbine start optimization for power generation).

Mobile device interfaces for applications in agriculture[311] (left, bottom, Fig 12b) and healthcare[312] (Fig 12b, bottom, right) may use Scratch-type GUI, workbenches and palette of tools supporting case-specific configurations for users to modify/optimize/explore. A "triage" dashboard may display a simulated outcome, before live deployment of modifications, to allow users to observe the results and impact of their modifications. For example, what if the scenario selected by user includes a nitrate value too low or too high? It may be informative to review how the user's nitrate value may impact the outcome as well as its relationship to global issues, for example, nitrogen availability in terrestrial ecosystems[313] (or phosphorous[314] pollution[315]).

Scratch at the edge for non-expert users is in sharp contrast to the traditional notion of centralized control exercised by experts. It resembles a decentralized distributed decision-making model which thematically lends support to the idea of data democratization without the illusion of digital twins. In the context of the complexity of nitrogen in (Fig 12b, left, bottom) and post-surgical PCA (patient-controlled analgesia, Fig 12b: bottom, right), can we apply the principles of retrosynthetic model to explore how to optimize behaviors for complex adaptive systems?

Using "crowd-informed" Scratch-esque tools in the hands of mobile users (non-experts), can we release the "joystick" of retrosynthetic analysis for the masses? In many scenarios, the "outcome" is community-specific and driven by economics. One shoe may not fit all. If a global model needs modification to fit the local need then who is better equipped to modify the model than the local end-user with a targeted outcome in mind? For example, a model of Nitrogen as a fertilizer may be best made useful by the local farmer for local use. Scratch may enable users to better control decentralized data and information to optimize services for micro-environments.

MATHEMATICAL MODELS: ALL MODELS ARE WRONG (SOME ARE USEFUL)

All models are wrong[316], but however incorrect, some models may offer a guiding hand to inform the structure of the infrastructure, which may serve as a "perch" (scaffold) for data, on the journey to make sense of data (analytics). While some models are useful, only a few survive unscathed, in practice, because models attempt to reach, capture, and encapsulate granularities far beyond its grasp. Digital twins suffer from lack of granularity because its proponents may choose to ignore the necessary minutiae either due to their lack of depth or the cost to delve into details. The canonical "quick & dirty", "fast & cheap", "shoddy & second grade" commercial endeavors cringe at science, depth, and detail, as factors that lengthen their 'time to market' metric. Hence, we see over-simplified pedestrian 'digital twins' (cardio, soil microbiome, earth).

On the other extreme is our fantasy of contemplating but never taking that quantum leap from quantum mechanics and quantum chromodynamics to explore the pragmatism of our lofty ideas (some of which were discussed in the preceding section, following Figure 11).

Is there any benefit from our elusive quest for middle ground between the race for profit, despicable[317] avarice and gluttony[318] vs the penchant for illumination, plight to be complete and ill-treating good[319] as the enemy of perfect? What if the *twins* are archenemies[320]? The chasm between the two cultures[321] is not about science but a revealing social cleavage between reason and power, or self-interest and societal good, or haphazard realities and moral hazard.

Our discussion following Figure 11 and in the next section (models of life) is an attempt to sketch a few examples from agriculture and healthcare. For better or for worse, for the richer and for the poorer, in sickness and in health, the progress of civilization depends on agriculture and health in addition to three other essentials: energy, water and sanitation, collectively referred to as FEWSH (food, energy, water, sanitation, health). The intricately intertwined interactions within FEWSH fuels life and living.

It is braggadocious to claim that we are "delving in details" when we haven't even scratched the surface. It is hubris if we claim "we know" because practically we almost know nothing either about science or about science and human values[322]. In this spartan landscape of our limited knowledge, we continue to return to what we can reasonably count on: connectivity, data and analytics within the cocoon of causality. All that which counts but cannot be counted[323] is left to the imagination of the readers.

In agriculture, healthcare and other living systems, can we create a repertoire of models or schemas? Mathematical models may serve as "engines" in backend applications ingesting contextually relevant data. Users can interact through Scratch-type tools on mobile UI (phones). From the miniscule arsenal of our knowledge, even the known factors which may affect the efficiency of nitrogen use in agriculture are far too numerous to design an adequate "efficiency" metric or target outcome using the retrosynthetic approach (where we first create a target or a metric as the goal). If we could find that target, we could work backwards to determine how to arrive at that targeted outcome by adjusting the "levers" within the interconnected systems.

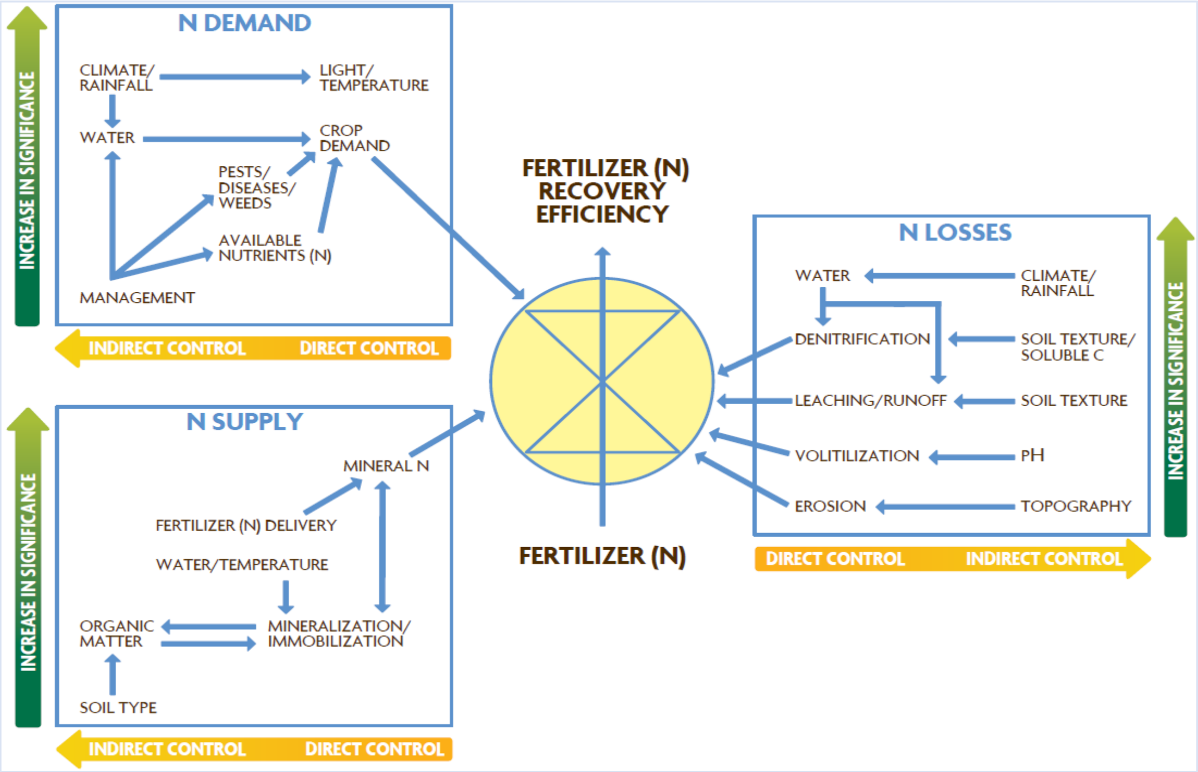


Figure 13: Crop, Environmental and Management Factors Affecting Nitrogen Use Efficiency: Conceptual model depicting the three main controlling processes (nitrogen demand, supply and loss), major mechanisms and factors regulating fertilizer (Nitrogen) use efficiency. The "control" in the center, influences the flow of fertilizer (N) into the crop (Balasubramanian *et al*, 2004[324]).

Dissecting the problem (previous section) reveals that water and temperature are common elements in three sub-domains. Can we focus on these two data-revealing (measurable) granular elements in this complex adaptive system? What we uncover/interpret may be extrapolated[325] beyond our grasp of the granularities, their causal factors, meaning and contextual significance.

Although error-prone, we may proceed to build mathematical models assuming that 'water' measurements and quantification will generate data for "water models" within the "universal" model of nitrogen efficiency. The sub-library of water models must be searchable using "discovery" tools and search engines. The models are expected to become increasingly complex depending on the plethora of features associated with water. Search engine optimization tools using keywords may be a failing strategy. The use of graph databases to contextualize water data in terms of relationships in *specific instances of data* (with other causes, if any) may be useful. Time-series data integrated with causal context in a time-stamped graph database of water data may be valuable for analytics, in any context, including digital representations.

Discovery of model repertoires increases value through re-usability of pre-created models in the library. Teams working on related agricultural topics (e.g., carbon cycle, phosphorous cycle) may search, find and use "water" models from Nitrogen efficiency. Models may be imported (inserted/integrated) using common APIs (application programming interfaces) or modified after import to adapt to user-specific tasks (but only if the pre-coded model language is interoperable with the language of the task at hand). This "newly" modified model may be also uploaded back to the source library and designated "water model x.y" to enrich the searchable repertoire. Crowdsourcing may gather "best practices" from "distributed science"[326] and increase diversity and granularity of models to amplify the range of explored scenarios.

Generally speaking, connectivity, data and analytics with respect to each factor in each sub-domain, is immersed in dependencies, relationships and dynamic ratios with one or more factor or network of factors. Hence, sub-domain models may need further reductionism to sub-component models and even more drilling down to define weights, rates and flows (associated data). In the sub-domain "N Demand" (Figure 13: top, left) we need sub-component models of "light" and "temperature" which are key elements used in multiple applications and may not be limited only to nitrogen efficiency in agriculture.

Thus, granular elements, such as, light, temperature, water, etc., are basal parameters which are parts of complex and comprehensive models stored in libraries. Context-dependent "drag and drop" actions by non-expert users may "pull-down" one or more of these models depending on the "match" with use-case, using Scratch-type tools. For example, "water" related models ought to be different for different cycles, e.g., "water" related to N cycle, "water" related to P cycle and "water" related to C cycle but stored under "water" within sub-folders water.N, water.P, and water.C (there may be many more versions of water.N if more "crowd-sourced" users work with the Nitrogen cycle and fewer individuals work with phosphorous or carbon). Cycle-specific and application-specific maintenance of models ("water" "light" "temperature") requires data feeds (from sensors?) where ingestion of data and analytical outcome, if any, must be auto-updated, but of course, humans in the loop may also be involved.

Streaming sensor data from pre-selected sources may be dynamically added/deleted. The source description of sensor data and its API for ingestion should be kept "open" with modifiable user exists to add/delete different sources or *ad hoc* access to specific data sources (real-time access to [wireless] sensor networks not usually integrated with data acquisition). The latter is a systems and data interoperability issue which can become rate-limiting, reduce efficiency and productivity, if proprietary interfaces inhibit advances or stymied by humans. Non-compliance between sensor data source, sensor database and data distribution standards[327] are reasons why data synchronization, analytical output and decision support systems are in a chronic state of underwhelming performance even after massive investments in technology[328]. It is unfortunate[329] that standards[330] may also suffer from problems in terms of interoperability[331].

Often, consulting companies in collusion with software manufacturers[332] coerce[333] customers and non-technical users to eschew call for common standards and open APIs. One goal is to maximize consultant fees by increasing "billable hours" and peddle proprietary[334] software (closed data dictionaries) to amplify sales. Aspirational leaps of progress are often frozen on the ladder between the aggressive for-profit-only[335] chant and the open-source mantra.

Still pursuing nitrogen [N], we observe N in model cropping system (Figure 14) can be quite different. Thus, mathematical frameworks become increasingly formidable even for small sub-segments. Enthusiasm for model building may be curtailed because discrete mathematical functions may fail to capture the intrinsic non-linearity of complex adaptive systems which are continuous (analog systems[336]) and are incomplete when transformed to discrete signals (digital representation, digital twins). Values, weights, data and information operate within ranges and create a "push-pull" dynamic scenario which leads to the outcome, perhaps not as optimal or as precise as mathematicians desire but a rational "approximation" in a "zone" where >80% of the problems may be addressed/solved rather than fitting >95% or >99% of the cases. Outcome of mathematical models, the frameworks they create, and the schemas which act as scaffolds for data, must act in concert to harmonize dynamic re-optimization for continuous complex systems.

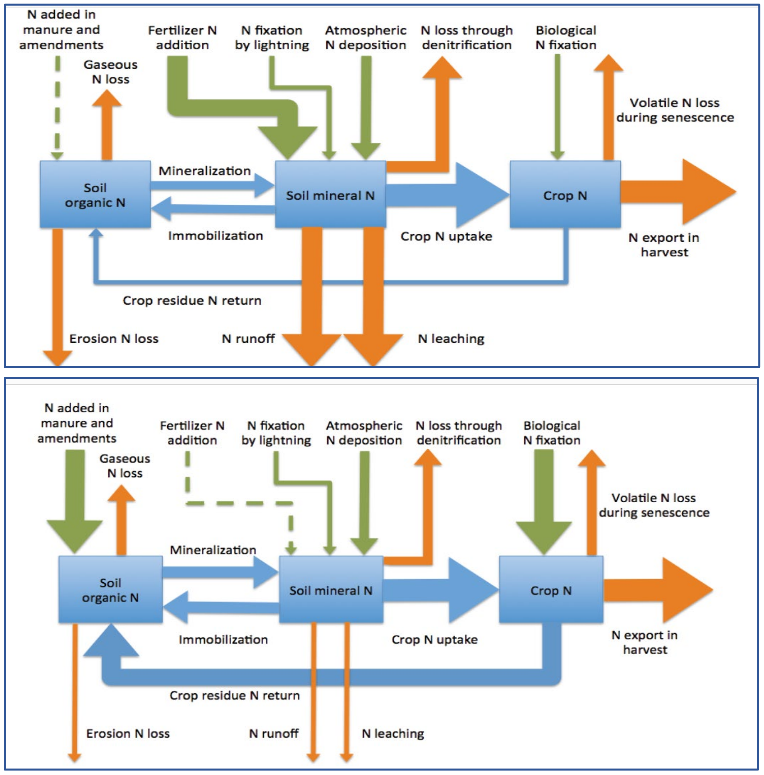


Figure 14: Hypothetical nitrogen [N] stocks and flows for a model cropping system[337] with high (top panel) reliance on mineral N inputs and low (bottom panel) reliance on mineral N fertilizer.

MODELS OF SYSTEMS: LIVING VS NON-LIVING (MECHANICAL SYSTEMS)

Having encouraged the creation of mathematical models it will be remiss not to point out that rigid frameworks and complex adaptive systems are not synonymous. The outcome from mathematical models must be linked to the trinity of connectivity, data and analytics. Data sources and models within sub-components of components (part of the sub-system and sub-domain) contribute, often in a hierarchical fashion, to system performance. The "systems" level performance of complex systems (Nitrogen in agriculture or PCA in hospitals) are not "points" in terms of performance but a fabric with flexibility, ranges, and tolerances which represents a continuum of adaptation and homeostasis, the hallmarks of complex adaptive living systems.

Living systems must accommodate volatility. The latter is not common to mathematical models. Frameworks must allow its operation to deal with fluctuating levels of fault tolerance in order for a schema to be a relevant contributor to systems performance. Data, information, value and action (DIVA) are connected and related but *weighted differently* because of their semantic distances[338] (semantic relatedness measure[339]) which may be subject to change based on context and/or specificity of use, application type, or the specific need of the end-user.

Mathematical models of value in the context of connectivity, data and analytics, must be also viewed through the lens of DIVA. Therefore, it begs to ask whether equation based models (EBM) of mathematical frameworks are copacetic as schemas for adaptive system performance? The rigidity of EBM versus the flexibility of software agent based models (ABM) may have to co-exist, unequally, because dynamic push-pull is a feature of living systems. Can EBM and ABM co-exist in a model? Are models suitable for the molecular dynamics of the "continuum" of adaptations that complex systems must achieve to attain homeostasis, survive, and evolve?

For example, in a specific instance of glucose metabolism, the equation based model may be the only model required to account for the outcome from hydrolysis of disaccharides, sucrose and lactose. The kinetics of enzymatic hydrolysis of each molecule of sucrose produces exactly one molecule of glucose and one molecule of fructose. With the same mathematical precision, one molecule of lactose, hydrolyzed, will generate one molecule each of galactose and glucose. In this scenario EBM = 1 and ABM = 0. In another instance, the concentration of glucose in blood (of humans) can vary from 60mg/dl to 600mg/dl. Extreme values will present a series of (fabric of) pathophysiological dysfunctions but as a whole for the human (systems performance) the outcome is unlikely to be death, at least, not immediately. In this scenario the inflexibility of mathematical frameworks makes their rigidity almost useless for any decision support system (requires humans in the loop). In this scenario, EBM = 0 and ABM = 1.

Mathematical models are not a panacea but could be an essential element in our quest for systems-level optimization. By definition, optimization may be an incorrect descriptor because unequal coalition of many sub-parts may lead to a sub-optimal level which addresses >80% of the system needs/attributes (rather than attempting 95% optimization of one system, at a great cost to another). The inclusion and balanced execution of these factors through a digital twin or digital cousin is utopian. Is it even necessary to explore digital representation in this context?

In our next example, the post-operative scenario of patient-controlled analgesic (PCA) is an infinitesimally tiny slice of hospital healthcare paraphernalia with remediable options to mitigate mortalities[340] due to overdosing of analgesics. PCA enables patients to self-administer morphine to reduce post-operative or post-obstetric pain, in patients with low pain threshold.

