From the Virtual Physiological Human to the Human Digital Twin

a 20-year journey toward in silico medicine

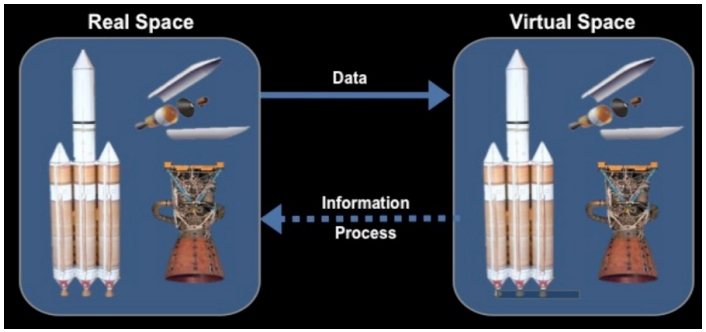
Marco Viceconti

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

Invited Lecture, University of Bath, 18 May 2022

Digital Twins in manufacturing industry

"A digital twin is a virtual representation that serves as the real-time digital counterpart of a physical object or process"
from Wikipedia



CHAPTER 7

Virtually Intelligent Product Systems: Digital and Physical Twins

Michael W. Grieves*

2002 Society of Manufacturing Engineers conference Troy (MI)

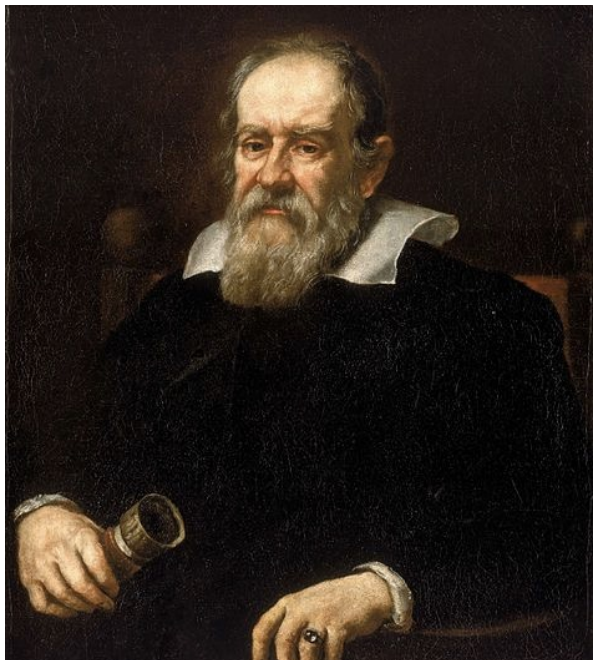
Digital Twins in healthcare

- Can we develop the digital twin of a patient, capable of predicting change in the health status of an individual, and provide decision support to the clinical management of such person?

Can we predict life?

- Can we predict changes in the health status of an individual patient on the basis of mechanistic knowledge we have of human physiology and of the specific disease that affect such patient?

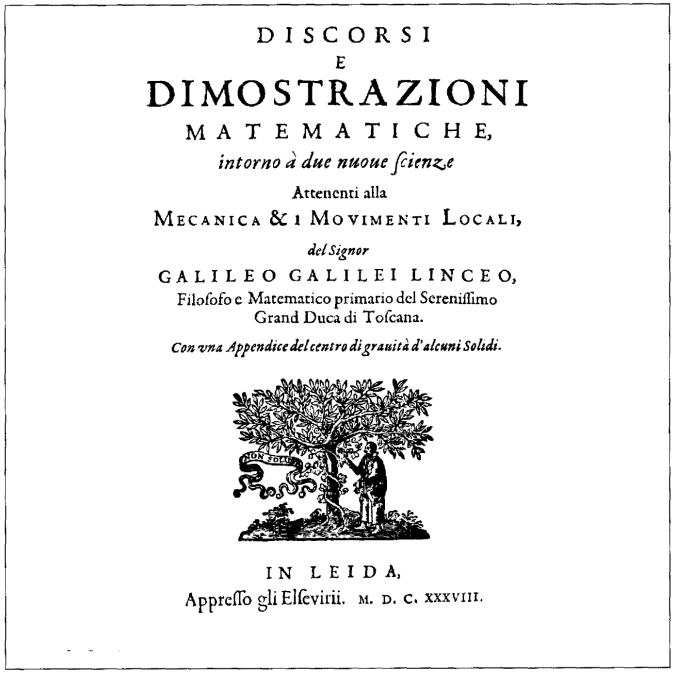
Can we predict life?



