From Digitization to Digitalization: Clinical Development in the Age of Intelligent Machines

Mark Wolff, M.S., Ph.D.
Chief Health Analytics Strategist
Global IoT Division
SAS Institute

October 13, 2019

Site Solutions Summit
PARTNERING FOR SUCCESS

2019 GLOBAL SITE SOLUTIONS SUMMIT
Future in Site

Faculty Disclosure

In compliance with ACCME Guidelines, I hereby declare:

I have financial/other relationships with the manufacturer(s) of commercial product(s) or provider(s) of commercial service(s) discussed in this educational activity.

Employee of SAS Institute

Mark Wolff, M.S, Ph.D.

A Ridiculously Simple History of Technology

How Important is IoT

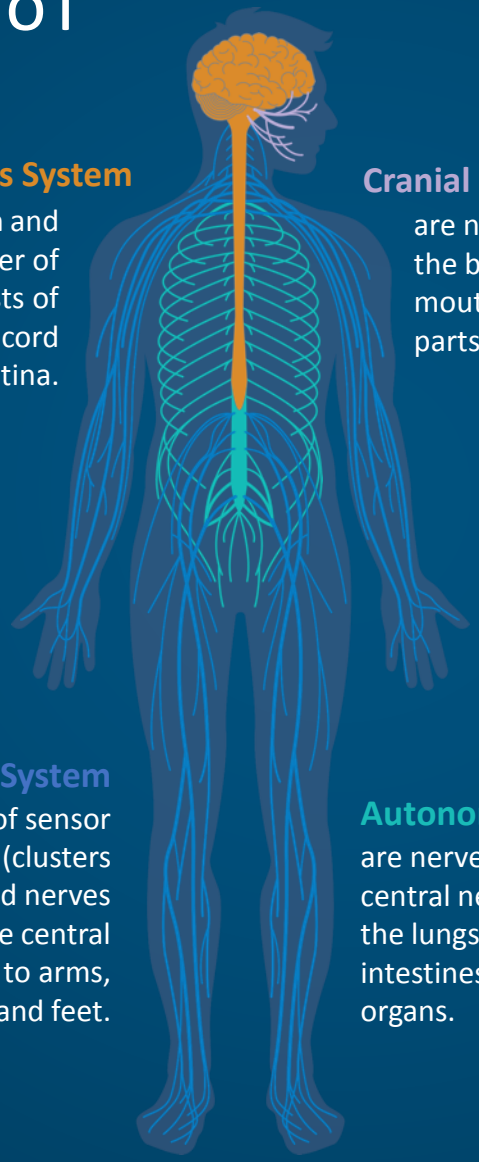
- Fire — Revolutionary
- Agriculture — Evolutionary
- Industrial Revolution — Evolutionary
- Information Revolution — Evolutionary
- IoT — Revolutionary

REVOLUTIONARY
Involving or causing a complete or dramatic change

EVOLUTIONARY
Relating to the gradual development of something

Recapitulating the Human Nervous System

A Model for Intelligent IoT



Central Nervous System
is the integration and command center of the body. It consists of the brain, spinal cord and retina.

FOG

Cranial Nervous System
are nerve that connect the brain to the eyes, mouth, ears and other parts of the head.

CLOUD

Peripheral Nervous System
consists of sensor neurons, ganglia (clusters of neurons) and nerves that connect the central nervous system to arms, hands, legs and feet.

SENSORS

Autonomic Nervous System
are nerves that connect the central nervous system to the lungs, heart, stomach, intestines, bladder and sex organs.

EDGE

Recapitulating the Human Nervous System

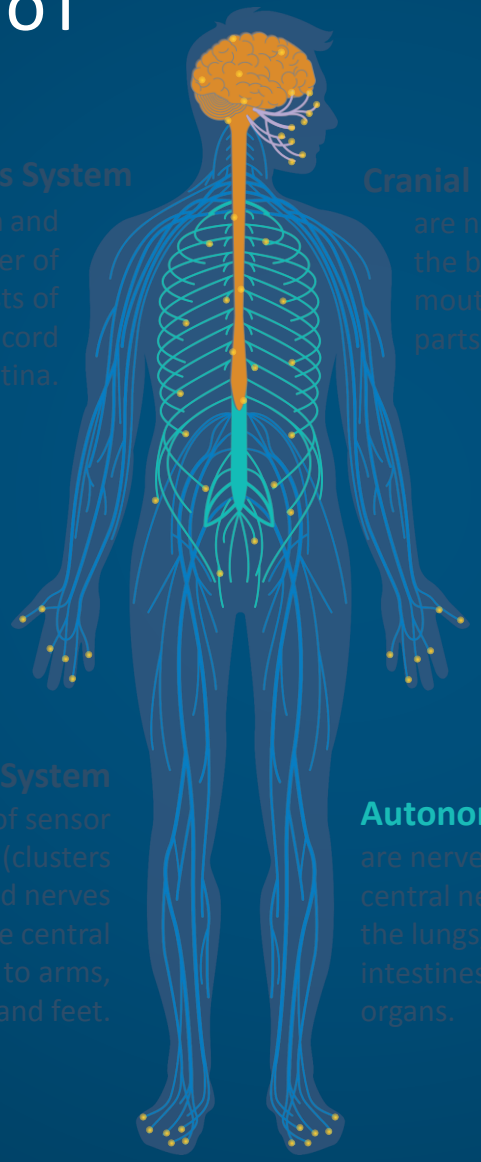
A Model for Intelligent IoT

ETL
Architecture
Interoperability
Edge Gateway

FOG

Central Nervous System
is the integration and command center of the body. It consists of the brain, spinal cord and retina.