PCA highlights the vital need for interoperability between and ***portability*** of models from one system or application to another (via open APIs). The idea of "mobile" models (frameworks, schemas created by humans) is an example of biomimicry. Transposons[341] and tycheposons[342] are ***mobile*** genetic elements[343] enabling genes to move between genomes. The discovery[344] challenged the conventional wisdom that genes[345] were static elements. Bio-mobile tools[346] for genetic modifications[347] may also confer immunity[348] even between species[349]. One example is the "shuttling of defense cargo" where plants[350] transmit nucleic acids (small RNA) to silence virulence in a pathogen. It is a disease control[351] model[352] worth exploring for response to pandemics, if we can delineate the molecular genetics[353] of virulence[354].

In the PCA cartoon (below, right) 3 parameters are indicated: blood oxygen saturation (SpO2), respiratory rate (RR) and end-tidal carbon dioxide (etCO2). These three are just the tip of the iceberg. A plethora of other factors and sub-factors (underlying co-morbidities) may be critical in determining patient-specific PCA in post-surgical care. Therefore, not only pain management but the whole patient must be monitored using **integrated information** platforms.

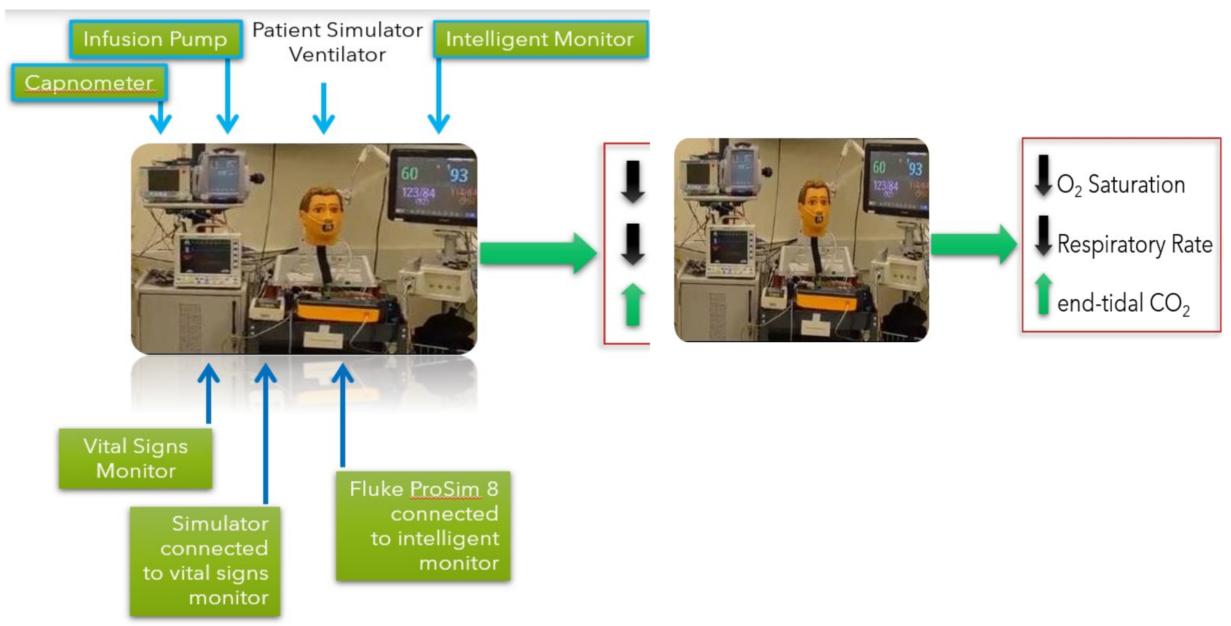


Figure 15: US opioid crisis (>100,000 deaths[355] in 2021) attributed to opioids, include heroin, codeine, hydrocodone, oxycodone, and morphine. We may need to re-evaluate approved patient safety protocols and medical device operations (false alerts?) to reduce mortality from patient-controlled analgesia (PCA) which uses morphine infusion for post-operative patients in hospitals.

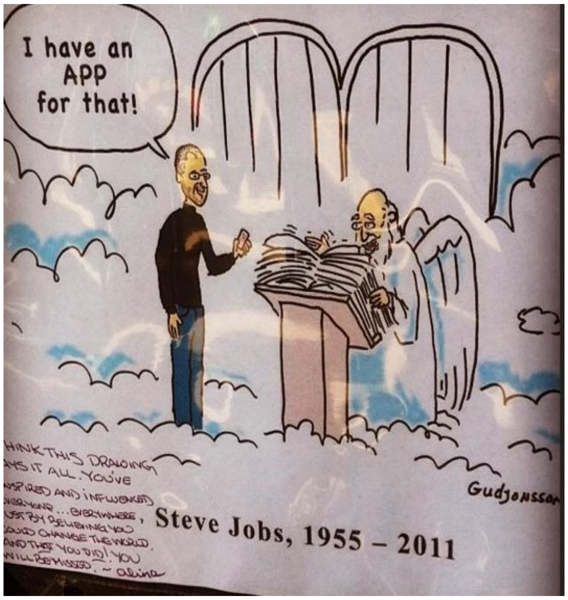
Opioid-induced episodes of bradypnea (abnormally slow breathing rate: adult respiratory rate (RR) is 12-20 breaths per minute) and desaturation (lowering of blood oxygen saturation) can escalate to respiratory depression (RD). Low RR (RD) may require rescue (ROSC, return of spontaneous circulation[356]) but in-hospital cardiopulmonary resuscitation[357] is successful in fewer than one in five patients. Hence, careful planning to administer PCA based on patient history and stringent synergistic integration of medical devices and device data are necessary (but only available if there are integrated systems for real-time "whole" patient monitoring).

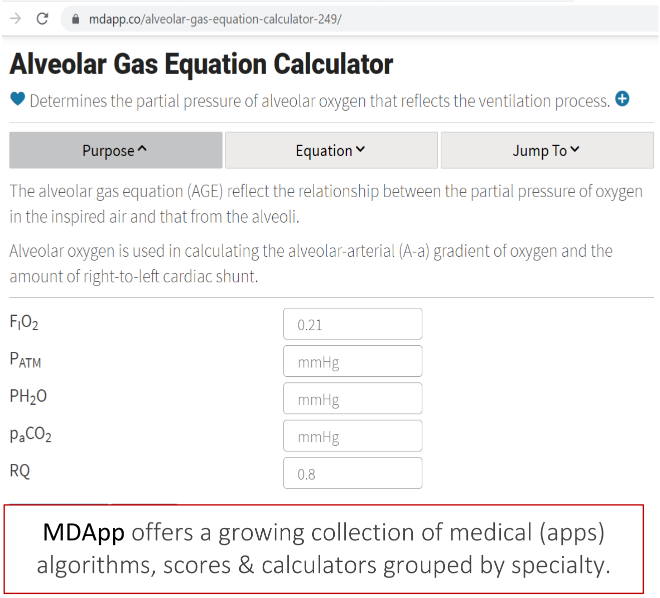
Reducing risks due to false alarms (spurred by *ad hoc* addition of medical devices) may reduce mortalities/morbidities (Makary *et al*, 2016) contributed by the lack of medical device interoperability. Medical devices involved in the PCA scenario include: [a] CPOX or continuous pulse oximeters[358] for oxygen saturation [b] respiratory rate[359] measurements have evolved from the pneumotachometer[360] to spirometry for standard[361] pulmonary function testing in a clinical setting to continuous measurements which may be reliable (in near future) using sensors[362] and [c] capnography[363] instrumentation to measure end-tidal[364] carbon dioxide[365] (pressure in mm Hg). Instrument sales ignore (?) how the data must be integrated for patient safety platforms to avoid anoxic brain injury from unrecognized post-operative respiratory depression (PORD[366]).

The problem is with the embedded middleware. In general, outsourced software used by device manufacturers are built by remote locations responding to a spec without any process feedback or synergy with hardware. Middleware is often the "blackbox" which holds a number of so-called workflows which are linked to "model fitting[367] functions" in the software which is processing the data based on its "fit" with the embedded model. The lack of harmonization between hardware and software OEMs (lower tier suppliers in the device supply chain[368]) may be a thorny problem. Usually the "first world" brand controls the IP, marketing, sales and profit. The brand uploads a device-specific bill of materials (BOM) to an e-portal (e.g. Alibaba) to source hardware, assemble (Wuxi, China) and ship from warehouses (Kaohsiung, Taiwan) to customers using labels from the (US/EU) brand owners. Somewhere in between the software files from Bangalore, India or Mexico City, Mexico are downloaded. What often costs less than $50 to procure is sold for $50,000 plus additional annual cost of device maintenance/upgrades.

Medical professionals may be clueless about these business models. But ignorance is not bliss when errors can kill patients. Limitations of "model fitting" arising from, for example, the dependence on limited number of training sets may lead to extrapolations ("how to fit" and "what to fit") which may introduce errors[369], corrupt the input data and usher bias (Sjoding et al, 2020). Various sources of discrepancy makes it unreliable to trust the scientific authenticity of the output from the device or find confidence[370] in the significance of the result. These minutiae only matters if the investigators are sufficiently astute. In most cases, the output from the device is automated[371] and/or viewed as sacrosanct, which is not the case if the raw data (inaccessible to the medical professionals due to proprietary lock on device data ports) can be deconstructed. Emerging[372] tools[373] are increasingly relying on calculations based on shrink-wrapped algorithms and "apps" allowing plenty of room for post-market errors and artefacts to thrive, unchecked.

The extrapolation from relationships between data from individuals to model fitting of individual data to generic models based on aggregated training sets, is disconcerting. Depending on the acuity, automated decision support or prediction analytics based on "learning" models can easily go awry and even prove to be fatal. Unsupervised processes are a minefield for healthcare information arbitrage. Data processing via stand-alone apps may become that nail on the coffin.





Alveolar Gas Equation Calculator

Determines the partial pressure of alveolar oxygen that reflects the ventilation process.

The alveolar gas equation (AGE) reflect the relationship between the partial pressure of oxygen in the inspired air and that from the alveoli.

Alveolar oxygen is used in calculating the alveolar-arterial (A-a) gradient of oxygen and the amount of right-to-left cardiac shunt.

F_IO_2 0.21

P_{ATM} mmHg

PH_2O mmHg

p_aCO_2 mmHg

RQ 0.8

MDApp offers a growing collection of medical (apps) algorithms, scores & calculators grouped by specialty.

Figure 16: "App" after death[374]? Tsunami of apps (MDApp[375]) generates value for commerce. Its contribution to healthcare is not without merit, either, but exercising plenty of caution is prudent.

The reductionist approach to make "bite" size things fit for "apps" is a profitable *modus operandi* for grocery store design teams aiming to please the mobile smartphone user in quest of rapid retail therapy. In healthcare, the risk of apps pandering to the lowest common denominator may not be without consequences. Equations are essential in mathematical models which are at the heart of the "fitting" engines that run in the background of many apps which ingests data to provide data-driven outcome. Often, if not always, the data-driven outcome is of a poorer quality and less dependable if compared to ***data-informed*** information.

For example, in the case of PCA, what happens in the alveoli of the lungs due to opioids (morphine in PCA) is of particular concern with respect to respiratory depression and potential for fatal consequences if PORD continues. Thus, accurate composition and partial pressures of alveolar[376] air are critical. It is pivotal to recognize that the alveolar air is unlikely to be in a state of equilibrium (see Figure 17) in a post-operative or post-obstetric patient. Metrics of diffusion and exchange of inhaled/exhaled breathing gases (air) at the alveolar-capillary unit interface may not ***fit*** model values in an app because of the physiological changes accompanying the use PCA.

This distinction is excruciatingly important when PCA patient data are evaluated using frameworks, models, apps based on data (mass balance[377], steady-state equilibrium) from normal individuals where values (normal range) of parameters may be drawn from equilibrium phase of gaseous exchange. The cheaper and quicker point-of-care easy-to-use app may transmogrify to become diabolical and deadly due incorrect interpretation and extrapolation.

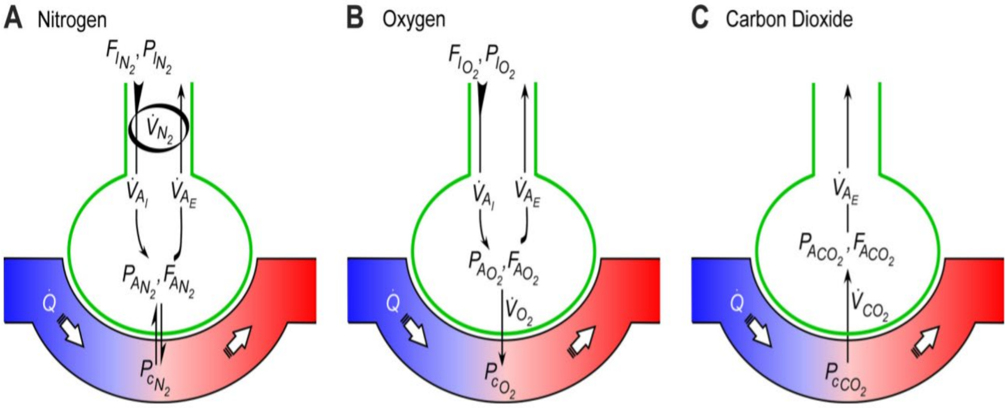
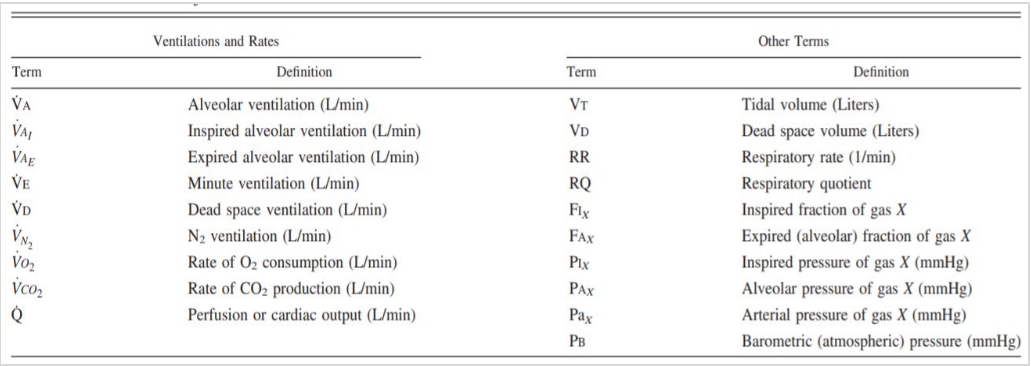
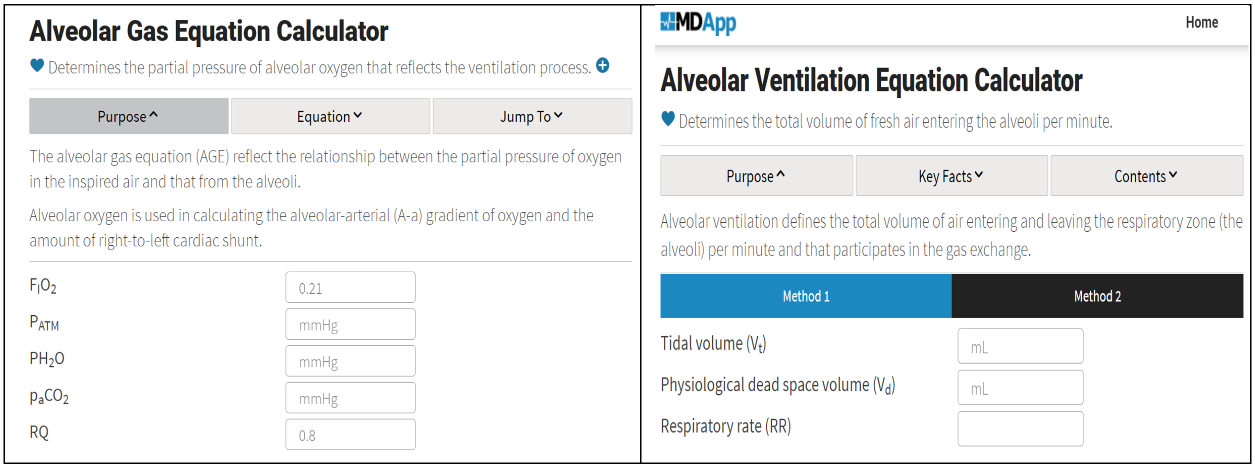


Fig. 1. Mass balance diagrams for N_2, CO_2, and O_2 in a representative alveolar-capillary unit. The principle of mass balance implies that, at steady state, the rate at which each gas enters the alveolus is equal to the rate at which each gas exits the alveolus. *A*: the rate N_2 is inspired equals the rate it is expired, denoted by $\dot{V}_{N_2}$. There is no net movement of N_2 between the alveolus (green outline) and the associated capillary (*c*). *B*: O_2 enters the alveolus by inspiration and leaves by two routes: *1*) net diffusion into the capillary, denoted by $\dot{V}O_2$, and *2*) expiration. *C*: CO_2 present in inspired gas is negligible. There is net diffusion of CO_2 from the capillary into the alveolus, a quantity denoted by $\dot{V}CO_2$, which equals the rate of CO_2 expiration. See Table 1 for definitions of terms used.