Ritratto di Galileo Galilei (1636),
Justus Sustermans

«il Libro della natura è scritto
nella lingua della matematica»
Il Saggiatore (1623)

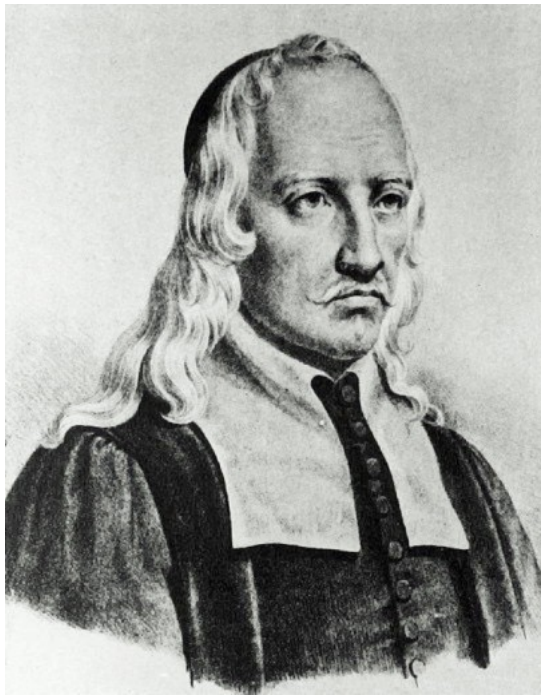
«Sensate esperienze e
necessarie dimostrazioni»
Discorsi (1638)



DISCORSI
E
DIMOSTRAZIONI
MATEMATICHE,
intorno à due nuoue ſcienze
Attenenti alla
MECANICA & I MOVIMENTI LOCALI,
del Signor
GALILEO GALILEI LINCEO,
Filoſofo e Matematico primario del Sereniſſimo
Grand Duca di Toſcana.
Con vna Appendice del centro di grauità d'alcuni Solidi.

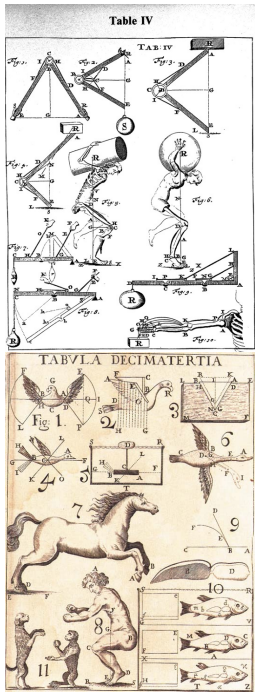
IN LEIDA,
Appreſſo gli Elſevirii. M. D. C. XXXVIII.

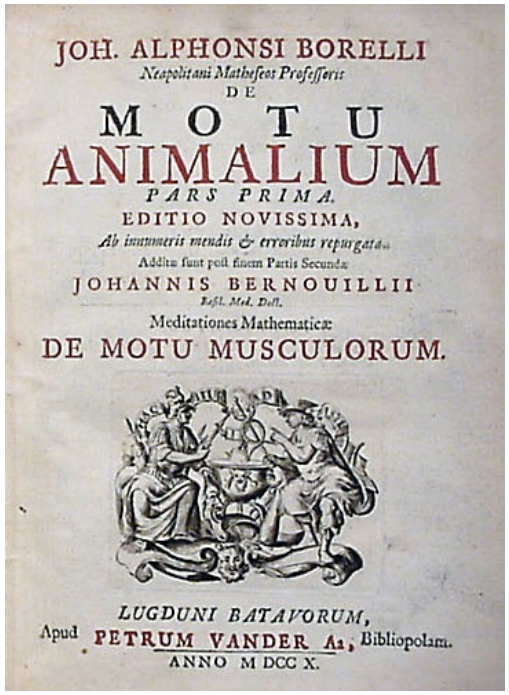
Borelli: de motu animalium



Giovanni Alfonso Borelli
(1608 – 1679)

Marcello Malpighi
(1628 – 1694)