Cranial Nervous System
are nerve that connect the brain to the eyes, mouth, ears and other parts of the head.



Central Processing Unit
Data Storage
Rules Engine
Machine Learning
Neural Network
Sensor Data Processing

CLOUD

Imaging
Sound
Temperature
Gyroscope
Accelerometer
Etc.

SENSORS

Peripheral Nervous System
consists of sensor neurons, ganglia (clusters of neurons) and nerves that connect the central nervous system to arms, hands, legs and feet.

Autonomic Nervous System
are nerves that connect the central nervous system to the lungs, heart, stomach, intestines, bladder and sex organs.

Autonomous Function & Control
Energy/Power Processing
Hardware Automation
Software Automation

EDGE

Ab Silico Ad Salus

Connected People, Devices and Environments

"While the individual man is an insoluble puzzle, in the aggregate he becomes a mathematical certainty"

Sherlock Holmes
Sign of the Four - 1890

Ab Silico Ad Salus

Connected People, Devices and Environments

"While the individual man is an insoluble puzzle, WHEN CONNECTED he becomes a mathematical certainty"

"The Paradox of Patient Centricity"

Sherlock Holmes
Sign of the Four - 1890

The Connected Patient

Digitization - Digitalization - Connectivity

"…new digital technologies exist to optimize the clinical development process, and more broadly the entire Research and Development (R&D) value chain. Research shows that digitalization will be fueling one-third of the growth and an estimated 40 percent of the profitability in the pharmaceutical market by 2020".

accenture

- **Digitization** is simply changing from an analog to digital form.
- **Digitalization** is leveraging technology to revamp a business model to invoke new value-producing capabilities.
- **Connectivity**

Gartner

…in the Beginning

Reasoning Foundations of Medical Diagnosis

"The purpose of this article is to analyze the complicated reasoning processes inherent in medical diagnosis. The importance of this problem has received recent emphasis by the increasing interest in the use of electronic computers as an aid to medical diagnostic processes. Before computers can be used effectively for such purposes, however, we need to know more about how the physician makes a medical diagnosis. "

3 July 1959, Volume 130, Number 3366 **SCIENCE**

Reasoning Foundations of Medical Diagnosis

Symbolic logic, probability, and value theory aid our understanding of how physicians reason.

Robert S. Ledley and Lee B. Lusted

The purpose of this article is to analyze the complicated reasoning processes inherent in medical diagnosis. The importance of this problem has received recent emphasis by the increasing interest in the use of electronic computers as an aid to medical diagnostic processes (*1*, *2*). Before computers can be used effectively for such purposes, however, we need to know more about how the physician makes a medical diagnosis.

If a physician is asked, "How do you make a medical diagnosis?" his explanation of the process might be as follows. "First, I obtain the case facts from the patient's history, physical examination, and laboratory tests. Second, I evaluate the relative importance of the different signs and symptoms. Some of the data may be of first-order importance and other data of less importance. Third, to make a differential diagnosis I list all the diseases which the specific case can reasonably resemble. Then I exclude one disease after another from the list until it becomes apparent that the case can be fitted into a definite disease category, or that it may be one of several possible diseases, or else that its exact nature cannot be determined." This, obviously, is a greatly simplified explanation of the process of diagnosis, for the physician might also comment that after seeing a patient he often has a "feeling about the case." This "feeling," although hard to explain, may be a summation of his impressions concerning the way the data seem to fit together, the patient's reliability, general appearance, facial expression, and so forth; and the physician might add that such thoughts do influence the considered diagnoses. No one can doubt that complex reasoning processes are involved in making a medical diagnosis. The diagnosis is important because it helps the physician to choose an optimum therapy, a decision which in itself demands another complex reasoning process.

This complex reasoning process must be integrated by the physician with a large store of possible diseases. It is widely believed that errors in differential diagnosis result more frequently from errors of omission than from other sources. For instance, concerning such errors of omission, Clendening and Hashinger (*3*) say: "How to guard against incompleteness I do not know. But I do know that, in my judgment, the most brilliant diagnosticians of my acquaintance are the ones who do remember and consider the most possibilities."

Computers are especially suited to help the physician collect and process clinical information and remind him of diagnoses which he may have overlooked. In many cases computers may be as simple as a set of hand-sorted cards, whereas in other cases the use of a large-scale digital electronic computer may be indicated. There are other ways in which computers may serve the physician, and some of these are suggested in this paper. For example, medical students might find the computer an important aid in learning the methods of differential diagnosis. But to use the computer thus we must understand how the physician makes a medical diagnosis. This, then, brings us to the subject of our investigation: the reasoning foundations of medical diagnosis and treatment.

Medical diagnosis involves processes that can be systematically analyzed, as well as those characterized as "intangible." For instance, the reasoning foundations of medical diagnostic procedures are precisely analyzable and can be separated from certain considered intangible judgments and value decisions. Such a separation has several important advantages. First, systematization of the reasoning processes enables the physician to define more clearly the intangibles involved and therefore enables him to concentrate full attention on the more difficult judgments. Second, since the reasoning processes are susceptible to precise analysis, errors from this source can be eliminated. Of course, the methods presented in this paper are not designed for immediate, direct application; rather, they serve as a suggested basis from which more practical procedures can be developed. However, a consideration of foundations is always essential as the first step in the development of practical applications.