Ventilations and Rates		Other Terms	
Term	Definition	Term	Definition
$\dot{V}A$	Alveolar ventilation (L/min)	VT	Tidal volume (Liters)
$\dot{V}A_I$	Inspired alveolar ventilation (L/min)	VD	Dead space volume (Liters)
$\dot{V}A_E$	Expired alveolar ventilation (L/min)	RR	Respiratory rate (1/min)
$\dot{V}E$	Minute ventilation (L/min)	RQ	Respiratory quotient
$\dot{V}D$	Dead space ventilation (L/min)	FI_X	Inspired fraction of gas *X*
$\dot{V}_{N_2}$	N_2 ventilation (L/min)	FA_X	Expired (alveolar) fraction of gas *X*
$\dot{V}O_2$	Rate of O_2 consumption (L/min)	PI_X	Inspired pressure of gas *X* (mmHg)
$\dot{V}CO_2$	Rate of CO_2 production (L/min)	PA_X	Alveolar pressure of gas *X* (mmHg)
$\dot{Q}$	Perfusion or cardiac output (L/min)	Pa_X	Arterial pressure of gas *X* (mmHg)
		PB	Barometric (atmospheric) pressure (mmHg)

Figure 17: Pulmonary physiology at the heart of PCA depends on the alveolar gas equation[378] (oxygen equation) and the alveolar ventilation equation (carbon dioxide equation). Derivation of these equations[379] (top cartoon) are not trivial. The apps in Figure 18 use standard equations and normal ranges. The principle of mass balance relevant to physiology of multiple organ systems, is also applicable to pulmonary physiology. Relative rates with which substances (chemicals, air, gases, water) enter and exit these systems are subject to multiple conditions which can vary between individuals. Steady-state equilibrium occurs when the rates of entry and exit are equal under "normal" conditions. If existing tools are computed based on mass balance then one must question whether steady state equilibrium is applicable during opioid administration in PCA.



Alveolar Gas Equation Calculator

Determines the partial pressure of alveolar oxygen that reflects the ventilation process.

The alveolar gas equation (AGE) reflect the relationship between the partial pressure of oxygen in the inspired air and that from the alveoli.

Alveolar oxygen is used in calculating the alveolar-arterial (A-a) gradient of oxygen and the amount of right-to-left cardiac shunt.

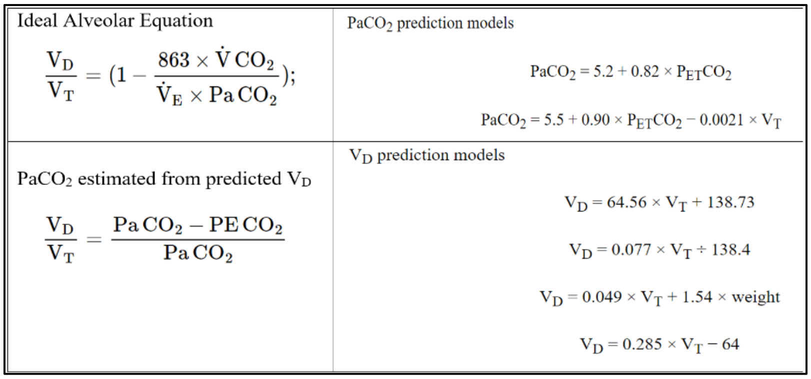
F_iO_2	0.21
P_{ATM}	mmHg
PH_2O	mmHg
p_aCO_2	mmHg
RQ	0.8

Alveolar Ventilation Equation Calculator

Determines the total volume of fresh air entering the alveoli per minute.

Alveolar ventilation defines the total volume of air entering and leaving the respiratory zone (the alveoli) per minute and that participates in the gas exchange.

Tidal volume (V_t)	mL
Physiological dead space volume (V_d)	mL
Respiratory rate (RR)	



Ideal Alveolar Equation $\frac{V_D}{V_T} = (1 - \frac{863 \times \dot{V}\,CO_2}{\dot{V}_E \times Pa\,CO_2});$	$PaCO_2$ prediction models $PaCO_2 = 5.2 + 0.82 \times P_{ET}CO_2$ $PaCO_2 = 5.5 + 0.90 \times P_{ET}CO_2 - 0.0021 \times V_T$
$PaCO_2$ estimated from predicted V_D $\frac{V_D}{V_T} = \frac{Pa\,CO_2 - PE\,CO_2}{Pa\,CO_2}$	V_D prediction models $V_D = 64.56 \times V_T + 138.73$ $V_D = 0.077 \times V_T \div 138.4$ $V_D = 0.049 \times V_T + 1.54 \times \text{weight}$ $V_D = 0.285 \times V_T - 64$

Figure 18: The holy grail of physiology is the maintenance of homeostasis. For pulmonary physiology it means the parameters for steady state equilibrium must optimize and maintain gaseous exchange within ranges suitable for normal functions and states of activity. Gas exchange in the alveoli is a sub-part of the recorded gas exchange in the lungs because conducting airways (connecting air passages) do not have gas exchange potential and referred to as "dead" space volume ("wasted" breath) denoted by V_D. V_D was calculated via 'ideal' alveolar equations, whereas $PaCO_2$ or V_D models were based on end-tidal CO_2 tension ($P_{ET}CO_2$), tidal volume (V_T), and/or weight. Breathing faster or deeper enhances gas exchange while rapid shallow breathing tends to be less efficient at gas exchange. For PCA standard "models" of breathing may not apply due to post-operative respiratory depression (PORD). Destruction of alveolar walls in patients with pre-existing chronic obstructive pulmonary disease (COPD) can result in coalescing of multiple alveoli, giving rise to enlarged air spaces that are poorly perfused (e.g., emphysema). In this instance the physiological dead space volume in PCA patients with COPD are a sum of V_D due to connecting air passages (dead space without gas exchange potential) and V_D due to alveolar air that no longer participates in normal alveolar respiratory gas exchange. Thus, the true value of V_D must be taken into account for PCA. Is this granularity of data in the context of PCA likely to be a part of the status quo embedded in the app? Similar scenarios may be presented due to pulmonary embolism which may block perfusion to entire alveolar capillary units and will significantly alter the alveolar gas equations[380]. Medical vigilance of digital representation can make the difference between life and (app-driven) death.

The ability to adapt mathematical models and frameworks for specific scenarios (unlikely for apps) may deliver benefits for precision medicine but not in the hands of brain-less digital twins. We are practicing imprecision medicine if we chose to remain ignorant about the software, middleware and apps-on-models incapable of changing or adapting the "fit" to fit what the patient needs. Fitting the equation to the patient is highly recommended and desirable but not an easy task. The "fitting" to patient will require patient-specific data for multiple parameters which may be difficult to obtain (and configure the app) for post-operative patients.

Theoretically, if we had workbenches or user interfaces with each parameter provided in a menu of choices, then an expert may be able to partially adjust/adapt the values. Will these tools and effort improve point-of-care services, patient safety, quality of care and efficiency?

DIDS is a vision worth pursuing. Tools for DIDS include SCRATCH-friendly UIs, Lego Mindstorms approaches and Ansys-esque[381] workbenches. But these are ideas and tools must be orchestrated in order to be adapted for meaningful use relative to specific domains.

The future workforce of millennials growing up on a diet of short-cuts, videos and apps tend to gravitate to user-friendly user interfaces. Such habits accelerate through undergraduate years and spillover into medical school, residency and fellowships. Digital representations in healthcare are beneficial but knowledge must be combined with wisdom to know when to avoid digital interpretations in favor of incisive tools from Nature (e.g., allosteric[382] machines[383]).

The immutability of mathematical constructs and the adaptive complexity inherent in biological flexibility indicates that there are "transforming principles" which are practiced by Nature, unbeknownst to humans. For example, the mathematics and physics of temperature (heat and cold) are biologically rendered and interpreted by the nervous system, when we perceive heat (ion channel TRPV1[384]) or cold (ion channel TRPM8[385]).

This research[386] encourages us to build mathematical models because we recognize that bridges exist to ferry between mathematically rigorous laws of physics and (often laissez-faire) biological systems. Uncovering the mechanisms to enable suitable application-specific balance between immutability and flexibility may be one way to build knowledge bridges. Some bridges may lead to point solutions[387] while others may connect to swarms[388].

The principles and practice of DIDS is a call to harness the power of mathematical rigidity in the service of society through case-specific interpretations. Any branch of decision science, for example DIDS, which involves humans, must find tools and technologies to dissect, curate and synthesize the convergence of rational and irrational. Even while immersed in the quagmire of rules and tools, one must remain creatively cognizant of the fact that the inevitable irrational (non-deterministic?) accompanies the rational (deterministic?) not only by chance but also by choice, the irrational[389] choices[390], made by human design.

IMMUNIZING DIGITAL TWINS AND COUSINS FROM CYBERSECURITY RISKS

Being cognizant about device/instrument security/cybersecurity in mission-critical applications is a mandatory dimension in the 21st century. Billions or trillions of devices connect with apps which may not possess any provision for cybersecurity even when used in critical applications, for example, in energy, infrastructure, healthcare. For unprotected devices in the post-market phase, the science[391] of cybersecurity must find ways to deliver threat-proportionate dose of cybersecurity to uphold the key tenets of availability, integrity, and confidentiality[392] for information and data in any digital representation (IoT, CPS, digital twins, etc.).

Cybersecurity must be addressed with equal zest for digital representation of physical objects (including medical devices). We will focus on life saving ventilators, we have heard so much about during the pandemic. Even though we will discuss only a few details of ventilator function, the cybersecurity component is not specific for the ventilator but for medical devices (a hypothetical device-agnostic science of cybersecurity is discussed in Datta, 2022, unpublished).

Figure 15 indicates that integrating *ad hoc* objects/devices may be a necessity. Devices and apps added to geospatially networked system introduces risks by violating trust boundaries. Poor attention to cybersecurity by design and complexity or lack of standards influence device manufacturing in healthcare as well as other sectors (e.g., energy, infrastructure, transportation). Pre-market and post-market gaps in cybersecurity amplify vulnerabilities for attacks. The usual cybersecurity approach to mitigating risks when dealing with connected devices (e.g., IoT, CPS, digital twins) uses threat models as a guide to track and analyze suspected cyber intrusions.

The spread of ransomware in healthcare[393] and hospitals[394] has kept pace[395] with the pandemic which has resulted in an epidemic[396] of cyberattacks. Response from agencies[397] indicate[398] that models (e.g., ATT&CK[399]) are necessary[400] but thinking beyond conventional[401] culture[402] will save lives since lives[403] are increasingly inextricably linked with the networked physical world[404] system (Engels *et al*, 2002). Ubiquitous[405] computing may include trillions of devices[406] manufactured by millions of companies, with geographically dispersed global supply chains which vary significantly in their competencies. It is difficult for regulatory agencies[407] to provide oversight[408] for these devices which may connect to and communicate via the internet.

Systems integration of devices, including IoT-type cyberphysical systems (CPS) and the emergence of digital twins/cousins will add value to systems performance. But, cybersecurity risks[409] ***after*** systems integration must be re-evaluated[410] and mitigation strategies updated if systems integration violates the trust boundaries created during pre-market system design. Cybersecurity risks/threats introduced into systems due to integrating external devices may be dynamic, cryptic or volatile. Examples include sensors[411] in vehicles[412], digital diagnostics[413], medical devices[414], control-valve actuators in power plants[415] and photovoltaics in distributed energy resource optimization (micro-grids). Connectivity between these physical entities and their digital representations over the open internet increases the risks due to cybersecurity.

Cybersecurity by design, in general, is an aspirational goal due to lack of good security abstractions[416] as a guide. For device manufacturers the incorporation of cybersecurity is neither a core competency nor a business priority. Supply chain network planners relegate procurement functions to OEMs (original equipment manufacturers) mostly located in low-cost geographies who are less aware, ill-equipped and resource constrained even to consider cybersecurity in their design. Trillions of sub-systems, sub-components or spare parts are percolating globally without any form of place-holder protection from cybersecurity attacks or cybersecurity awareness.

Most businesses lack transparency, visibility and accountability with respect to supply chain assurance from their network of supply chain partners (Sarbanes-Oxley Act[417] of 2002). These actors source goods and services from sub-layers of the value network but businesses may be unaware of cryptology-based markers for supply-chain assurance. Hence, cybersecurity by design may be a delusional expectation for products with multi-tier supply chains extending into small and medium enterprises. The elusive quest to "build secure" during the pre-market phase is worthy in principle but may remain an illusion for cybersecurity protagonists who are irrationally optimistic in their expectation about the notion of global diffusion of cybersecurity, in practice.

Guidance for manufacturers[418] promotes the "build secure" adage but the glacial pace of change reflects how manufacturers may view or resist cybersecurity unless mandated, regulated, enforced or incentivized to better optimize specific outcomes, for example, end-point security[419]. Risks due to gaps[420] between principles (guidance) and practice (implementation at point of use) in mission critical operations (energy, power grid, infrastructure, hospitals, healthcare) could be fatal. Lack of cybersecurity may increase the risk of mortality and morbidity in healthcare[421], hospitals, telemedicine[422] for war fighters and medical devices for home health monitoring. Programs to mitigate cybersecurity risks due to vulnerabilities arising from systems integration of devices may become an unsurmountable and unmanageable problem of gigantic proportions if a device-specific[423] approach was the only *modus operandi*. There is no known panacea solution for device-level cybersecurity in the post-market phase.

In terms of digital twins, one example of edge-dependent dynamic variant reconfiguration incorporates digital twins as a "mirage" for apps running *Shadow Figment*[424] where intruders are tracked[425] via *honeypots*[426] using a "digital shadow" (fake digital duplicate / digital twin) of the actual operation (which stays protected/secured). Digital twins can change depending on the application running the honey pot-esque project[427] "Shadow Figment" created by PNNL[428]. It is an innovative application of digital representation to boost cybersecurity and conceptually may converge with hardware and software executing Agent-driven tasks[429].

To find new horizons, convergence may be key and history may be a good guide. Insights from 1945[430] partially captured the concept of ubiquitous[431] computing in the 1990s. Progress[432] over a century created computing which can sense, predict, plan, process data, execute complex applications and continuously compute across distributed systems for performance optimization, load-balancing, fault tolerance as well as other functions, but not without a few problems[433].

From the IC (integrated circuits) to the ICU (intensive care units) computing today is a complex orchestration of CPUs (central processing unit), GPUs (graphics pu) and NPUs (neural pu). Cybersecurity for devices on land (mobile edge devices) communicating with data centers under the sea[434] or cloud computing on MARS via the interplanetary internet[435] (interplanetary internet of things) must expect the unexpected. If the questions are correct, we are likely to uncover data to inform our knowledge.

For the current discussion, the device-agnostic platform approach to device cybersecurity will focus on the ventilator, a medical device used in intensive care units (SICU, NICU, surgical, neonatal), emergency departments as well as for home health[436]. Microprocessor (IC) controlled mechanical ventilators[437] have rudimentary computational needs but saves lives. These devices are regulated by handful of variables (Tables 3 and 4) with pre-loaded instructions (algorithms). Medical professionals can change parameters based on patient-centric variables and available resources. The "digital twin" equivalent of a hospital ventilator via a mobile phone app provides near real-time connectivity with the patient's data, analytical tools and point-of-use knowledge. It is unlikely to be feasible as a global model but in highly affluent nations such a digital twin may not be very far from the horizon, if the model can successfully capture key functions/data.

Ventilators, like most devices, are potentially at risk from malicious events (unauthorized users/intruders). Vulnerabilities in design may become fatal without cybersecurity provisions because ventilators are not only a device for data acquisition but also a device that performs semi-autonomous or autonomous data-informed actuation in cases of acute respiratory care to maintain breathing functions. Monitoring the amount of oxygen (fraction of inspired oxygen, Fi[438]) delivered to the patient (FiO_2) is a critical data[439] element which must be secured to avoid hyperoxia or hypoxia. There is a glut of ventilator designs from engineers[440] and enthusiasts[441] in response to the pandemic in affluent nations[442] as well as low-cost ventilators[443] for resource-limited[444] settings. Cybersecurity by design does not appear to be a part of this response.

Malicious tampering with ventilators may induce oxygen toxicity[445] or poisoning[446] leading to cessation of breathing (respiratory arrest/failure). Hypoxemia, hypercapnia and hypoxia may result in brain injury[447] within 3-4 minutes. Severe brain damage and/or coma may lead to brain death[448] followed by clinical death. However, after cessation of breathing the case/patient-centric time to death varies[449] widely.

Cybersecurity of acute care medical devices is a life and death matter, in a span of a few minutes. In hospitals, ventilators can be monitored by professionals who are in proximity of the device but home health users may request remote changes to the device (ventilator) depending on the physiological status. Cybersecurity for remote monitoring require additional stringency with respect to endpoint identity[450], device user identification and internet protocol (IP) security. Using IP-based identification[451] with security and routing[452] controls are necessary for trust in asset management, authentication, authorization, and remote maintenance/activities.

Traditionally, one or more passwords may be used to authenticate the patient receiving services at home and the medical professional authorized to deliver the services. In an open networking environment, beyond firewalls, a tool such as MIT-Kerberos[453] authentication[454] server uses a coded format of passwords which are compared to a time-stamped code string but the actual passwords are never sent across open networks. After authentication is complete only then traditional IP transport layer security (TLS[455]) is established.