Little history of empirical biology

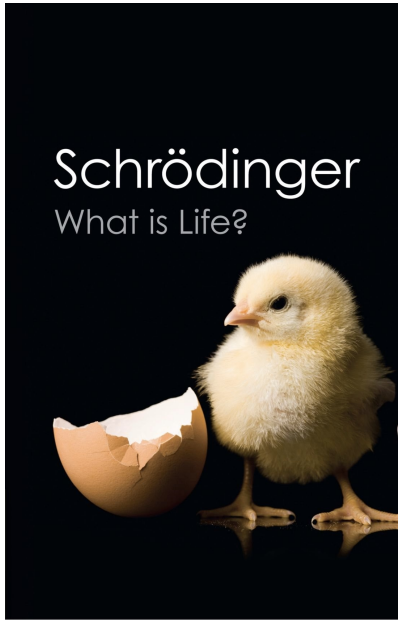
- Al-Jāḥiẓ (781-869): the concept of food chain
- Al-Dinawari (828-896): describes 637 plants
- Ibn Sina (Avicenna) (980-1037): his “Canon of Medicine” introduces the concept of clinical trial
- Avenzoar (1091-1161): introduces the autopsy
- Ibn al-Nafis (1213-1288): first describes coronary and respiratory circulation
- Andries van Wesel (Vesalius, 1537) *De Humani Corporis Fabrica* starts modern descriptive anatomy
- William Harvey (1628), *De Motus Cordis*, describe circulatory system

Physical sciences lost the battle

- **Complexity**
  - For a long while mathematical methods (and our ability to solve them) severely limit our ability to model living organisms, if not by using radical idealisation frequently totally unrealistic

- **Agnosticism in science**
  - Monism: everything is matter – Dualism: matter and spirit
  - Science is born in the 16th century, in a world where dualism is dominant; science develops around a weak ontology, agnostic with respect to this debate
  - Physics focus on inanimate matter, where mechanistic explanations do not offend spiritualists
  - Biology develops around a radical agnosticism, where life is observed but not explained

The thermodinamics of life



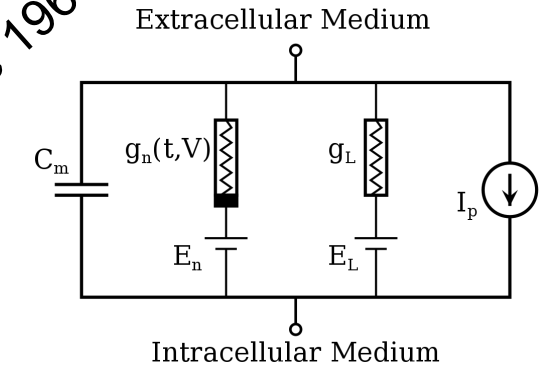
What Is Life? The Physical Aspect of the Living Cell (1944)

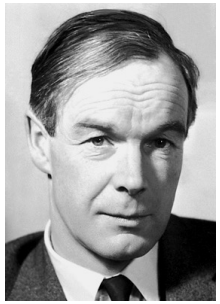
Based on a course of public lectures delivered in February 1943, at Trinity College, Dublin.

Erwin Schrödinger (1887-1961)

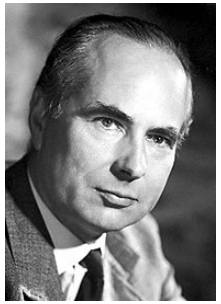
1958: Model of action potential in neurons

Nobel Prize 1963

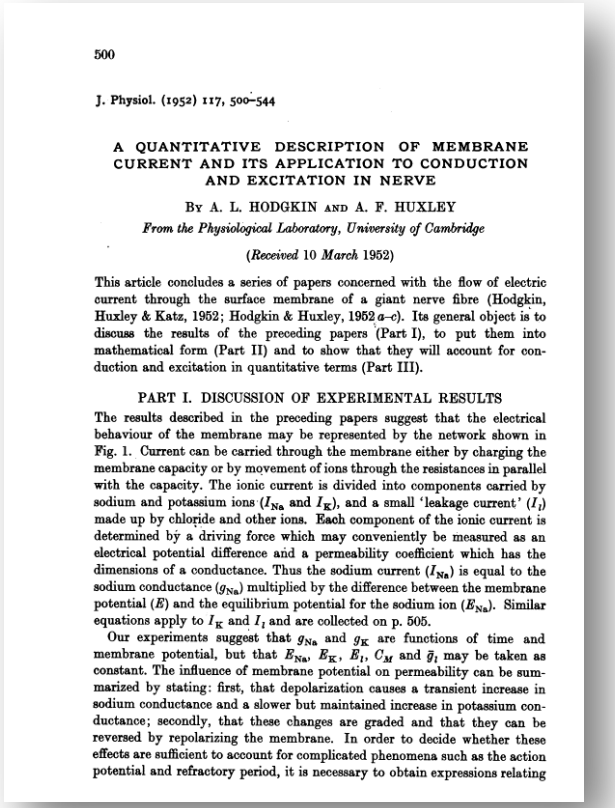




Alan Hodgkin
(1914-1998)



Andrew Huxley
(1917 –2012)



500

J. Physiol. (1952) 117, 500–544

A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE

BY A. L. HODGKIN AND A. F. HUXLEY

From the Physiological Laboratory, University of Cambridge

(*Received* 10 *March* 1952)