The reasoning foundations of medical diagnosis and treatment can be most precisely investigated and described in terms of certain mathematical techniques. Before material to illustrate these techniques was selected, many of

Dr. Ledley is a part-time member of the staff of the National Academy of Sciences-National Research Council, Washington, D.C., where he is principal investigator of the Survey and Monograph on Electronic Computers in Biology and Medicine. He is on the faculty of the electrical engineering department of George Washington University and mathematician at the Data Processing Systems Division of the National Bureau of Standards. Dr. Lusted is radiologist and associate professor at the University of Rochester School of Medicine, Rochester, N.Y.

3 JULY 1959

the *New England Journal of Medicine*

9

1959

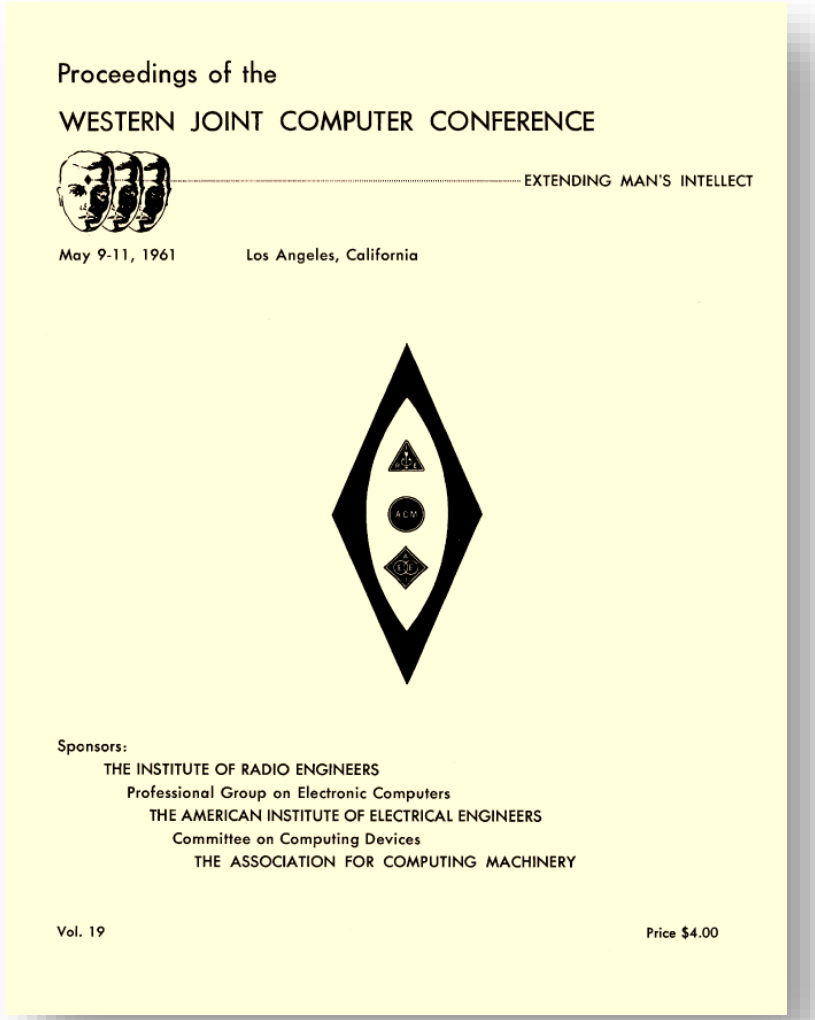
"The mathematical techniques that we have discussed and the associated use of computers are intended to be an aid to the physician. This method in no way implies that a computer can take over the physician's duties. Quite the reverse; it implies that the physician's task may become more complicated. The physician may have to learn more; in addition to the knowledge he presently needs, he may also have to know the methods and techniques under consideration in this paper. However, the benefit that we hope may be gained to offset these increased difficulties is the ability to make a more precise diagnosis and a more scientific determination of the treatment plan."

…in the Beginning

Development of Intelligent Machines

"Machines can be made as intelligent as we please, but both they and Man are bounded by the fact that their intelligence cannot exceed their powers of receiving and processing information."

W. Ross Ashby - 1961


Proceedings of the

WESTERN JOINT COMPUTER CONFERENCE

EXTENDING MAN'S INTELLECT

May 9-11, 1961 Los Angeles, California

Sponsors:

THE INSTITUTE OF RADIO ENGINEERS

Professional Group on Electronic Computers

THE AMERICAN INSTITUTE OF ELECTRICAL ENGINEERS

Committee on Computing Devices

THE ASSOCIATION FOR COMPUTING MACHINERY

Vol. 19 Price $4.00

Intelligence

Definition

The ability to acquire and apply knowledge and skills.