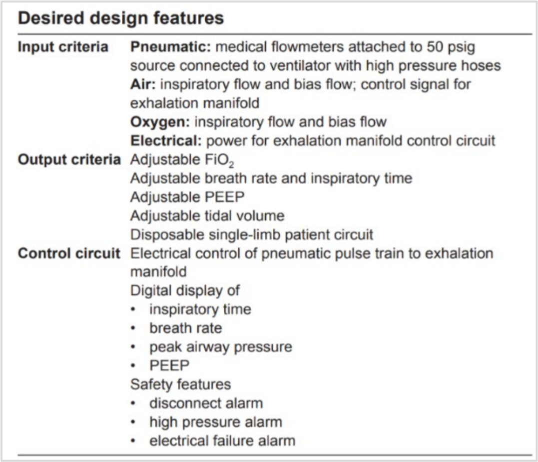
Ventilators assist with improving pulmonary perfusion which requires certain design criteria and performance indicators (Tables 3 and 4). For patients who are unable to breath on their own it provides mechanical "lung assist" and delivers a mixture of oxygen to improve perfusion. Ventilators[456] provide different types of assisted breathing functions[457] (volume assist/control; pressure assist/control; pressure support ventilation; volume SIMV [synchronized intermittent mandatory ventilation]; and pressure SIMV). From a cybersecurity perspective the microprocessor is involved in the execution of a set of algorithms for machine trigger variables and machine cycle variables as well as some compensatory mechanisms (SIMV) for respiratory optimization (Figure 19, Table 3).

Direct (through device) or indirect (through digital twin) cybersecurity attacks may disrupt mechanical assistance or oxygen concentration, which, if undetected, may lead to severe brain damage, coma and/or clinal death (for example, lack of brain-stem responses). Simple "bit dribbling" by malicious intruders can slightly increase or decrease the range of values (low/high) to induce cessation of assisted breathing or alter the gaseous composition of inhaled breath leading to brain death and congestive heart failure (CHF).

In the context of medical devices, a "by-product" is the proliferation of device-specific (status) alarms[458] triggered when values (data/measurement/metrics) falls above or below the threshold/range (pre-set, hard-coded). Altering values may perturb thresholds/ranges and trigger automatic alarms. Cybersecurity attacks could trigger tens or hundreds of alarms in a hospital to deliberately sow debilitating confusion. Reduction[459] of alarm events[460] is a thorny issue. What if it was a false positive or what if the alarm caused a fatal distraction?

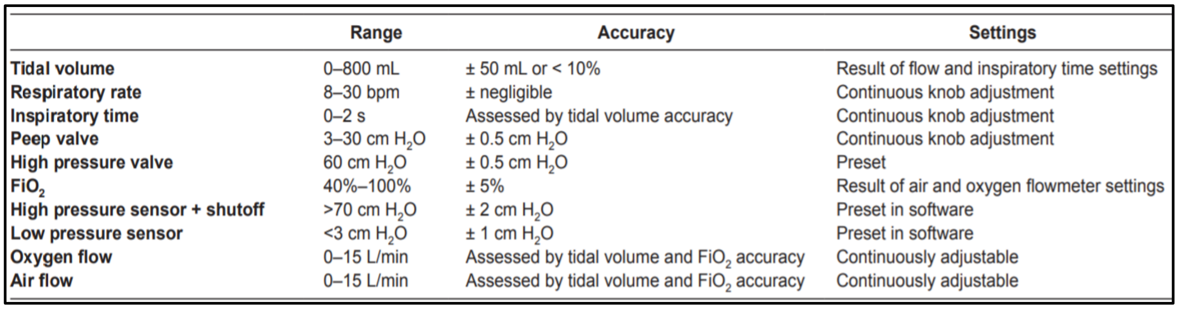
Performance of alarms and the criteria governing their on/off status are complex legal issues at the heart of patient safety. Table 3 indicates "***disconnect alarm***" is a required "safety feature" but in contrast Table 4 emphasizes ***need for alarm***. Alarms are linked to a network of physiological variables (Table 3, bottom panel) which are measured and communicated in near real-time to determine the status of the patient. Addressing this tug-of-war requires continuous data analytics by combining data from different devices (different device manufacturers). The analysis of data instructs embedded/coded routines for triggering safety protocols, including alarms, which are essential elements of patient safety. Alarms in the context of patient safety should be secured and cannot be selectively turned on/off without medical authorization. Breach of cybersecurity in any device with an alarm may be as simple as to turn-on or turn-off the alarm (why "on-off" state machine security is not trivial and the consequences may be fatal).

Table 3:
Desired design features for ventilators (right). Performance criteria/indicators[461] to maintain physiological breathing in adults (bold, panel).



Desired design features

Input criteria	**Pneumatic:** medical flowmeters attached to 50 psig source connected to ventilator with high pressure hoses **Air:** inspiratory flow and bias flow; control signal for exhalation manifold **Oxygen:** inspiratory flow and bias flow **Electrical:** power for exhalation manifold control circuit
Output criteria	Adjustable FiO_2 Adjustable breath rate and inspiratory time Adjustable PEEP Adjustable tidal volume Disposable single-limb patient circuit
Control circuit	Electrical control of pneumatic pulse train to exhalation manifold Digital display of • inspiratory time • breath rate • peak airway pressure • PEEP Safety features • disconnect alarm • high pressure alarm • electrical failure alarm



	Range	Accuracy	Settings
Tidal volume	0–800 mL	± 50 mL or < 10%	Result of flow and inspiratory time settings
Respiratory rate	8–30 bpm	± negligible	Continuous knob adjustment
Inspiratory time	0–2 s	Assessed by tidal volume accuracy	Continuous knob adjustment
Peep valve	3–30 cm H_2O	± 0.5 cm H_2O	Continuous knob adjustment
High pressure valve	60 cm H_2O	± 0.5 cm H_2O	Preset
FiO_2	40%–100%	± 5%	Result of air and oxygen flowmeter settings
High pressure sensor + shutoff	>70 cm H_2O	± 2 cm H_2O	Preset in software
Low pressure sensor	<3 cm H_2O	± 1 cm H_2O	Preset in software
Oxygen flow	0–15 L/min	Assessed by tidal volume and FiO_2 accuracy	Continuously adjustable
Air flow	0–15 L/min	Assessed by tidal volume and FiO_2 accuracy	Continuously adjustable

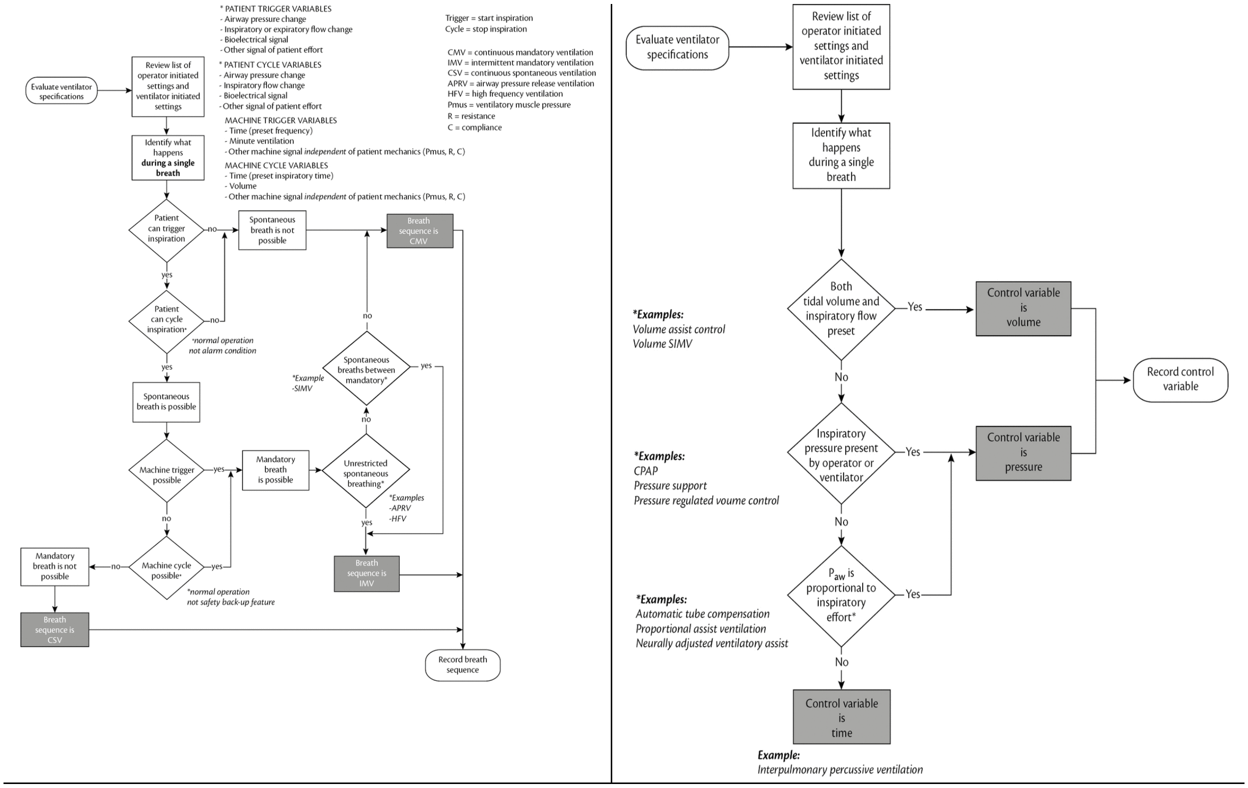


Figure 19: Decision tree for ventilators (Chatburn, 2016) are guided by patient data & feedback.

Ventilator Variables	What happens/comments if changed/altered. Nodes where cybersecurity may be essential.
Respiratory Rate (RR) (breaths per minute) between 6 – 40 (normal).	
I/E Ratio (inspiratory/expiration time ratio) recommended start 1:2; range of 1:1 – 1:4.	
Assist Control is based on a *Trigger* Sensitivity (trigger variables, see Figure 2). When a patient tries to inspire, they can cause a dip (2 to 7 cm H_2O) with respect to PEEP pressure (not necessarily equal to atmospheric pressure). Airway pressure must be monitored continually (units in cm H_2O) Maximum pressure: 40 Plateau pressure: 30 Passive mechanical blow-off valve: 40 PEEP* 5–15 cm (required) Patient-centric need 10–15	Respiratory Rate (RR) of 6-9 are applicable to Assist Control.
*Positive end-expiratory pressure (PEEP) is a value set up in patients receiving invasive or non-invasive mechanical ventilation.	Failure conditions must result in an alarm and permit conversion to **manual clinician override.** If automatic ventilation fails, the conversion to manual ventilation must be ***immediate.***
Tidal Volume (TV) (air volume pushed into lung) between 200 – 800 mL (patient-centric, based on patient weight)	
etCO_2 (end-tidal CO_2 is the amount of carbon dioxide in exhaled air**)** assesses ventilation (35-45 mmHg or 4.0-5.7kPa, kiloPascals) and perfusion (gaseous exchange in the lungs). High etCO_2 signals good ventilation, while low etCO_2 signals hypoventilation.	Capnometric data (partial pressure of CO_2 in exhaled air, etCO2, generated as waveform data - capnograph) is the fastest indicator to assess ***if ventilation is compromised***. ***Immediate*** action is recommended without waiting for pulse oximetry data which may be subject to some degree of phase equilibration since pulse oximetry assesses the amount of *oxygen bound to RBC* (red blood cells).

Table 4: Nodes of control in ventilators which, if altered, may affect mortality and morbidity. Ventilator settings and values are obtained from MGH[462] ICUs (CoVID-19 patients).

Data analysis, feedback and decision support at point-of-use may have *cyber* components linked with the ecosystem of the *physical* medical instrument or device. The supply chain of this closed loop *cyberphysical* system[463] (CPS[464]) must be secured. The weakest link is a penetration point to corrupt data or exfiltrate data and information. Corrupt data, if stored and analyzed, may lead to harmful decisions, including death (Figures 28 and 29).

Lateral persistence and lateral movement of intruders exploiting the gaps in cyberdefense may be catastrophic. Intruders "tunnel" from edge devices to storage devices, e.g., from the ventilator's digital twin to the electronic health records or electronic medical records (EHR, EMR). Tunneling through routers (wired/wireless networks) to access devices and gain special privileges to data stores are a part of the ecosystem where the reality of threats from ransomware could become deadly. Ransomware at the device level is annoying (device can be replaced) but databases are the Achilles heel for systems, unless dynamic redundancy is a daily/hourly ritual.

In an ecosystem-centric view, if the network is compromised, device cyber-security becomes exponentially significant to prevent data tampering at the point-of-use. Can sensor devices store data (data persistence?) rather than transmitting the data if the network is not secure? Ubiquity of sensors makes this a serious problem with life and death consequences in certain cases. For example, oxygen sensors[465] in ventilators are vital to prevent hyperoxia or hypoxia by using FiO_2 data (Fig 19, left) to adjust the composition of the inhaled gaseous mix.

Low cost sensors without cybersecurity characteristics may introduce higher risks (the cost savings appears to be penny wise but pound foolish). It is an open question whether low cost sensors without "local cache" or tiny databases are suitable for critical operations. It may be useful to revisit DARPA Smart Dust[466] with respect to sensor networks (tinyOS[467], tinyDB[468]), cybersecurity of data, *data acquisition* from devices[469] in hospitals, industry and the edge e.g. IoT-type wearable photoplethysmography[470] (see related suggestion in Figure 5).

Devices which generate/collect continuous waveform data[471] are vulnerable to minor changes (see Figures 28 and 29). Intermittent sampling periods for continuous variables (gaps in time series data[472]) could change the data profile and alter the data-informed analytical outcome. Storage[473] of waveform data "samples" (sampling time) in patient records (EHR[474]) may be detrimental to healthcare due to errors in diagnosis, prognosis, treatment and medication. Deliberate artefacts[475] introduced[476] into data under the guise of efficacy[477] further degrades the data and even more corrupted data are stored in electronic health / medical records (EHR, EMR).

Errors also arise due to proprietary restrictions in data handling enforced by device manufacturers and software vendors (EHR, EMR) who ruthlessly maintain inaccessible data dictionaries (Epic Systems) which prevents data distribution between different software and middleware between clinics and hospitals. Vendor-Implemented Legal Exclusion (VILE) deliberately obstructs data distribution using open data distribution standards (DDS) and prevents data interoperability. VILE contributes to medical errors and has made medical errors the 3rd leading cause of death[478] in the US. Patient safety[479] is a *vicious* task even without cybersecurity risks and new classes of threats from digital twins at home and the hospital.

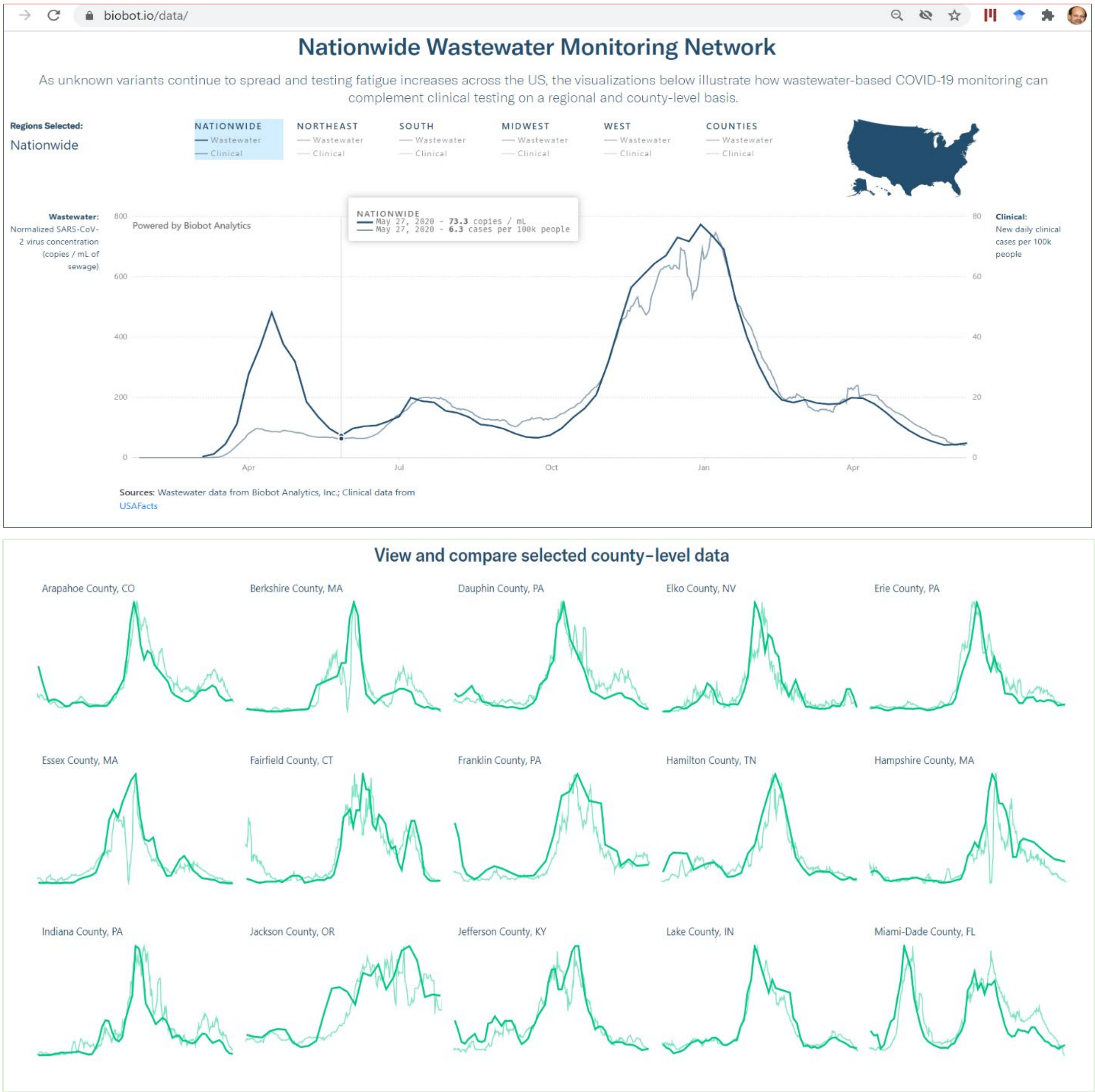
SEWERS: KILLER APP FOR DIGITAL TWINS?