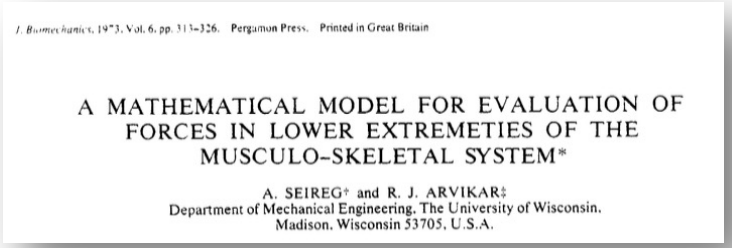
This article concludes a series of papers concerned with the flow of electric current through the surface membrane of a giant nerve fibre (Hodgkin, Huxley & Katz, 1952; Hodgkin & Huxley, 1952*a–c*). Its general object is to discuss the results of the preceding papers (Part I), to put them into mathematical form (Part II) and to show that they will account for conduction and excitation in quantitative terms (Part III).

PART I. DISCUSSION OF EXPERIMENTAL RESULTS

The results described in the preceding papers suggest that the electrical behaviour of the membrane may be represented by the network shown in Fig. 1. Current can be carried through the membrane either by charging the membrane capacity or by movement of ions through the resistances in parallel with the capacity. The ionic current is divided into components carried by sodium and potassium ions (I_{Na} and I_K), and a small 'leakage current' (I_l) made up by chloride and other ions. Each component of the ionic current is determined by a driving force which may conveniently be measured as an electrical potential difference and a permeability coefficient which has the dimensions of a conductance. Thus the sodium current (I_{Na}) is equal to the sodium conductance (g_{Na}) multiplied by the difference between the membrane potential (E) and the equilibrium potential for the sodium ion (E_{Na}). Similar equations apply to I_K and I_l and are collected on p. 505.

Our experiments suggest that g_{Na} and g_K are functions of time and membrane potential, but that E_{Na}, E_K, E_l, C_M and $\bar{g}_l$ may be taken as constant. The influence of membrane potential on permeability can be summarized by stating: first, that depolarization causes a transient increase in sodium conductance and a slower but maintained increase in potassium conductance; secondly, that these changes are graded and that they can be reversed by repolarizing the membrane. In order to decide whether these effects are sufficient to account for complicated phenomena such as the action potential and refractory period, it is necessary to obtain expressions relating

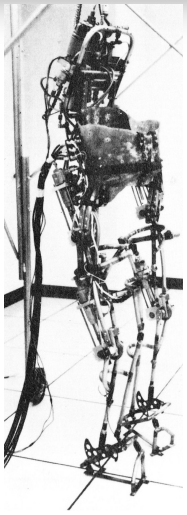
1973: Musculoskeletal dynamics

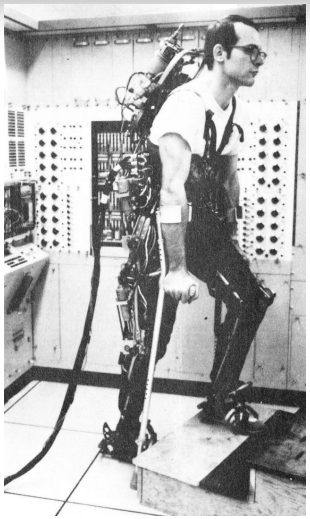


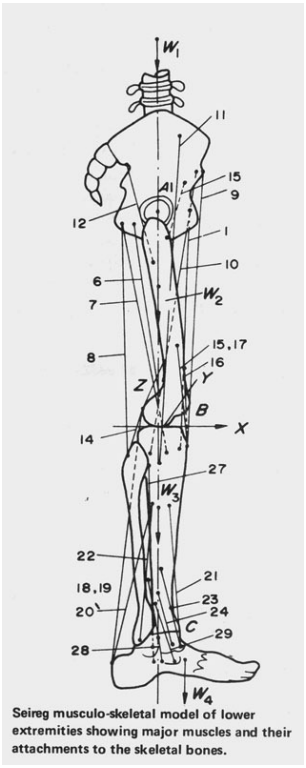
J. Biomechanics, 1973, Vol. 6, pp. 313–326. Pergamon Press. Printed in Great Britain

A MATHEMATICAL MODEL FOR EVALUATION OF FORCES IN LOWER EXTREMETIES OF THE MUSCULO-SKELETAL SYSTEM*

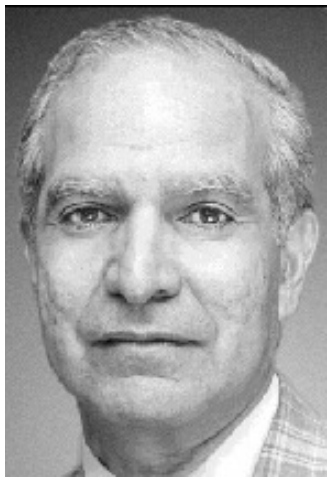
A. SEIREG† and R. J. ARVIKAR‡
Department of Mechanical Engineering, The University of Wisconsin, Madison, Wisconsin 53705, U.S.A.