Latin *intelligentia*, from *intelligere* ‘understand’

English
Oxford Living Dictionaries

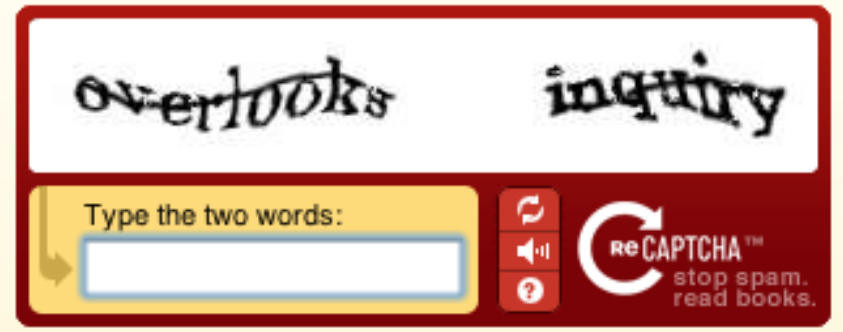
Human Intelligence

Machine Intelligence

Intelligence / Understanding

Completely Automated Public Turing Test To Tell Computers and Humans Apart

There are two important properties that any system that mediates robust object recognition must have;



INVARIANCE - The ability of the system to respond similarly to different views of the same object.

SELECTIVITY - Systems' components … produce different responses to potentially quite similar objects (such as different faces) even when presented from similar viewpoints.

"It is straightforward to make detectors that are invariant but not selective or selective but not invariant. The difficulty lies in how to make detectors that are both selective and invariant."

UNDERSTAND 1)Perceive the intended meaning 2)Infer something from information received

IoT Wont Work Without AI

- IoT will produce a treasure trove of big data – data that can…
  - Predict accidents and crimes
  - Give doctors real-time insight into information from pacemakers or biochips
  - Enable optimized productivity across industries through predictive maintenance on equipment and machinery, create truly smart homes with connected appliances
  - Provide critical communication between self-driving cars.

IoT Will Give Rise to AI

- Patterns, problems, and correlations will be easier to address.
- Intelligent automation will make huge strides—leading to a revolution in predictive analytics—and proactive intervention will be truly possible.

- Machine learning may start with chatbots, but AI is the true potential of IoT.

- The processing of this data (and likely the interpretation and learning of it) will happen in the edge-computing realm. This will be fast and uninhibited.

Forbes

The Hyper Connected Patient

A New Reality

The NEW ENGLAND JOURNAL of MEDICINE

Predicting the Future — Big Data, Machine Learning, and Clinical Medicine

Ziad Obermeyer, M.D., and Ezekiel J. Emanuel, M.D., Ph.D.
N Engl J Med 2016; 375:1216-1219 | September 29, 2016 | DOI: 10.1056/NEJMp1606181

Internet of Medical Things

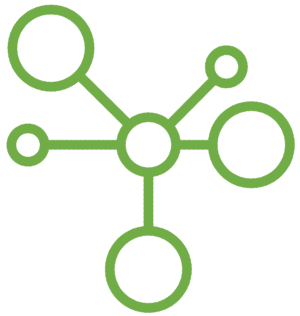
IoMT

- Applications and hardware that can connect to healthcare information technology systems via networking technologies
- Connected people, environments and machines facilitate the transfer of clinically relevant data over networks
- Integration of these data within monitoring, alerting and decision support systems will enable dramatic transformation in care delivery and accelerate the adoption of Value-Based Health Care

Intelligent IoT

Analytics at the Point of the Sensor

By 2019, at least 40% of IoT-created data will be stored, processed, analyzed and acted upon close to, or at the Edge.



- The edge includes physical devices or sensors that interact with the world and collect data
- They can be very small in terms of their computing power, perhaps only able to collect their data and transmit it over an industrial protocol
- They can also be very powerful, with built-in computing and the capability to route data directly over the network – they are the data producers

U.S. Food and Drug Administration

Digital Health

- Many medical devices now have the ability to connect to and communicate with other devices or systems.
- Devices that are already FDA approved or cleared are being updated to add digital features.
- New types of devices that already have these capabilities are being explored.

Many stakeholders are involved in digital health activities, including patients, health care practitioners, researchers, traditional medical device industry firms, and firms new to FDA regulatory requirements, such as mobile application developers.

- Wireless Medical Devices
- Mobile medical apps
- Health IT
- Telemedicine
- Medical Device Data Systems
- Medical device Interoperability
- **Software as a Medical Device (SaMD)**
- General Wellness
- Cybersecurity

Clinical Decision Support

Regulatory Considerations

News | 06 August 2018

FDA backs clinician-free AI imaging diagnostic tools

Mark Ratner

Nature Biotechnology **36**, 673–674

Crit Care Med. 2018 Apr;46(4):547-553. doi: 10.1097/CCM.0000000000002936.

An Interpretable Machine Learning Model for Accurate Prediction of Sepsis in the ICU.

Nemati S[1], Holder A[2], Razmi F[1], Stanley MD[3], Clifford GD[1,4], Buchman TG[3,5].

FDA News Release

FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

July 3, 2018

Diagnosing Fractures With AI

Rebecca Voelker, MSJ

JAMA. 2018;320(1):23. doi:10.1001/jama.2018.8565

An artificial intelligence (AI) algorithm that can help clinicians detect wrist fractures in adults has received FDA approval.

The Imagen OsteoDetect is a type of computer-aided detection and diagnostic software that uses machine learning techniques to identify signs of distal radius fracture during reviews of posterior-anterior and medial-lateral x-ray images of the wrist. The software marks the location of a fracture on the image to aid clinicians with their diagnoses.