If *we are what we eat*[480] then it follows that *we are what we excrete*[481] (excrements). This centuries-old observation was scientifically[482] substantiated[483] in the 1960's yet the principles are still not a part of science[484] or education[485] in schools. Public health[486] practices lack systemic implementation and dissemination of this crucial information was lacking from public discourse, until very[487] recently, but only as a knee-jerk reaction from the great awakening catalyzed by the global catastrophe we are still experiencing from the CoVID-19 pandemic due to SARS-CoV-2.

Figure 20: Wastewater-based epidemiology is crucial to monitor disease outbreaks and other public health threats (e.g., illicit[488] drugs[489]) yet it remains just an idea for many cities. Half-truths seeded by consulting companies[490] has resulted in trillions of dollars of waste due digital transformation (ZoBell, 2018) yet the wealth of consultants and their companies grew beyond civilized imagination. This photograph from UC Davis (Safford *et al* 2022) is one indication how corporate belligerence about "digital transformation" has starved investments for public good. Flying taxis[491] are worth "guiding" and the press[492] is coy while cooing about investments flying high and celebrating deception[493]. In the century which has witnessed the Mars Rover[494] it is hard to fathom why public health surveillance[495] must rely on people literally *going down the drain* for sample collection, while the nefarious lot are peddling drones[496] and the unscrupulous promotes sales of home[497] robots? Is it justified for the public if they chose to be indignant?

```
U=Araihazar
M=Khaserkandi
V=Khaser Kandi
Start>=85'
Fail=22/100
Average arsenic 44 ppb
42 safe of 71 wells
 45- 90'  40 of  69
115-130'   2 of   2
```

Figure 21: Water contamination[498] is a health[499] risk and chronic[500] Arsenic[501] toxicity[502] affects millions in Bangladesh[503] (top panel: symptoms[504] of Arsenic poisoning[505]). Sensing[506] (bottom, right) Arsenic in surface water[507] can save lives[508] if the feasible systemic solution may venture beyond measuring[509] and alerts - bottom, left (van Geen *et al*, 2006). Digital representation of Arsenic concentration (parts per million) in drinking water (GIS map) may mimic the experiment (Nokia UI, bottom, left) and disseminate the geo-tagged data. What is the value of science[510] or data for a thirsty child, without a mobile phone, in front of a tube well[511] for water?



Nationwide Wastewater Monitoring Network

As unknown variants continue to spread and testing fatigue increases across the US, the visualizations below illustrate how wastewater-based COVID-19 monitoring can complement clinical testing on a regional and county-level basis.

Sources: Wastewater data from Biobot Analytics, Inc.; Clinical data from USAFacts

View and compare selected county–level data

Figure 22: Cartoon of data from Biobot[512] network of wastewater treatment plants: is there any information in the data[513]? At least for affluent nations[514] if the digital economics[515] of digital twins of wastewater surveillance for public health is feasible, it may provide ***value***. This may be a 'B2B' business with a twist. Businesses creating tools for surveillance will sell to municipal customers (for sewers). Business to government sales is not *new* but public health surveillance involves people, directly, in a manner analogous to domains touched by FDA and CDC. Will public health surveillance businesses still focus on shareholder value or deliver science for society? Will it fashion itself as a social business with morals or seek 501(c)n[516] exemptions?

However paradoxical it may seem, it may be only a tiny bit of an exaggeration to state that sewer systems may become the new paradigm for global health and an indicator of public wellness. Data from sewers may inform molecular epidemiology of communities, local and global. To acquire a better handle on quality of life should we consider digital representations and digital twins for sewer systems? Epidemiologists armed with time series data can mine patterns of activity in sewer systems and perhaps predict emergence of potential pathogens before they can reach critical mass or exceed thresholds to become emergencies. This thinking suits nations where managed sewer systems are the norm and sanitation services are under municipal supervision (open defecation[517] continues[518] to be a problem in many nations).

Implementing some sort of a sewer digital twin implies that data from sewers will feed the digital representation. Geo-tagged sensor data from the sewer wireless sensor network (**SWSN**), can be uploaded through a gateway to the internet and accessed by any digital device. *Sensor in the sewer*[519] is analogous to the 19th century practice of *canaries in the coal mine*[520].

The ***science of the data*** from SWSN will be influenced by [1] the molecular science of the target (what do we wish to detect from the sewer) and [2] sensor engineering with respect to signal acquisition and signal transduction. Without the science we don't know what it is that we are detecting and without the engineering we lack the **connectivity**, hence, the **data** to **analyze**, whether we detected our target (or anything), at all. If we solve the science and engineering issues, is that success in principle or success in practice? If we succeed, can we implement a physical SWSN and design a digital representation of SWSN?

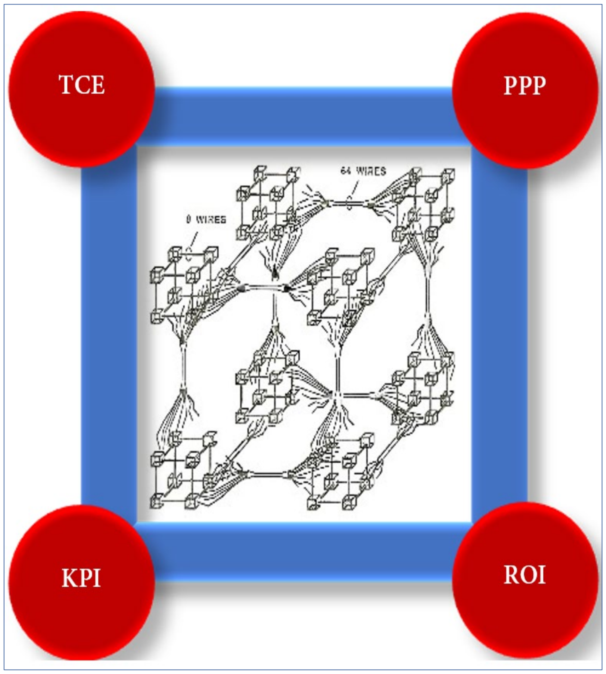


Figure 23: Success in principle is not success in practice. Solving science and engineering issues does not guarantee implementation and adoption unless the economics of technology[521] are favorable. Cartoon shows business pillars which must be standing to uphold SWSN as a tool. TCE[522] (Transaction cost economics), KPI[523] (Key Performance Indicators), ROI (Return on Investment) & Public Private Partnerships (PPP). The interrelationships between these factors are illustrated as agents[524] in a cube-of-cubes[525]. Can SWSN and ethical profitability co-exist? Can entrepreneurial innovation seed SWSN as a social business with the potential to be a catalyst for local/global economic growth?

SEND	**SAMD**
Sensor is installed *inside* the sewer → sensor Detects target molecule(s) → data transmitted to gateway and uploaded to internet → users auto download data from internet to device.	**Sample of sewer fluid is extracted → sample is tested to Detect target molecule(s) at a testing facility** → data uploaded to internet → users auto download data from internet (for Figures 20 and 22).
The difference between the two lies with the science of SEND vs the engineering of SAMD.	

The science of data with respect to SWSN for public health epidemiology may be significantly different depending on the sequence of events: **SEND** or **SAMD** (above). In the section "*science behind the data*" we discussed why and how the bio-recognition element of the sensor must ***bind*** the target molecule we wish to detect. If detection is due to the binding then the sensor transduces the data after the binding, but the sensor material ***stays bound*** to the target molecule. Binding triggers signal transduction and data is transmitted but the sensor is used up ("consumed"). The sensor is no longer available to bind another target molecule. Unless the sensor is replaced, target molecules may be still in the sample but there will be no new data from the sensor which is no longer available to bind, again.

If the target we wish to detect was light, motion or temperature, then light sensors, motion sensors and temperature sensors continuously sense, using waveforms for detection. The sensor is not "consumed" and keeps detecting the target wave as long as the sensor has adequate energy (battery life of sensor). In the wave scenario, by eliminating the "binding" of molecules or particles, we have improved the usability of the sensor system which does not need frequent replenishment to continue sensing and generating data.

Due to our very limited knowledge, the ability to detect molecules using waves or reflection/refraction of waves is currently an open research question (we don't know). At the less than 100 nanometer (nm) range (virions, proteins, our targets for detection) the wavelength of visible light (374-749nm, "white" light) is unlikely to detect changes in a complex colloidal soup (sewer sample, wastewater) between the absence or presence of very small molecules.

Waveform detection ***without binding*** may help to install sensors ***inside*** sewers. One option involves Terahertz (THz) radiation but the road to a THz solution may need quite a few inventions and research into unknown unknowns.

Terahertz (THz, 1 trillion Hertz or 10^{12} Hertz) occupies the spectrum range 0.3 -3.0 THz or 0.3×10^{12} - 3×10^{12} Hertz (Hz) to the left (Fig 24) of visible light (400×10^{12} – 800×10^{12} Hertz or 4×10^{14} to 8×10^{14} cycles per second or Hertz). Terahertz has the potential for applications in communication[526], sensing, spectroscopy and imaging due to its non-ionizing photon energy, ability to penetrate optically opaque materials (abundant in sewers, wastewater, soil), unique spectral signatures for macro-molecules and chemicals (most desirable properties for sensors in the sewer, wastewater and soil).

The combination of sensing (spectral signature[527] from molecular dynamics[528] of folded proteins[529]) and communication (data transmission) on a THz chip[530] may unleash the flood of sensors for sewers which can ***continuously detect*** without binding and transmit data when it detects the target (analogous to light, motion, temperature sensors). Submillimeter range THz spectroscopy is expected to yield macromolecular motions as ***protein signatures*** in aqueous environments[531] but calculation of the absorption spectra may suffer from (uncertain?) absorption of THz by water (attenuated by the presence of water). Probing the science of this problem may uncover solutions which may lead to some form of standardization of spectral signatures for proteins. If a THz spectral signature for SARS-CoV-2 Spike protein is a reality and if we have a THz sensor in the sewer which elicits this spectral signature, then the data will reveal that the THz sensor detected SARS-CoV-2[532] in the sewer (sewer sample, wastewater). If and when we have a THz sensor for ***continuous*** monitoring in sewer systems for SARS-CoV-2, the cost may be $50,000 per sensor. If the sensitivity and specificity of the sensor is reliable and reproducible then we have a robust product ($50,000 per sensor). After decades of innovation, reduction in transaction cost and economies of scale, an improved sensor using Terahertz spectroscopy may be ubiquitous in sewer systems and may cost even less than $1 per sensor.

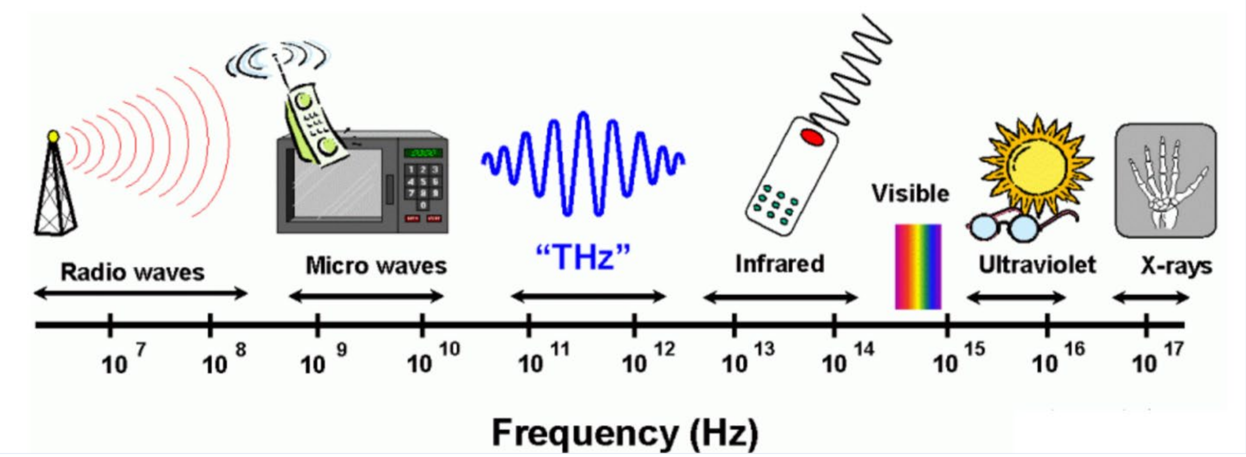


Figure 24: The economics of technology and value proposition will determine if THz sensors in the sewers may fly, adapt or die[533]. Let us explore Ampex, they pioneered the video recorder market in 1956. Each VCR unit was priced at $50,000. Masaru Ibuka, co-founder of Sony and Yuma Shiraishi at JVC, set out to produce VCRs that would cost 1% of Ampex's price. In the 1980's, VCR sales went from $17 million to $2 billion at Sony, $2 million to $2 billion at JVC, $6 million to $3 billion at Matsushita[534]. By 2000's VCR's were ~$50 and VHS tapes were ~$1. Millennials don't even know about VCRs. What about microprocessors, memory, storage? To develop a low-cost sensor for resource constrained[535] communities the initial "sticker" shock (high cost) may be the price of excellence and the recognition that the next billion users deserve effective tools, trusted[536] systems and *knowledge to build a better compass, to create new roads* (not just a road map, to merely find new roads).

The discussion about wave, e.g., Terahertz radiation, as the sensing medium is due our search for reusable sensors for continuous monitoring with no or ultra-low hysteresis[537]. Sensors which bind molecules exhibit very high hysteresis, that is, sensor characteristics are permanently changed. The failure to return to baseline criteria (default factory specifications) makes the sensor useless or highly error-prone, after initial binding. Changing sensors in the sewer after each binding event makes such sensors a non-starter for SWSN (sewer wireless sensor network).

The science of waveform sensing using Terahertz spectroscopy is not hypothetical. But, can we create an *implementable* ***sensor product*** required to detect viruses and bacteria in sewers or in the agricultural industry for food safety? It may not be impossible to create a working prototype in a lab but installation in sewers will require idiot-proofing to withstand manhandling.

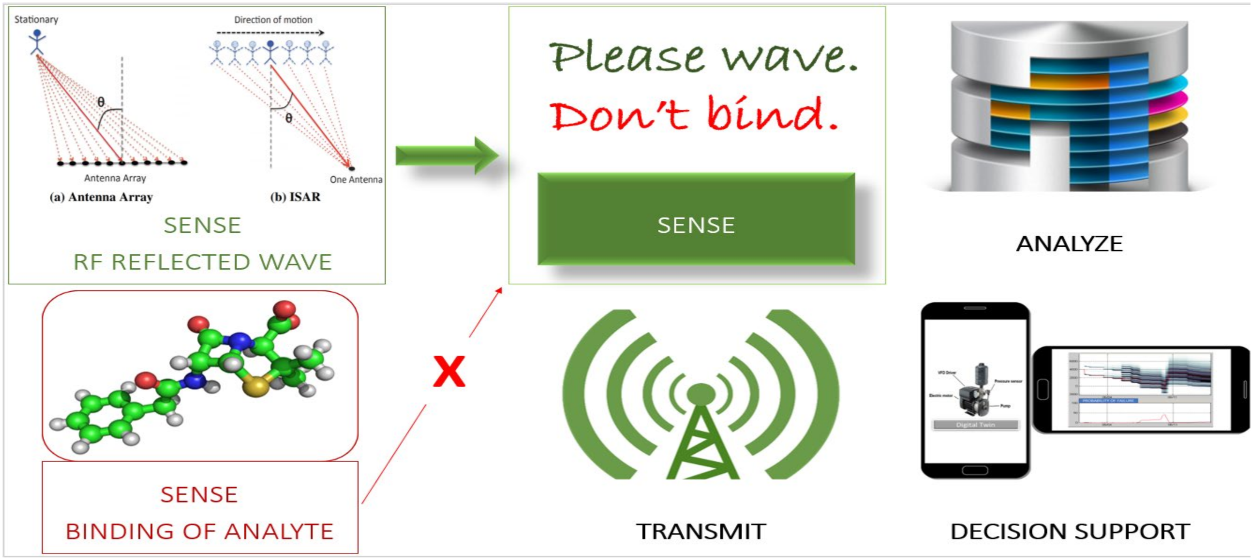


Figure 25: Science behind the data: wastewater monitoring in sewer systems must address the science of hysteresis (vastly reduce or eliminate hysteresis) in order to repeatedly reuse sensors to continuously monitor and transmit data from SWSN (may be digitally represented as a digital twin). Since we are immersed in natural spectrum of waves, objects in motion will collide with waves and reflect waves (pebble in a pond). Reflected radiofrequency (RF) waves indicate direction of motion (top, left corner). ISAR[538] (inverse synthetic aperture radar[539]) is an old technique used for mapping surfaces of Earth and other planets. ISAR uses movement of a target to emulate an antenna array (see [a], top, left corner) to locate an object by steering its beam spatially. In [b] the moving object itself emulates an antenna array and acts as an inverse synthetic aperture. Wi-Fi Vision[540] (Wi-Vi) leverages this principle (Adib & Katabi, 2013) in order to beamform the received signal in time (rather than in space) and ***locate** the moving object.* Wi-Vi can signal movement (humans[541], animals[542]) but in sewers locating the movement of nanometer (viruses) or micrometer (bacteria) sized particles or molecules (3,4-Methyl enedioxymethamphetamine[543] metabolites[544]) is a challenge seeking new "eyes", new thinking.