Seireg musculo-skeletal model of lower extremities showing major muscles and their attachments to the skeletal bones.



Alí Seireg
(1927-2002)

1978: Model of cardiac contractility

J. Physiol. (1978), **280**, *pp.* 155–168
With 9 text-figures
Printed in Great Britain

THE ACTION OF ADRENALINE ON PACE-MAKER ACTIVITY IN CARDIAC PURKINJE FIBRES

BY IRA COHEN, DAVID EISNER AND DENIS NOBLE
From the University Laboratory of Physiology, Oxford and the Department of Physiology and Biophysics, SUNY, Stonybrook, New York, U.S.A.

(*Received 24 October 1977*)

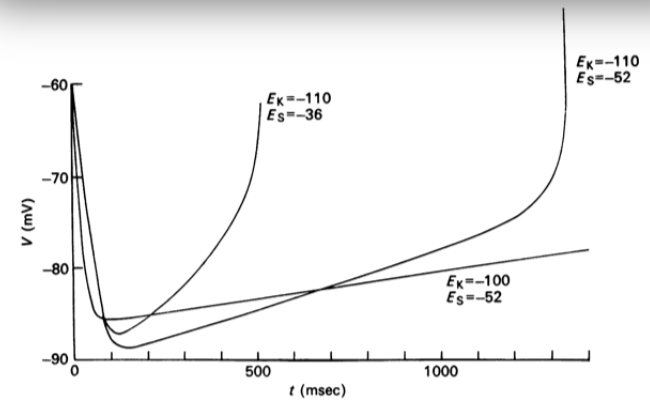
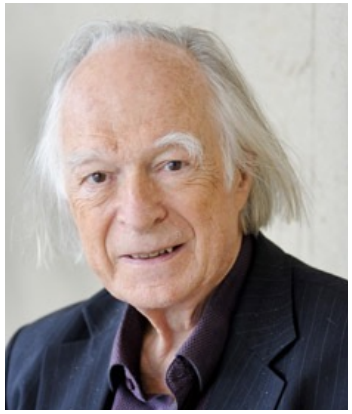


Fig. 5. Computer simulation of the effects of an E_K shift on diastolic depolarization. When E_K is initially −100 mV, a 10 mV negative shift in E_K increases both the maximum diastolic potential (MDP) and the slope of diastolic depolarization. When the s_∞ curve is shifted the slope of diastolic depolarization is increased further but the MDP declines.



Denis Noble
(1936 -)

1984: Bone remodelling

Calcif Tissue Int (1984) 36:S19–S24

Calcified Tissue International
© 1984 by Springer-Verlag

Mechanical Loading Histories and Cortical Bone Remodeling

Dennis R. Carter

Design Division, Department of Mechanical Engineering, Stanford University, Stanford, CA 94305; and Rehabilitation Research and Development Center, Palo Alto Veterans Administration Medical Center, Palo Alto, CA 94304, USA

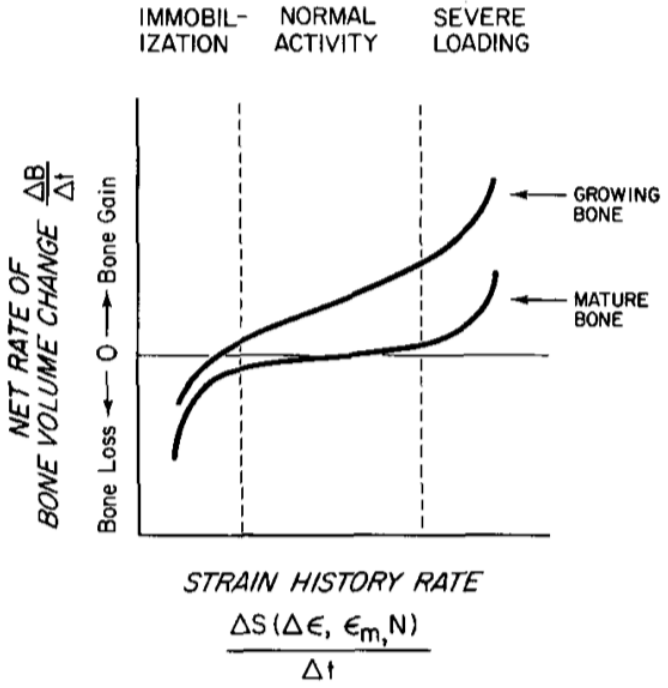
J. Biomechanics Vol. 20, No. 11/12, pp. 1135–1150, 1987.
Printed in Great Britain

0021-9290/87 $3.00 + .00
Pergamon Journals Ltd.