Acta Orthop. 2017 Nov; 88(6): 581–586.
Published online 2017 Jul 6. doi: 10.1080/17453674.2017.1344459

PMCID: PMC5694800
PMID: 28681679

Artificial intelligence for analyzing orthopedic trauma radiographs

Deep learning algorithms—are they on par with humans for diagnosing fractures?

Jakub Olczak,[1] Niklas Fahlberg,[2] Atsuto Maki,[3] Ali Sharif Razavian,[1,3] Anthony Jilert,[2] André Stark,[1] Olof Sköldenberg,[1] and Max Gordon[✉1]

Virtual Clinical Trials

1 NOVEMBER 2018 COMMENT

Virtual Clinical Trials: Are Site-less Trials the Future?

SHARE

Sensor Based Motion Analysis

Connecting digital mobility assessment to clinical outcomes for regulatory and clinical endorsement (Mobilise-D) brings together clinicians, scientists, prominent academic centres, businesses, and the world's largest pharmaceutical and medical industries to revolutionise assessment of mobility loss using digital technology, leading to a game changer for clinical trials and clinical management of mobility.

Imagine being able to monitor your mobility and health with the help of small sensors worn on your body, coupled with personalized algorithms – and to do this on a daily basis, without the need to see your physician or go to a clinic.

Impossible?

Mobilize-D

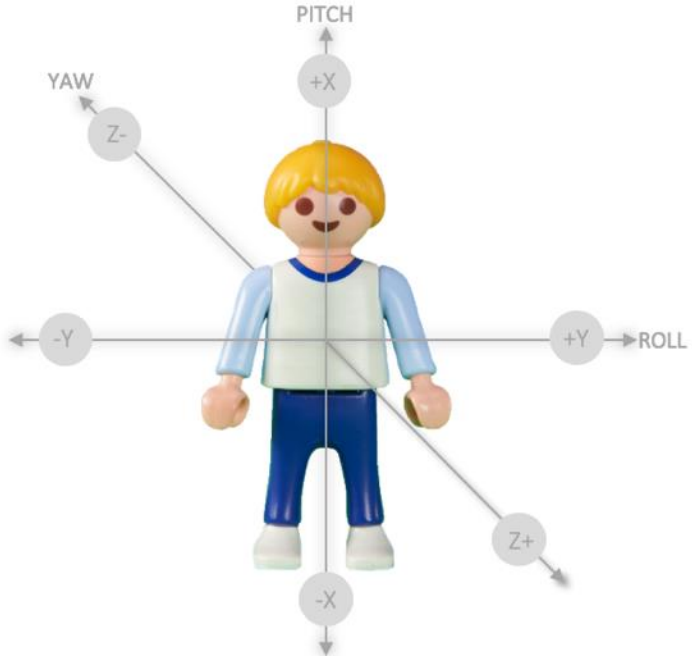
Consortium Partners

Use Case

Motion Analytics

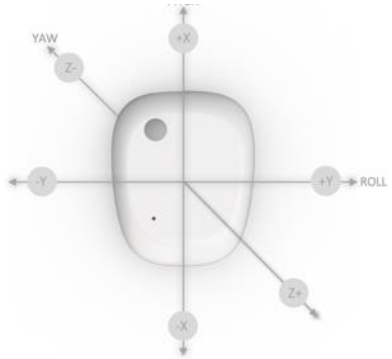
Application of Machine Learning to Motion Sensor and Image Analysis of Mobility Outcome Measures for Automated Clinical Assessment

Mark Wolff, M.S., Ph.D.
Chaz Henry, M.S.C.S.
SAS Institute



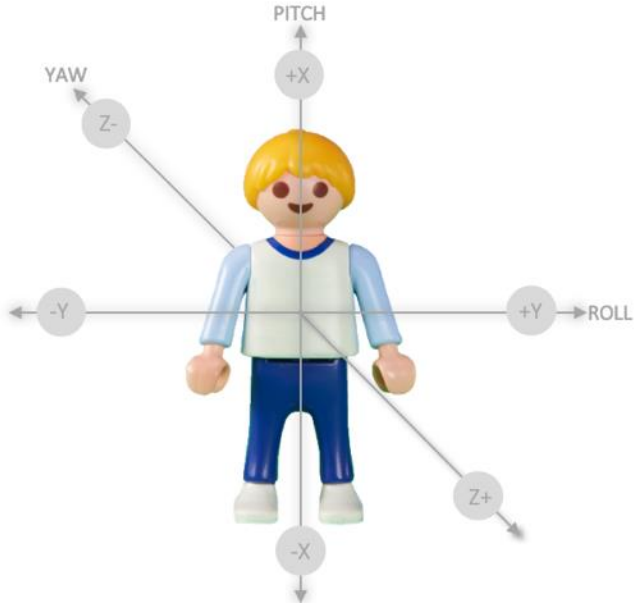
Sensor Hardware
Video and IMU

Intel RealSense depth & tracking **camera**



mbientlab MMR
9-axis IMU and Environmental Sensor

The MetaMotionR (MMR) is a wearable device that offers real-time and continuous monitoring of motion and environmental sensor data.