In the SAMD option, a sample is collected from the sewer for testing. Such tests may not need sophisticated waveform sensing, even if it is available and feasible. However, there must be a better way to sample wastewater from sewers compared to the operation shown in Figure 20. A drone-mounted robotic collection arm using specified outlet/exhaust sewer pipe (as a location to access wastewater) may be an engineering task for school students inspired by robotics[545].

Figure 26: Hypothetical cartoons by Powerpoint enables diffusion of ideas. For tools, in this cartoon, to reach the less affluent world (80% of population) the power from economies of scale (next billion users) must be harvested. The disconnect between science and human values erupts from the grave discord between advances in usable technologies vs the economics of technology in the context of applications and sustainable operations[546]. Democratization of data enabled by the explosion of software defined services has catalyzed convergence of science, engineering, and technology to reach the masses, albeit unequally[547]. Peddling prosperity for the affluent few (less than 20% of the global population) excludes thinking and designing tools and technology to help farmers, sewer workers and laborers (who aren't invited to Davos) to contribute to poor[548] economics, participate in global economic growth, and pursue development as freedom[549].

ETHICS: PLEASE DON'T LEAVE HOME WITHOUT IT

Human life is at the center of our discussion on healthcare, medicine, and social welfare, in general. Ethics is at the functional core of healthcare and its relation to science-based medical care of people through detection (diagnosis[550]), prevention (prophylaxis[551]) and treatment[552] (therapy) of their physical and mental illnesses. Medical ethics deals with values and norms that individuals, groups, and organizations use as a basis for their engagement and justification[553] of health related practices[554]. The principle of patient beneficence is of importance in relation to healthcare technologies. Can we improve quality of patient care by embracing the idea of digital twins and the promise of digital representation to optimize operations through data transparency?

Do humans have the knowledge to optimize human systems with digital tools? The physical functions and mental characteristics (consciousness, attitudes, behaviors) of humans are infinitely complex (more than cars, aircrafts, submarines). Mars Rover, mass spectrometry and mining operations for rare earth metals, at a systems engineering level, pales by comparison to viruses which are measured in nanometers but can change the future of human healthcare with unpredictable severity for the next 50-100 years (e.g., SARS-CoV-2, Ebola). Is the thought of even a dribble of digital twin for health[555] or healthcare just a ludicrous tempest in a teacup?

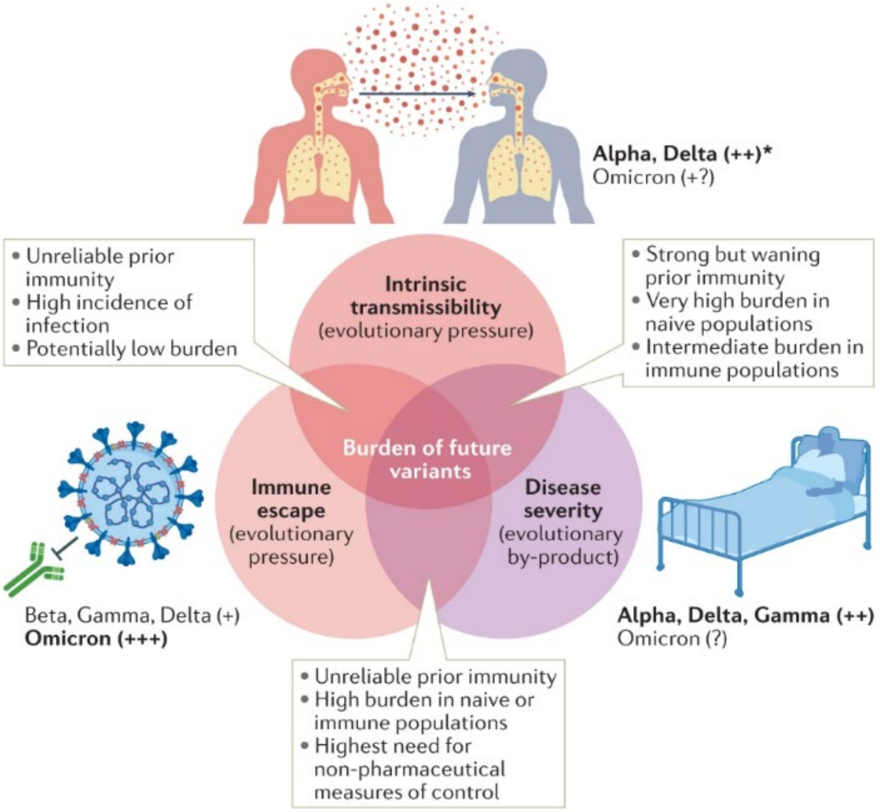
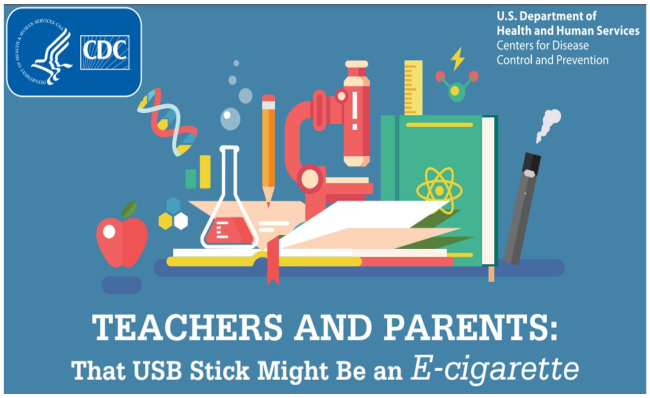
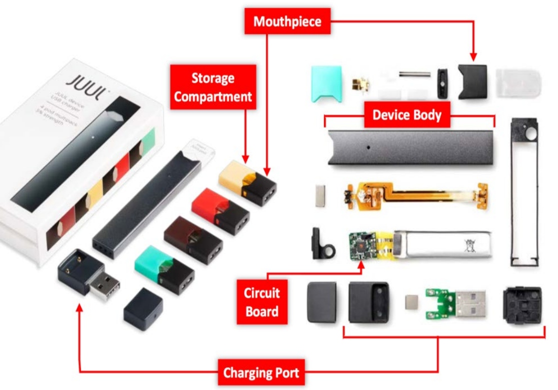


Figure 27a: Immense consequences for human health of unpredictable[556] severity will unfold in the 22nd century due to viral antigenic drift (e.g. SARS-CoV-2 evolution[557]). This is in addition to viruses[558] predicted to possess pandemic potential[559] and millions of other[560] unknown pathogens. Discoveries[561] and ethics, *combined*, will determine fate of planetary[562] health.

Ethics demand protection of patient interests. Patient care, patient safety and advocacy for the patient (welfare) should take precedence agnostic of the socio-economic milieu. Maximization of the interests of economic stakeholders is unethical if it reduces the patient's quality of life index.






E-cigarette maker Juul is raising $150 million after spinning out of vaping company

Figure 27b: Unethical takes a whole new meaning in this phantasmagoric horror show starring JUUL e-cigarettes designed[563] to be disguised[564] and especially marketed[565] to school students, teens, and young adults. Alert from CDC[566] did not discourage shark tanks from swimming[567] along with this deception. In this shocking moral hazard, the investors and the manufacturers are risk-free with respect to the social cost of long term healthcare effects due to mortality and morbidity, teens and young adults may experience in the future due to induction by JUUL to develop nicotine addiction. Health problems due to vaping[568] may lead to cancer, too. It took years for the judicial system to address these health atrocities and issue a gentle reprove[569].

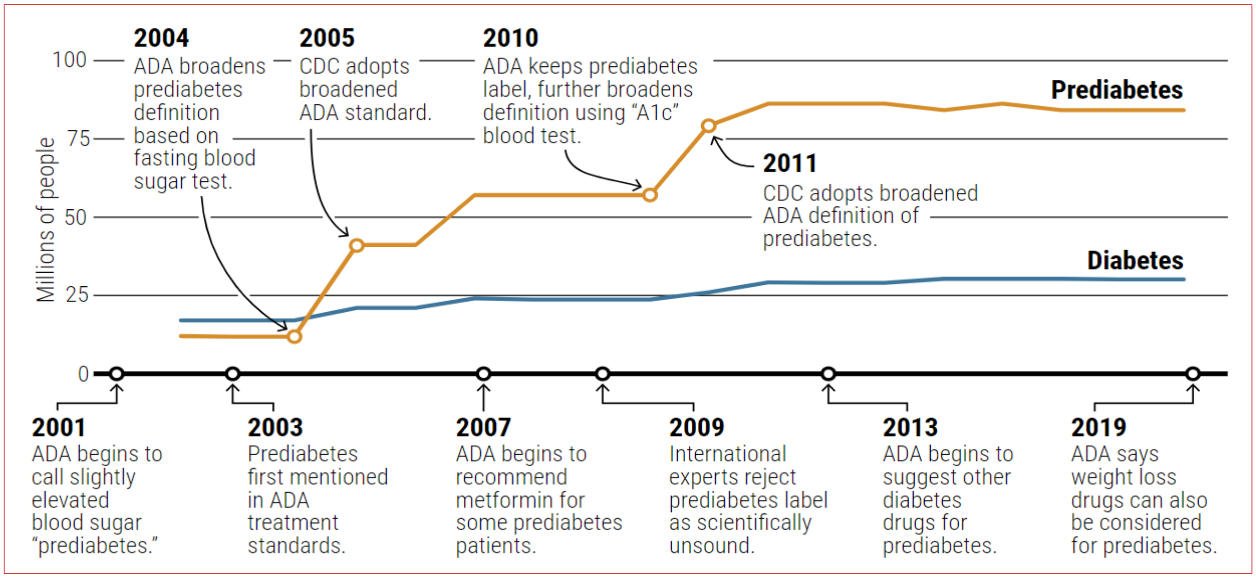


Figure 27c: Unethical practices in healthcare enforced by medical associations in collusion with big pharma with support from politicians is the most malignant form of treachery, in progress. The march of unreason continues even after medical experts[570] exposed unscientific[571] claims.

Almost two decades ago, by lowering the range of fasting blood glucose level the ADA (America Diabetes Association) committed scientific fraud. The ADA's actions opened the flood gates for sales of medication, "potions" and home monitoring kits after every meal, irrespective of the diabetic status of the person. Retailers for grocery items (coffee, dairy, sugar substitute) besieged the Food and Drug Administration (FDA) to label these products as items which prevent diabetes. Life coaches and fitness gurus came out of the woodwork to pamper the worried starlets in the "real housewives of Beverly Hills" and the wailing men from Wall Street since ADA tied body mass index with prediabetes. The latter is not untrue but using the labels from ADA and CDC the disreputable market practices became disproportionately amplified from lifestyle suggestions to fear-mongering "medical treatment" for prevention of prediabetes. The result was a viciously unstoppable transmutation of disingenuous tabloid fodder to veritable truth catalyzed by pseudo-science hacks, social gurus, and glib PR campaigns from pharmaceutical companies to drum up "prediabetes" patients by the millions, as *sacrificial lambs* for retail health[572], healthcare organizations and the biomedical industrial complex[573]. These activities are rationalized using data based on criteria[574] (slide 26) promoted by supposedly responsible and venerable organizations such as the ADA and CDC. In 2012, the pre-diabetes market was $44 billion and total cost of diabetes was $245 billion in the US. The cost of diabetes in 2017 was $327 billion according to the ADA[575]. In a five year span (2012-2017) the ADA helped to funnel almost $100 billion to the supply chain partners who are the beneficiaries of ADA's lowered standards: medically, morally, and unethically.

TEMPORARY CONCLUDING COMMENTS: MORE THOUGHTS ABOUT DATA

Stupidity (Schwartz, 2008) in scientific research is an asset if it induces one to imagine and think thoughts to advance science and even better if such science can serve society. The profound need for stupidity to ignite the ability to think differently is an adage, a rule. Therefore, it reasons that the aphorism, *the exception that proves the rule*, should apply. Stupidity as a rule is desired for scientific creativity. The exception that proves the latter is the report of a digital twin[576] for a human disease (multiple sclerosis) without regard to what *causes*[577] the disease and absence of data related to various *causal* factors[578]. The latter is a glaring example why digital twins for any living entity or system may be far beyond the grasp of those who are living.

Digital representation related to living systems may not be abandoned (by obsequious readers) but digital twins for human disease (Voigt *et al*, 2021) is an incorrigible waste of resources. Granularity in the meaning of connectivity, data and analytics in the causal context of the target/problem is key. Incremental advances in the candle industry did not result in the electric light bulb. What was untrue for the electric light bulb may be true for digital twins for living systems. Small steps and incremental advances may result in tiny but ***meaningful*** digital representation of living systems (plants, animals, humans) to improve transparency of data.

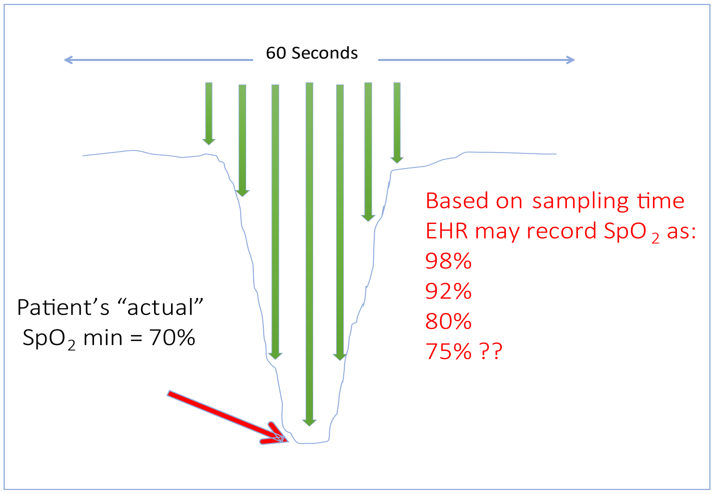
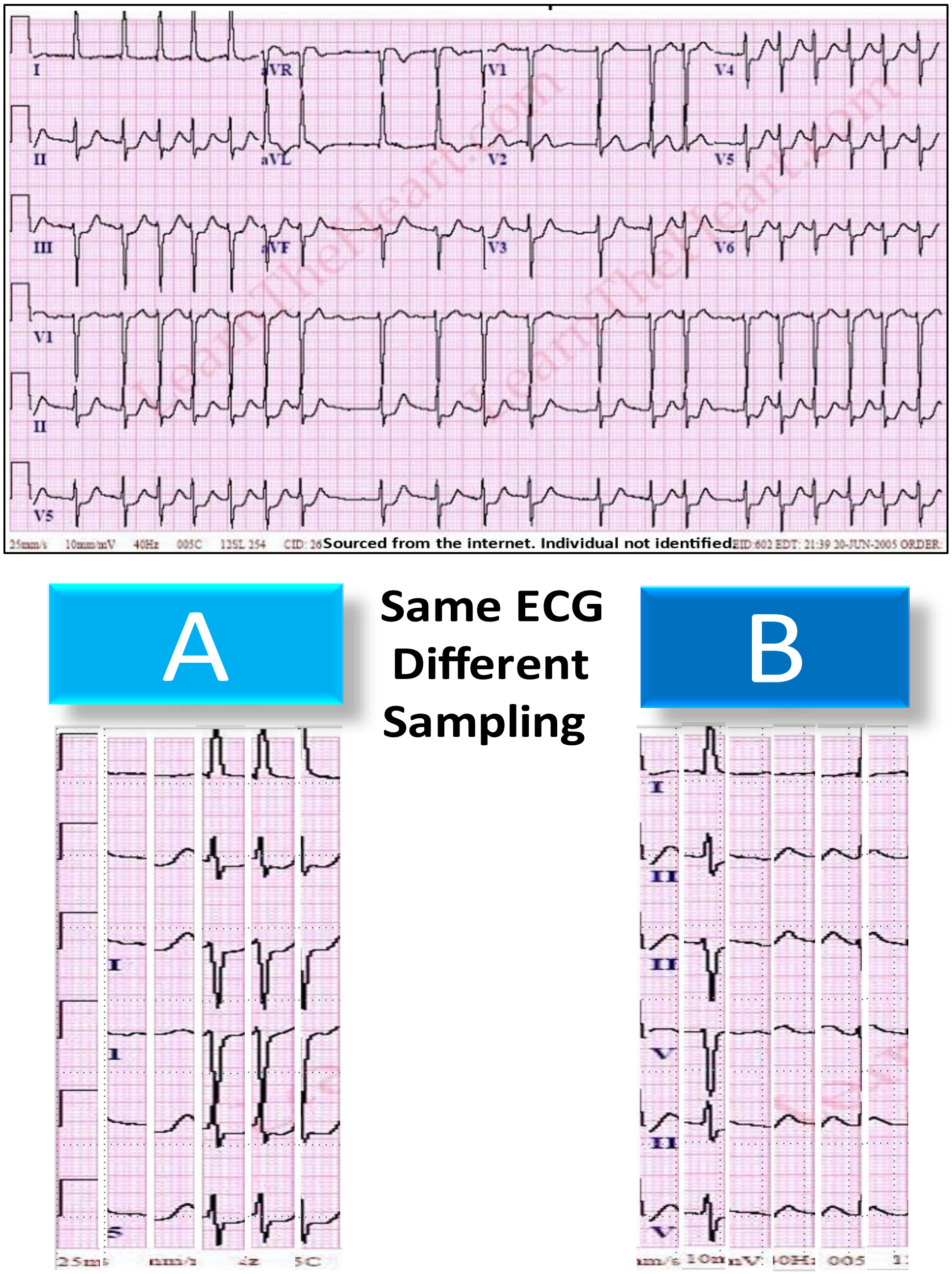


Figure 28: Error prone data is stored due to sampling time choices (sample points show 1-minute period). Which value will be recorded by the electronic health record (EHR) database? Data from pulse oximetry shows blood oxygen levels via an oxygen saturation measurement called peripheral capillary oxygen saturation, or *SpO_2* (percentage of oxygen in blood). Sampling point data vulnerabilities (sampling frequency, time between samples) may introduce egregious errors in cumulative time series data which can be device-centric or patient-specific. Maintaining data integrity for digital twins (cybersecurity for confidentiality) requires the ***context*** of the raw data to make sense of analytics[579] for micro-decisions (patient-specific, precision medicine) as well as gaining a macro-understanding i.e., the *value* network (see page 63 of 94 in DATA[580]).