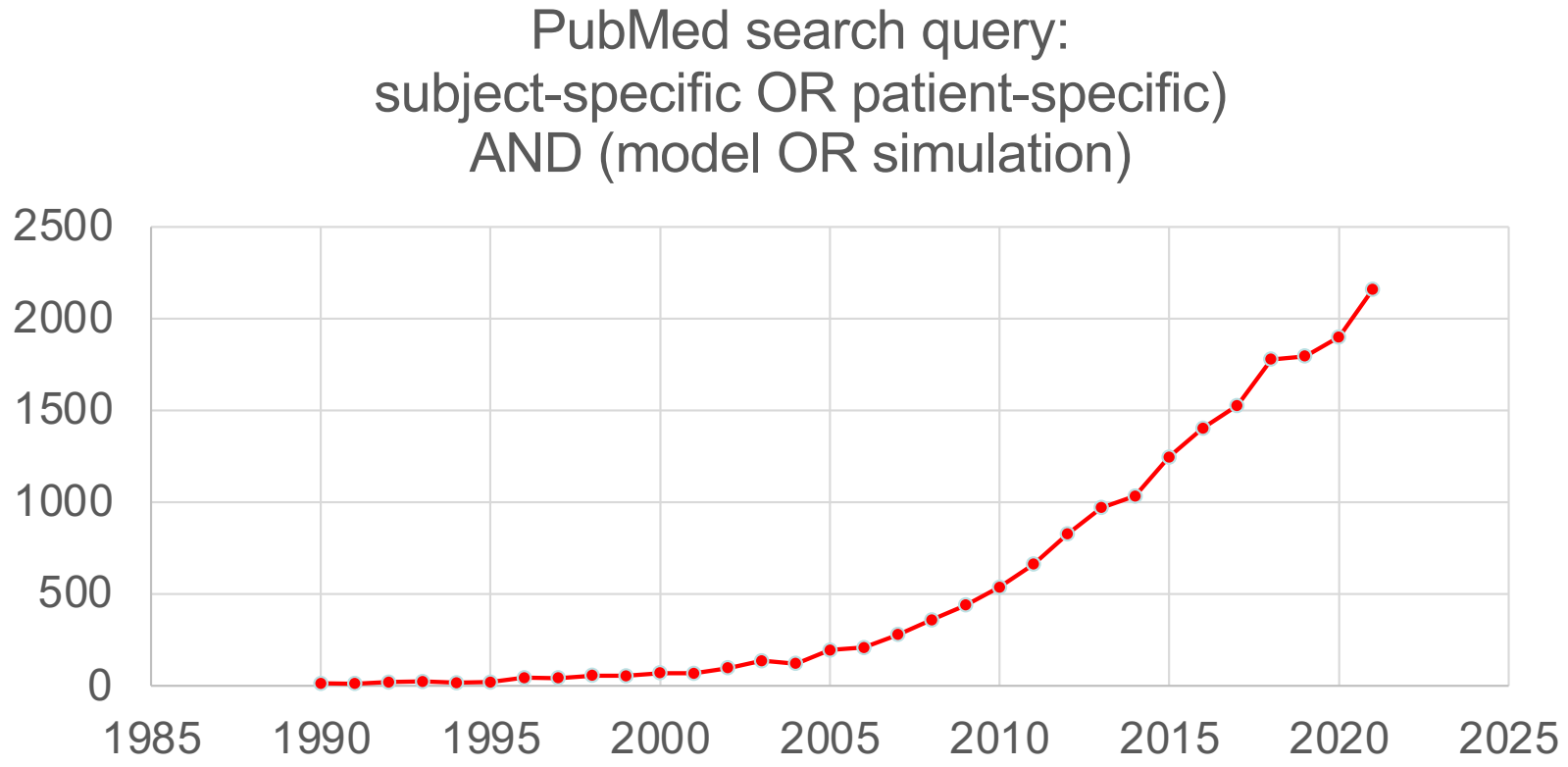
ADAPTIVE BONE-REMODELING THEORY APPLIED TO PROSTHETIC-DESIGN ANALYSIS*

R. HUISKES, H. WEINANS, H. J. GROOTENBOER†, M. DALSTRA, B. FUDALA and T. J. SLOOFF

Biomechanics Section, Institute of Orthopaedics, University of Nijmegen, 6500 HB Nijmegen, The Netherlands; †University of Twente, Enschede, The Netherlands