Berg Balance Scale Assessment

Qualitative Analysis by Trained Clinician

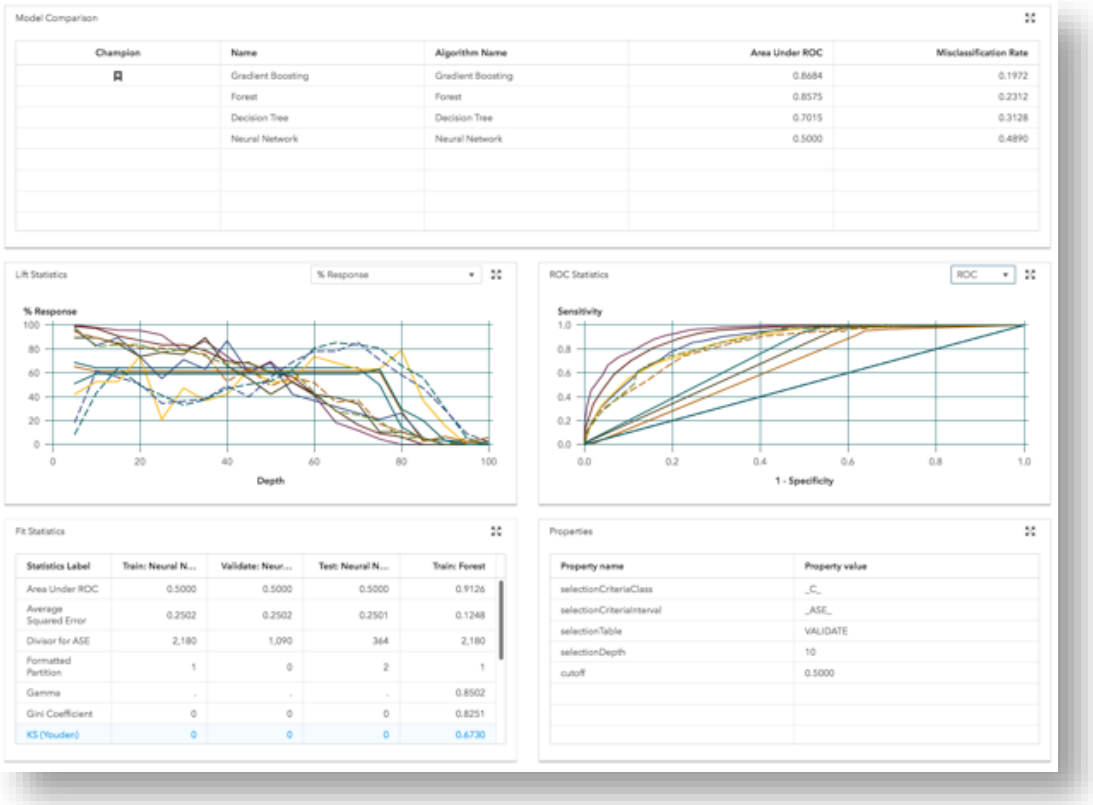
Berg Balance Scale (BBS)

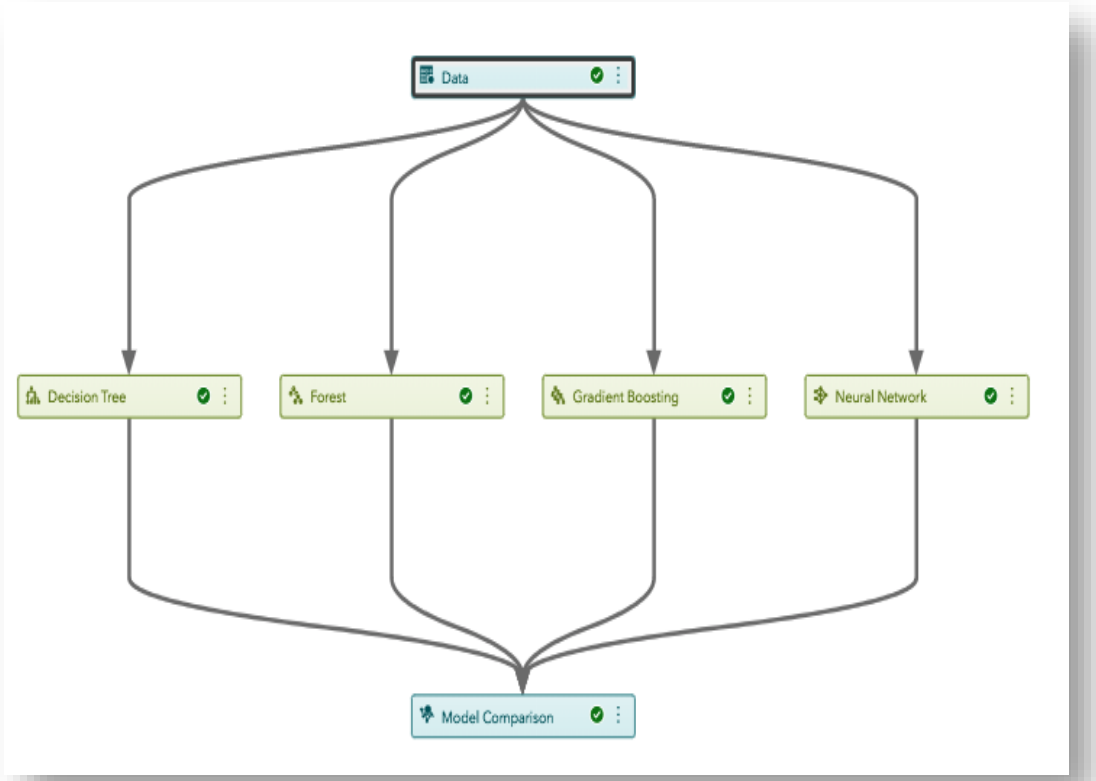
Item Description:	SCORE (0–4)
_____	1.Sitting to standing
_____	2.Standing unsupported
_____	3.Sitting unsupported
_____	4.Standing to sitting
_____	5.Transfers
_____	6.Standing with eyes closed
_____	7.Standing with feet together
_____	8.Reaching forward with outstretched arm
_____	9.Retrieving object from floor
_____	10.Turning to look behind
_____	11.Turning 360 degrees
_____	12.Placing alternate foot on stool
_____	13.Standing with one foot in front
_____	14.Standing on one foot
_____	Total