Sourced from the internet. Individual not identified

Figure 29: ECG waveform data (top) shows atrial fibrillation with rapid ventricular rate[581]. Waveform data is "sampled" for storage[582] in electronic health records (EHR). Depending on ***sampling time interval***, patient-specific time series ***data may be corrupted*** (bottom: A,B) before it is stored (see page 77 of 94 in "DATA", see reference number in Figure 28). In the future misdiagnosis is likely based on A/B which differs from raw waveform data (top). Data integrity of the waveform is crucial patient-specific time series data for any representative tool. Is this a likely candidate for digital twins[583] or just flamboyant gimmicks promoted by fake[584] pundits?

Non-living entities with a known number of components (e.g. cars ~30,000 parts, planes ~6 million parts, submarines ~10 million parts) may be eventually amenable to some form of twining, albeit at the sub-system or sub-component level. Digital representation will continue to advance in parallel with advances in the use of data. It is not simple. Except for those who are members of the Association for Snake-oil Salesmen (ASS) none will venture to claim that we know what to do with respect to veracity of real data (not synthetic data[585]) in digital twins.

In mechanical systems, no matter how detailed, the digital representation may be precise with respect to number of dependencies/interrelationships and accurate descriptions or values of characteristics, attributes, and role. There is nothing non-deterministic (except if the physical entity explodes). Humans know how each of the thousands or millions of parts were designed, manufactured, and integrated as a system. Thus, digital twin of a sub-system may be a college project. It is unnecessary to revive digital twins as the *tulipmania*[586] of the 21st century.

In humans, data represented erroneously may cause mortality and morbidity, illustrated in Figures 28 and 29 (cartoons of actual instances). In humans, we have very little idea about the networks and circuits that we collectively refer to as physiology. In the tiny "real estate" of a human body we may have 30-40 trillion human cells[587] (each cell has 6 billion base pairs of DNA per diploid genome[588]) interacting between cell-types[589] and some of them probably also interacting with 30-40 trillion bacteria[590] (each bacteria have ~4 million base pairs[591] of DNA per haploid genome). Roughly, each human body has ~2.4x10^{26} base pairs of DNA which may be interacting in ways still mostly unknown[592]. DNA (base pairs per human) outshines the number of observable stars in the Universe (7x10^{22}) and far exceeds the total number of grains of sand[593] on Earth (7x10^{18}). DNA controls genetics and single cell RNA sequencing is revealing that cell type specific expression may vary widely within the same individual under physiological stress, infection, or dysfunction. What will happen[594] to precision public health if population genetics meets single cell sequencing? Albeit temporary, but it may not be unreasonable to conclude that one may be wise to avoid using the terms "digital twins" and "living systems" in the same sentence, in the same century. Digital cousins[595] may be the shoddy and hapless alternative.

The hypothetical suggestion in Figure 5 and the reality of the emergence, growth, and obsolescence of the video cassette recorder in the 20th century (Tellis and Golder, 1996) offers profound lessons and parallels, a few of which are permanently implanted in our imagination. Mobile phones for the ultra-wealthy had to be carried by the valet (in a box) but now they dangle from ear lobes of women in Argentina, Belgium and Cameroon. Computers which occupied football fields are now in our palms (smartphones have more computing power[596] than what was available for NASA's Apollo mission to the Moon). Data-informed reservations about the value of digital representation is clear. It is unclear whether it is a matter of *time* when *trusted* digital representations may become digital twins or digital cousins. Depending on the complexity of the target, the unit **t_3 ("*time to trust*")** may be in decades or perhaps, centuries.

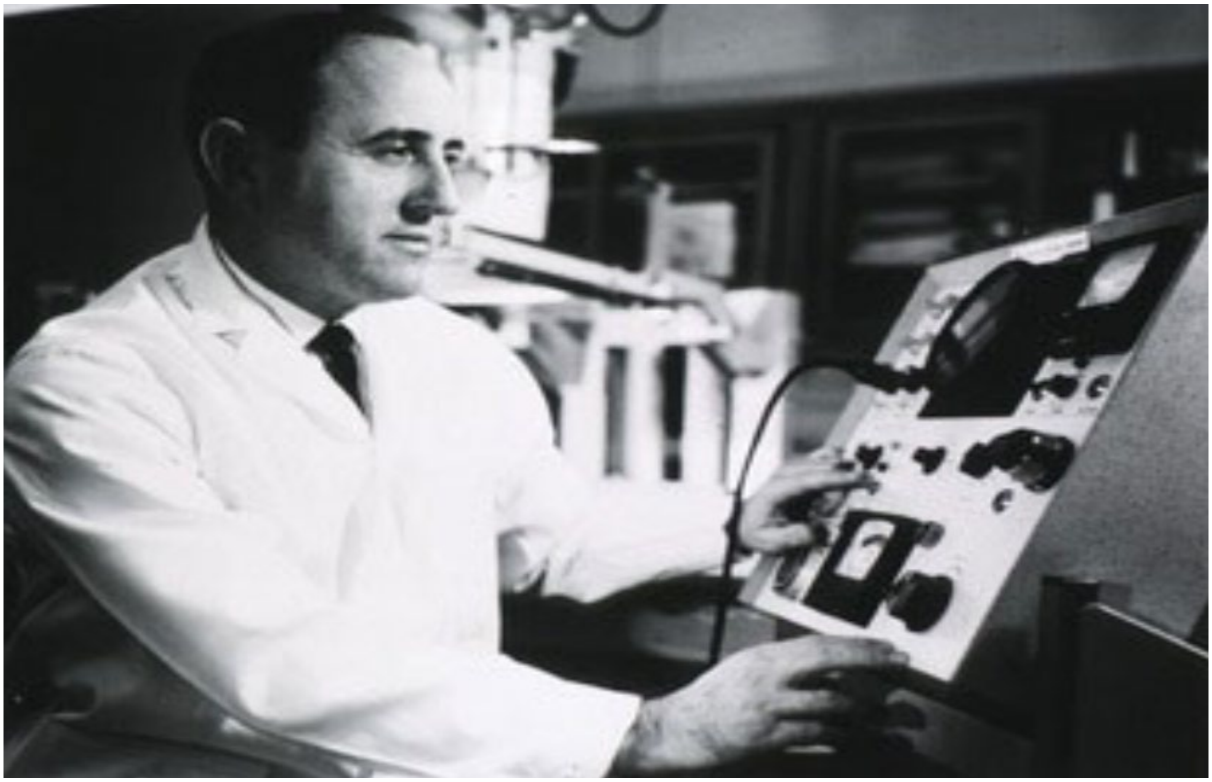
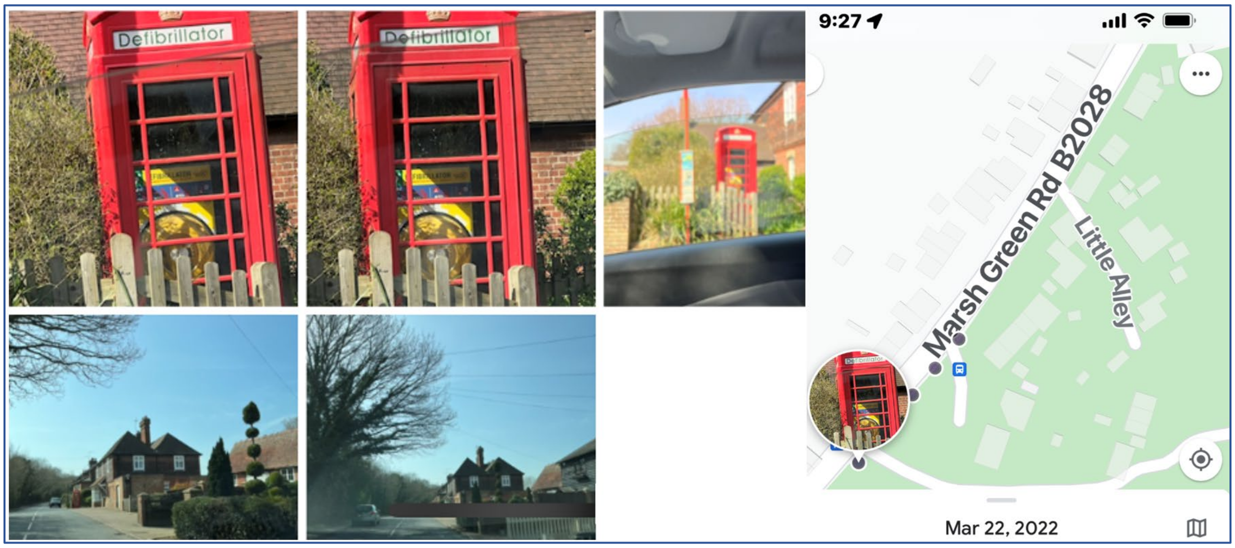


Figure 30. Bernard Lown[597] (1961) of Brigham and Women's Hospital, Harvard Medical School, is credited in the Western world with initiating the modern era of cardioversion[598]. He combined direct current defibrillation and cardioversion with portability and safety[599]. The obsolescence of landline phones in UK vacated the iconic phone boxes, which now houses AED (defibrillators). Roadside defibrillator in the village of Marsh Green (below), near Edenbridge.



APPENDIX: MOUNTAINS BEYOND MOUNTAINS

Lab-grown diamonds are a gem of a (chemical) synthesis but its social consumption[600] as a commercial entity is a problem in search of a solution. The idea of digital representation as a *twin* was transformative in the mechanical context and rescued the astronauts aboard Apollo 13.

The socio-economic context of advanced ideas are often slow to be recognized, even slower to be adopted or consumed, and often ridiculed[601] by highly decorated colleagues[602]. Robert Langer's method to use nanoparticles and lipid molecules to encase drugs and nucleic acids for sustained delivery *in vivo* was met with great derision by the elite scientific community because it was "too" innovative for 1976[603] but saved much more than an estimated 20 million[604] lives in 185 countries in about an year when used as the medium of delivery for the mRNA vaccine for CoVID-19.

On the other hand, at least in the US, the ignorant and the uneducated sects of people who remain resistant to science, constitute the unvaccinated population, directly exacerbating the population public health crisis due to the ongoing pandemic. Fake information and blatant lies are fueling hesitation or refusal to be vaccinated against COVID-19 at a cost of millions of additional deaths (>1 million preventable deaths in the US) and a cost in excess of $13 billion[605] which is a conservative estimate in view of the projected $4 trillion[606] lost by the economic ecosystem. This catastrophe begs to ask the question: beyond the immediate detrimental effect to population public health what are the broader societal concerns?

Through the "bean counting" lens, in terms of broader societal impact, perhaps it is fitting to indulge in introspection with respect to the adage *the educated customer is our best consumer*.

Future vaccine sales and sales of "digital twins" products/services depend on the degree to which the public is aware, educated, and cognizant about the value due to vaccines and digital twins. Vaccines and digital twins are farthest apart in any category/view but both are completely dependent on education in science, technology, engineering, medicine, & mathematics (STEM).

There is no quick fix for science and mathematics education (STEM) but if we fail to heed the writing on the wall then we will wither away the supply chain of talent which is central to commerce[607] and economy[608] to preserve our democracy[609] and freedom[610].

Digital twins are an advanced tool which needs a plethora of converging science and engineering principles to even begin to start crawling. Its success depends on K-12 education. The success of K-12 education starts with teachers who are the catalysts for learning that needs to occur in primary, elementary, secondary and tertiary levels (**K-16** STEM education)

The knee-jerk reaction is to bemoan inadequate funding for education in technology for professional development of teachers[611]. Corporate politicians carefully crafted technology initiatives to push forward computer science (digital twins are not about computer science) but ignored the other subject specifically mentioned in that call for CS[612] by the "coder-in-chief" (a pathetic moniker designed to grovel for attention from TV news producers). The message was re-shaped in a form which blatantly pandered for publicity and peddled prosperity for a sub-sector of technology, in the name of helping STEM. Vaccine, digital twins and STEM are synonymous but they are ***not*** synonymous with technology, alone.

STEM is not synonymous with technology, alone. It should not be framed by corporate and/or political shenanigans for the sake of corporate profitability and political expediency. Technology should not be glorified at the expense of science, engineering, and mathematics. But, mathematics is hard and news cycles are short, hence the even "faster" approach of "coding" is taken up by funding agencies to provide glitter and glamour but the veneer is not even worth the gutter. It is better than doing nothing but computer science (CS) deserves equal and essential complementarity by improving diffusion of and rigor in mathematics (among other things) and the understanding that coding is only a very tiny part of CS. Coding is ***not*** CS.

Mathematics and science has taken a back seat in K-16 education where "tools" are celebrated but the "fundamentals" are left in the cold, as boring, and hard. This is the "new delusion" brought on by the scientific illiteracy of politicians and political illiteracy of scientists. It will be remiss of the author (SD) to avoid the discussion for sake of "pleasantries" or to make things "palatable" to readers because the educating the consumer is key to global development.

As a basic scientist, the author (SD) may be intrinsically biased toward science (physics, chemistry, biology), medicine and mathematics. However, analytically, there is nothing wrong with promoting computer science and/or programming (coding) even though there is an immense chasm of difference between computer *science* as a scientific/engineering discipline vs coding, which is a tool, similar to a recipe.

Some of those who create recipes are indeed gifted researchers who are also deeply grounded in the fundamentals of science[613] even though the outcome or external "impact" surfaces merely as a recipe in a cookbook or an online "pop-up" when e-shopping for grocery delivery using a smartphone. If one delves deeper into this line of reasoning, it may be awe-inspiring to observe that the simple process of browning[614] bread (regulated during the process of baking bread), if used in a Montessori[615] approach in school projects (project-based[616] or problem-based learning, PBL[617]), could enable students to learn about convergence of trans-disciplinarity in the real world. Browning of bread can teach chemistry, biology, food, nutrition, physiology, cardiovascular disease, diabetes and related[618] aspects (chemical engineering, software, data analytics, physics about instrumentation) as well as mathematical[619] rigor quintessential for quantitative analyses and metrics embedded in each sub-topic. Chemistry can be taught at any K-16 level just by asking children if they like chocolate[620] or what is in their paintbox[621] or discussing restoration of old paintings[622] with middle/high school children. Lithium-ion battery[623] and redox[624] will keep children engaged, while the chemistry of shaving[625] may generate some pubertal guffaws. The wireless TV remote is an excellent item for a project-based understanding of convergence. These discussions can teach entire science and mathematics curricula. However, it is very difficult to execute such multi-disciplinarity and complementarity in the K-16 curriculum because teachers may not have the grasp over various overlapping disciplines (or the ability to conduct assessment of learning). The reason for outlining this granularity is related to the fact that programming may be embedded in most of the items mentioned above, which is ignored when "coding" is just learning by rote.

Programs for coding in schools and colleges (e.g. *Girls Who Code*) often dive into programming specific languages[626] for the express purpose of writing "lines of" code as the index of success. There is value in this tool. Examples of economic growth from rural India is evidence. However, the socio-economic turmoil from India, headache and pennies as payment rarely makes it to the Wall Street Journal or BBC or ZDF. Is this distorted view of "affluence" the reason for US public education to push for "coding" as if it is a panacea, a solipsistic bliss?