Modelling life becomes popular

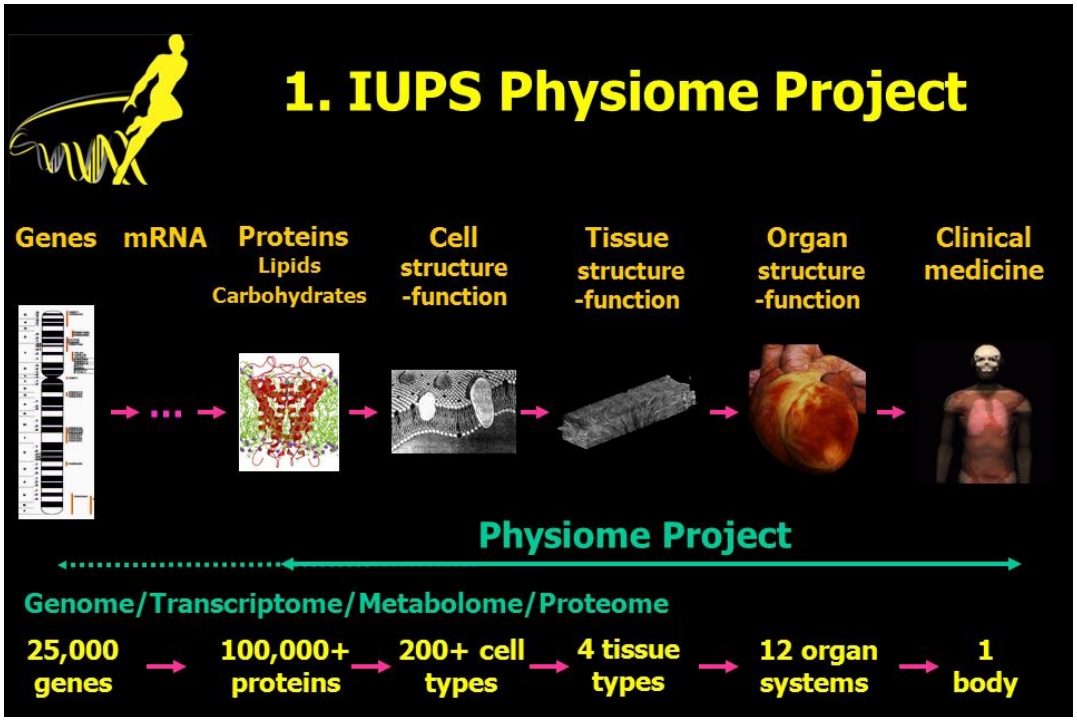


The Physiome

- The Human Genome Project was launched in 1990
- A digital representation of the entire human physiology: “The physiome describes the physiological dynamics of the normal intact organism”
- The idea was first proposed in 1993, but formalised in the IUPS Physiome project in 2001
- The launch in our community happens in 2002