Equipment needed:	Ruler, 2 standard chairs (one with arm rests, one without), footstool or step, stopwatch or wristwatch, 15 ft walkway
Time needed:	15–20 minutes
Scoring:	A five-point ordinal scale, ranging from 0–4. “0” indicates the lowest level of function and “4” the highest level of function. Total score = 28
Interpretation:	41–56 = low fall risk 21–40 = medium fall risk 0–20 = high fall risk <36 fall risk close to 100%

Machine Learning

Model Development





Modified Berg Balance Scale

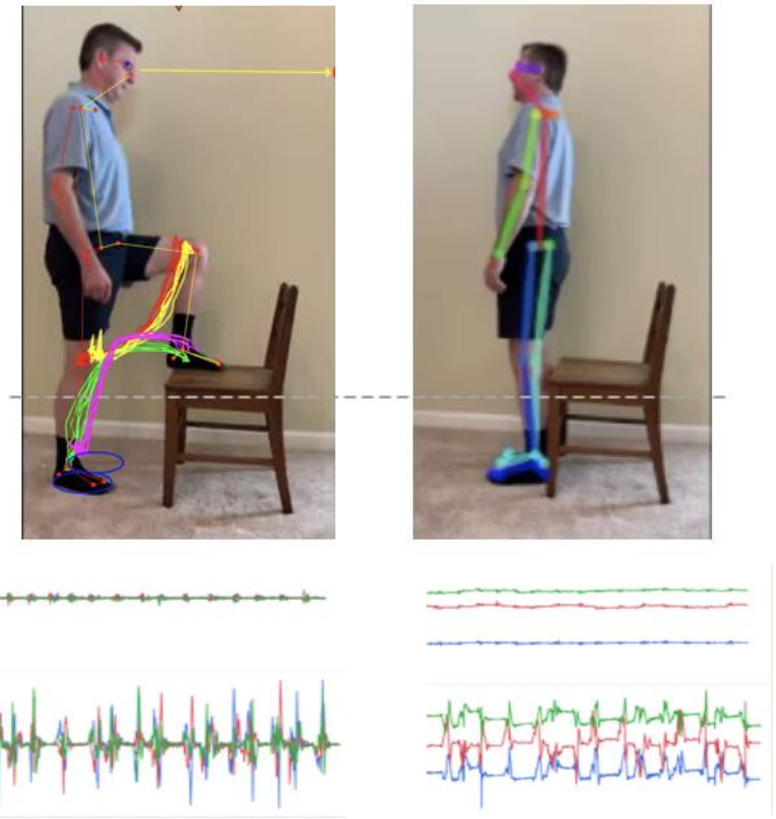
Quantitative, Digital, Automated Clinical Assessment

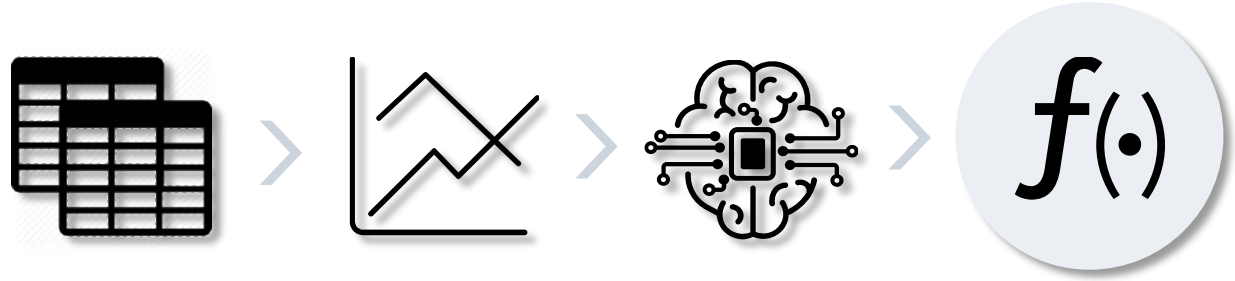
- Using a 9-Axis IMU and a Video Camera patients are assessed preoperatively and postoperatively in clinic.
- The Assessment establishes the base line patient parameters associated with their diagnosed condition prior to and immediately following surgery

- Assessment is based on a modified, digitized and automated version of the Berg Balance Scale
  - Mathematical models describe the preoperative condition of the patient as recorded during the assessment protocol
  - Models are used to score and track rehabilitation progress
  - Models are also used to evaluate the effect of the surgery on its therapeutic efficacy given the primary diagnosis