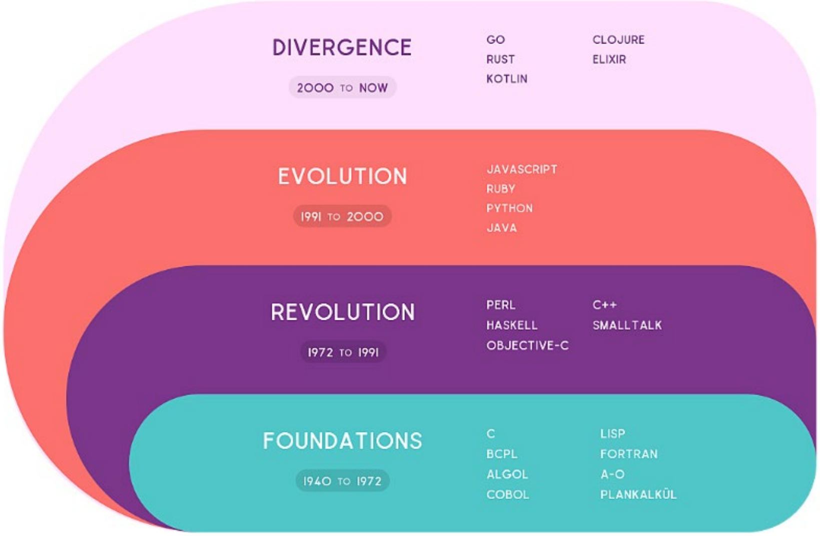
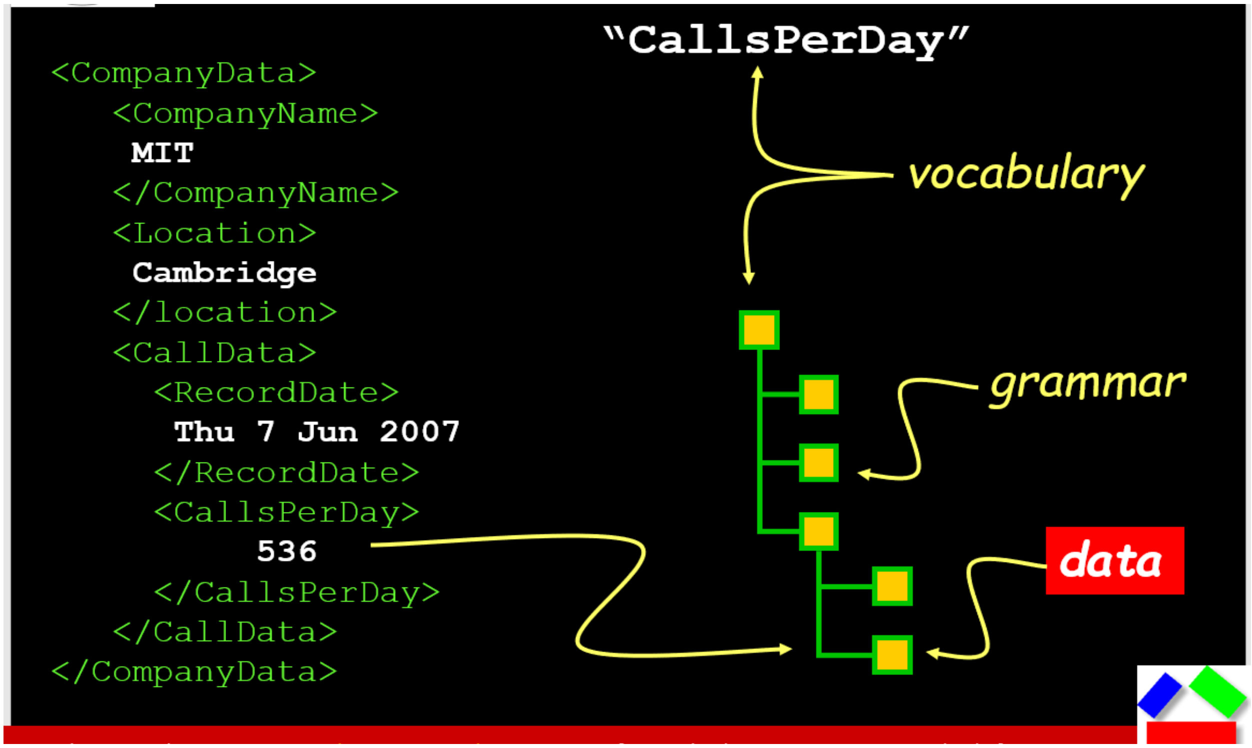


Figure 31: Lacking from K-12 Educational Initiatives: Philosophies of Software Languages[627]

Dissecting the extraordinarily rich trans-disciplinarity of programming (coding) and the foundations of languages may illustrate a few salient issues. Programming "language" is an outcome which tries to capture and learn from the attributes of natural languages, e.g., grammar (noun, pronoun, verb, adverb, conjunction, preposition), syntax[628] (descriptive content, subject, predicate) and semantics[629] (meaning). Programming and software is lost when it meets with lexical semantics and clueless when dealing with cognition (contrary to fake claims by the media, which corporations create for marketing purposes, where a lie can travel half-way round the world even before truth can put on its trousers[630]). Linguistics and study of the language infrastructure are critical foundations which informs the logic structure that generated the initial series of programming languages (code) during the middle of the last century (20th century). The combination of data and code through object oriented programming (OOP) was the "revolution" in the last few decades of the last century. The origin of this "revolution" may be traced back to "patterns" arising from architecture, designing and planning[631] cities and buildings. The 21st century evolution and differentiation is linked to predecessors, e.g., Julia[632] is a "modern" and improved language compared to Python, which was once considered progressive. Rust is even more linked to C++ and appears to resemble C, if C were to be developed in the 21st century.



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</CompanyData>
```

Figure 32: Data, Structure, Relations, Syntax, Semantics – elements lost in translation to binary. Linguistics, cognition, grammar and patterns in our mind during language development are influencers of programming[633] (coding) yet students (and teachers) are in the dark about the inextricable link between learning languages and coding. In this example, neither "RecordDate" nor "DateofRecord" are real words but programmers synthesize arbitrary syntax, intending to capture the same outcome (semantics). The syntax is created in the brain of a human, not in the computer. Code cannot capture causality (see Figure 3a). Programming (coding) and resultant software used by computers are semantically challenged (i.e., dumb). Syntax, as shown in this HTML example, is only good for the specific use case. Hence, this code in the software is incapable of merging data (for example, from different phone logs) because hard-coded syntax produced by different programmers are unlikely to be ***exactly*** *identical*.

If one can grasp the foundational tenets, then such an individual may be better suited to adapt, un-learn and re-learn whatever may follow in the market of programming languages (revolution, evolution, differentiation, divergence, convergence). Job insecurity due to changes in programming technology (code) may become less of a thorny socio-economic problem if students were acquainted with the *modus operandi* which is at the heart of change. Technology drifts every few years much to the chagrin of employees who may prefer job stability, regular paychecks, and peace of mind. Preparing students to deal with inevitable challenges due to the dynamics of technology may help them to be fortified when they are the adults in the workforce.

The foundations of programming languages are inherited from the foundations of natural languages which are built on the structure[634] of linguistic infrastructures[635] we are exploring[636]. Because we are clueless about knowledge representation (see Figure 3a), we have been unable to distill into programming languages the nature of semantics and cognition with respect to natural language acquisition and pattern development in the mind[637]. It is the reason for our complete failure to include causality through code. Elements of linguistics are at the core of programming languages. Syntax is language derived from and based on the natural language[638] of the programmer (varies immensely if the mother tongue of the programmer may be, for example, English, Chinese or Spanish). Individuals may choose to describe the same content (thing, object, process) in different forms of syntax. The choice of words is based on the linguistic proficiency of transforming thoughts into spoken words based on vocabulary. Programming instructors in K-16 are unlikely to discuss these facts which are not simple.

These problems are further exacerbated when programming extends into ill-understood (unknown) domains, e.g., artificial neural networks[639] (ANN). The vain attempt to generate "intelligent" software (mostly through marketing propaganda of "artificial intelligence") is plagued with inconsistencies of extrapolation and mimicry of biological functions (for example, neural networks) in human-designed programs or software processes. The basic circuitry of a neural network is regulated by electro-chemical signals which are extremely difficult (if not impossible) to reproducibly quantify in humans and higher animals. The claim that an "artificial" neural network may represent the logic patterns in our brains is infinitely cherubic, if one is familiar with the basic science of neurology and is aware of the granularity of details for even a simple (mono-synaptic) neural signal communication. Mimicry of artificial neural networks using patterns even from worms (*Caenorhabditis elegans*[640]) may be too complex with too many dependencies and/or interrelationships, some of which may be latent.

Let us assume that one has created a rudimentary Boolean[641] logic structure from some form of so-called artificial neural network with programming (coding) to perform operations. What are the operatives and what are the mathematical basis of the tools deployed/necessary for the operation? Can we transform the outcome to become information[642] which can offer value to users? Is making an app[643] the Holy Grail? Computation and programming is better suited to deal with the tsunami of data (humans cannot process large volumes of data). Logic, computer and programs (code) are only as good as rule based[644] expert[645] systems[646] which depend on the code and data that has been ***provided***.

Programs cannot think but excellent in performing mathematical operations based on pre-programmed logic, rules and embedded structure/procedures/protocols. Mimicry of neural signals and quantification of signal strengths (referred to as "weights") may serve as arbitrary guides but devoid of contributing any mode of "new" thought. The nature of programming proficiency is influenced by the structure of natural languages. Thus, we have a high performing logic tool which depends on code to enable computation at speeds unattainable by humans.

The trinity of mathematics, biology and languages, form the invisible part of the iceberg where coding or programming is the visible tip of computation. Our penchant for quick results and gratification may be fueling our desire to *polish the chrome* (coding) and kick the can of hard facts (mathematics, biology, language) down the road for somebody else to *tune the engine*. We are immersed in system of systems (akin to "mountains beyond mountains") which requires the ability to think in layers of thoughts and understand how to think and assimilate analyses.

Are we being delusional? Are we being myopic? What is the impact of this mechanism (the systems age) on the future of technology and the future of thought, in schools and colleges? We can make things entertaining and easy for students to feel accomplished, now, but only to observe social discontent, decades later. Is the design of information technology tools in public education skewed to statistically amplify the positives in our elusive quest for rapid rewards? Are we in denial about the nature of science education which is necessary to create the vaccines of the future to serve society and manufacture/program digital twins as commercial products? Are we still a nation[647] at risk?

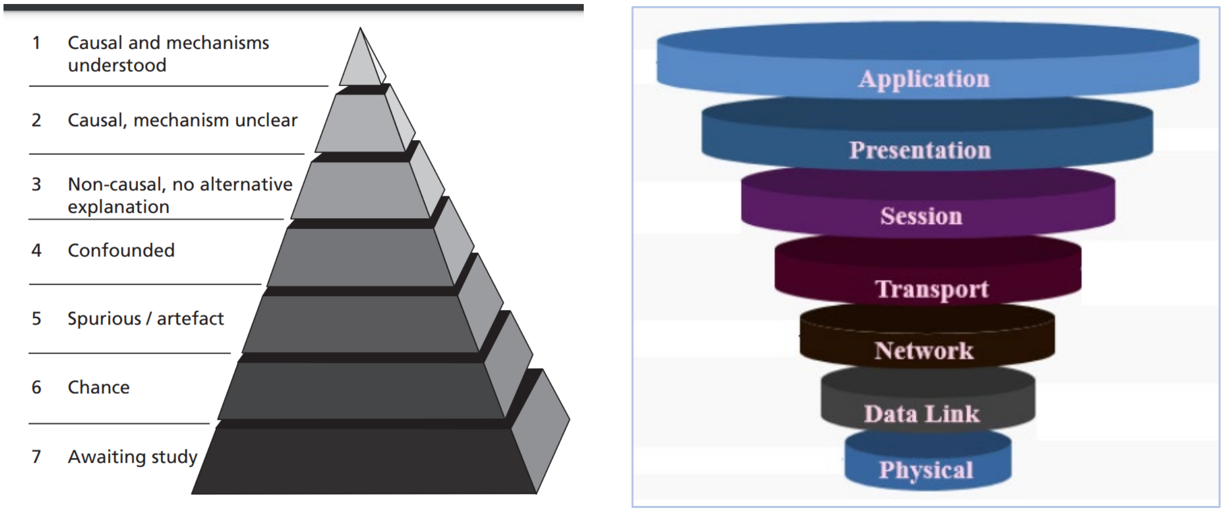

Figure 33: How to think about analytical thinking? It is rare for us to grasp the significance of the DIKW pyramid or attempt to explain how data, information, knowledge and wisdom (DIKW[648]) may be an inter-dependent "building" process, over time. Analytical thinking is key to progress yet poorly taught or understood. An easier approach is to catalyze students to ask "why" (i.e., concept of cause or causality). Cause and effect is not an abstraction but offers an abundance of instances from daily life, e.g., epidemiology of diseases[649] (7 layers, LEFT). The "build" concept in analytical thinking can be made most accessible to students by referring to the ubiquitous mobile phone, and the incessant war of "apps" (application) which could cease in an instant if the high speed flow of 0's and 1's are affected. The latter, a segue to explain the profound OSI (Open Systems Interconnection) information engineering reference model[650] (7 layers, RIGHT).

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Writing to please any specific target audience was not the intent. The intent was to add my two cents to the field[651] with respect to challenges[652] and opportunities, to be a voice of convergence to highlight the art of the possible without brevity or sugar-coating (Splenda-coating for diabetics), uncover the broad spectrum of uncomfortable problems peppering the pursuit of ideas, and point out a few remarkably positive signposts on the road to a resplendent future, where science and human values will uphold science as a service to society.

We are clueless if digital twins will meet the digital cousins, or if they will ever choose to undertake the strenuous climb of the steep path, to reach the luminous summit. That is a tryst with destiny, which we hope may eventually find its winding road through unknown unknowns.

If one is not offended by the commentary and chooses to explore, further, then it is suggested they delve deeper into the list of references and consider thinking about how to think differently with an eye toward implementing change or being a catalyst for growth. How do we start thinking about something that has never been thought? What happens to thoughts when we no longer think about those thoughts?

The unoriginal sub-title of the "APPENDIX" section in this article is a clue to a far bigger problem at the very beginning of the supply chain of talent necessary explore the *mountains beyond mountains*[653]. The borrowed title of this essay (book chapter) combines two published works, one just a smidgen more stellar[654] than the other[655], one is a drop in the ocean and the other is a pebble in the pond, *one without second is emptiness, the other makes it true.*

> *I have thanked the trees that have made my life fruitful, but I have failed to remember the grass that has ever kept it green. One without second is emptiness, the other makes it true.*
>
> - Rabindranath Tagore[656]

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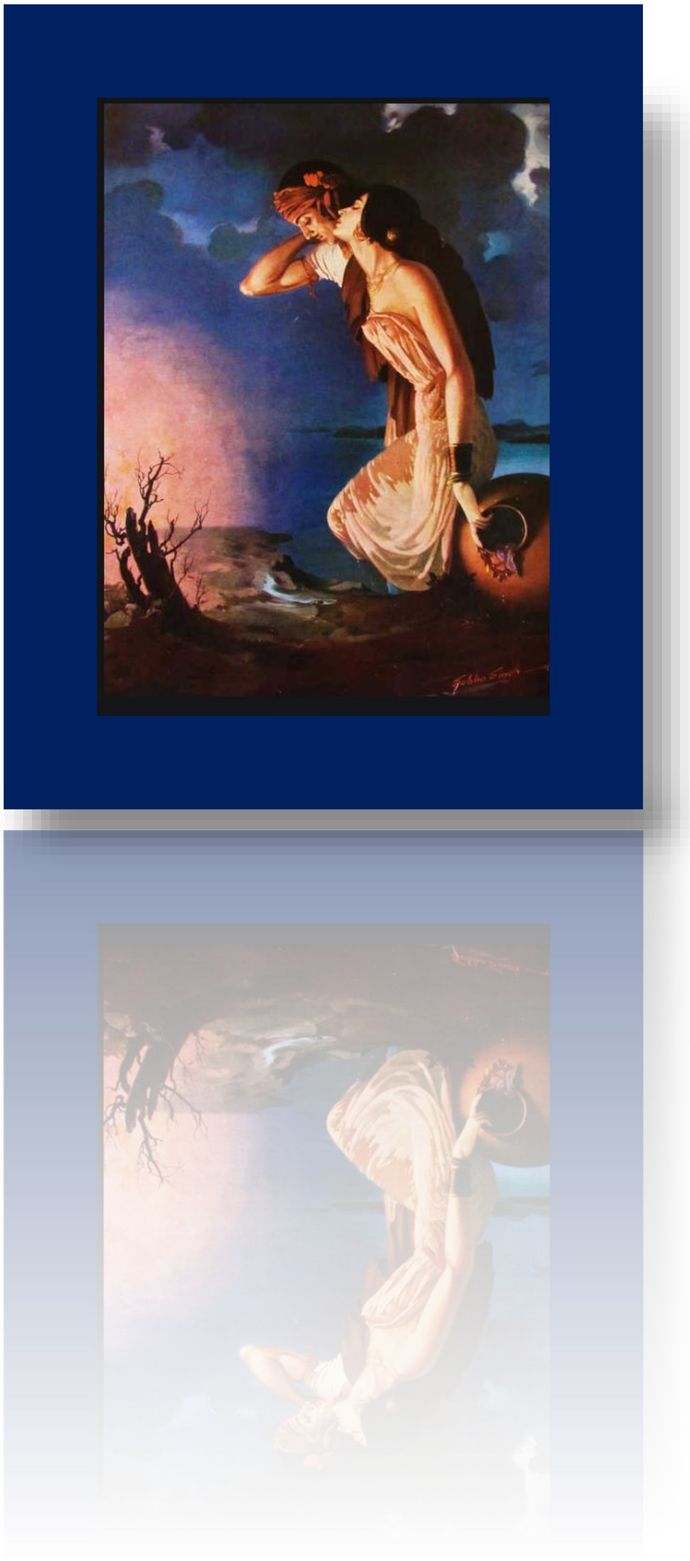
True knowledge exists in knowing that you know nothing. [Socrates]

TWINS: VISUAL CUE?



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