Data and Models

Video Training and Sensor Data





Knee Up/Down Modeling
SAS Data Step for Scoring Data

```
LABEL Prob_0= 'Predicted: TARGET=0';
LABEL Prob_1= 'Predicted: TARGET=1';


Prob_0=0;
Prob_1=0;
IF z_axis_g_>=0.441 THEN DO; Prob_0=Prob_0+0.00949809763486798;
Prob_1=Prob_1+0.990501902365132;
END;
ELSE DO;
 IF y_axis_g_>=0.08 THEN DO; Prob_0=Prob_0+0.0625819090296167;
Prob_1=Prob_1+0.937418090970383;
 END;
 ELSE DO; Prob_0=Prob_0+0.984192837130963; Prob_1=Prob_1+0.0158071628690365;
 END;
END;
```

Knee Up/Down Modeling
Python Code for Scoring Data

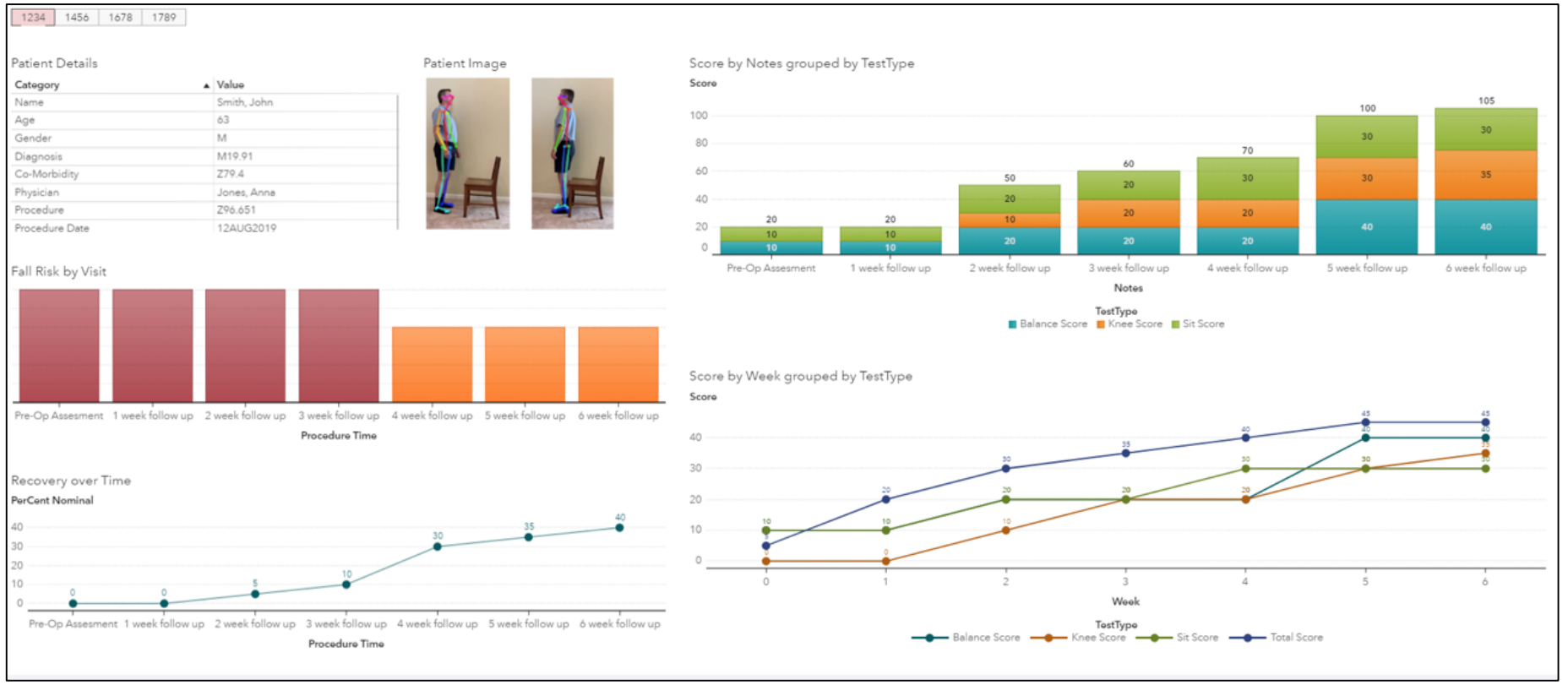
```
from __future__ import division
import jmp_score as jmp
from math import *
import numpy as np

""" Python code generated by JMP v14.2.0 """

def getModelMetadata():
return {"creator": u"Partition", "modelName": u"", "predicted": u"TARGET", "table":
u"MAW_KNEE_TRAINING", "version": u"14.2.0", "timestamp": u"2019-09-05T02:20:29Z"}


def getInputMetadata():
    return {
        u"y-axis (g)": "float",
        u"z-axis (g)": "float"
}
```

DASHBOARD


1234
1456
1678
1789
Patient Details
Category
Value
Name
Smith, John
Age
63
Gender
M
Diagnosis
M19.91
Co-Morbidity
Z79.4
Physician
Jones, Anna
Procedure
Z96.651
Procedure Date
12AUG2019
Patient Image
Fall Risk by Visit
Pre-Op Assesment
1 week follow up
2 week follow up
3 week follow up
4 week follow up
5 week follow up
6 week follow up
Procedure Time
Recovery over Time
PerCent Nominal
Procedure Time
Score by Notes grouped by TestType
Score
Notes
TestType
Balance Score
Knee Score
Sit Score
Score by Week grouped by TestType
Score
Week
TestType
Balance Score
Knee Score
Sit Score
Total Score

Thank You!