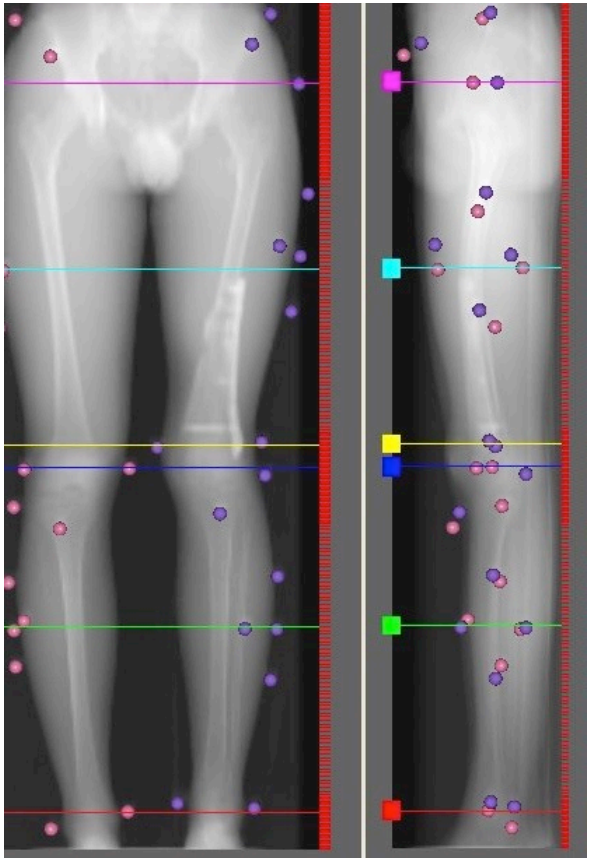
Calgary - August 4th, 2002

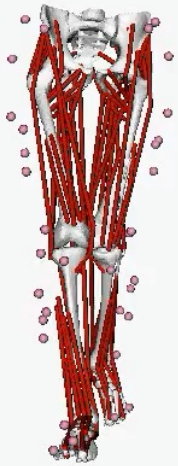
Prof Peter Hunter



4th World Congress of Biomechanics

Patient-specific MSK models





Taddei F, *et al*. Proc Inst Mech Eng H. 2002;216(2):95-104

The Virtual Physiological Human

- The VPH was born in 2005 as the UE version of the Physiome
- But from the beginning the focus was on the clinical application, focusing on diseases, and using models as decision support system

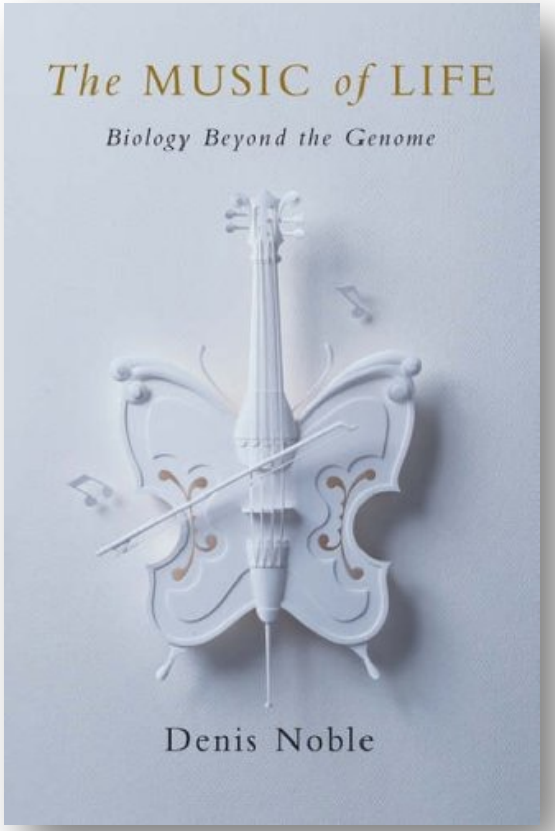
TOWARDS VIRTUAL PHYSIOLOGICAL HUMAN:
MULTILEVEL MODELLING AND SIMULATION OF THE HUMAN ANATOMY AND PHYSIOLOGY

Research challenges and intermediate steps to be addressed by future interdisciplinary research programs

DRAFT VERSION 2.8 of 4th November 2005

2006 – The Music of Life

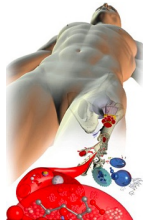
Denis noble and Peter Hunter doing the 'Hongi' a traditional Maori greeting



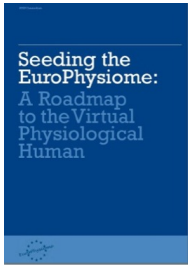
2002 – 2022: a 20 years journey

Physiome Project

2002: Physiome



2005: VPH

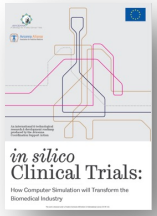


2007: STEP

VPH Institute
Building the Virtual Physiological Human

2010: VPH Institute

In these 20 years the idea of an In Silico Medicine and In Silico Trials with Digital Twins for each patient, moved from science fiction to an industrial reality



2015: Avicenna

Models can predict health

2001: a ML model predicts biochemical failure after radical prostatectomy with a 75% accuracy

Tewari A. *et al* Mol Urol. 2001 5(4):163-9.

2014: FDA allows marketing of HeartFlow vFFR-CT tool for optimal treatment of coronary stenosis

Gaus S, *et al*, JCCT 2013, 7(5):279-88.

2018: patient-specific models of bone strength are more cost-effective that DXA in clinical trials of bone drugs

Viceconti M, Curr Ost Rep 2018 16(3):216-223

2008: FDA approves Kovatchev-Cobelli diabetes simulator to replace animal experimentation

Zisser *et al* Diab Tech Th 2014 16(10):613-22.

2015: Oxford Virtual Assay in silico cardiotoxicity test wins 3R prize for animal replacement

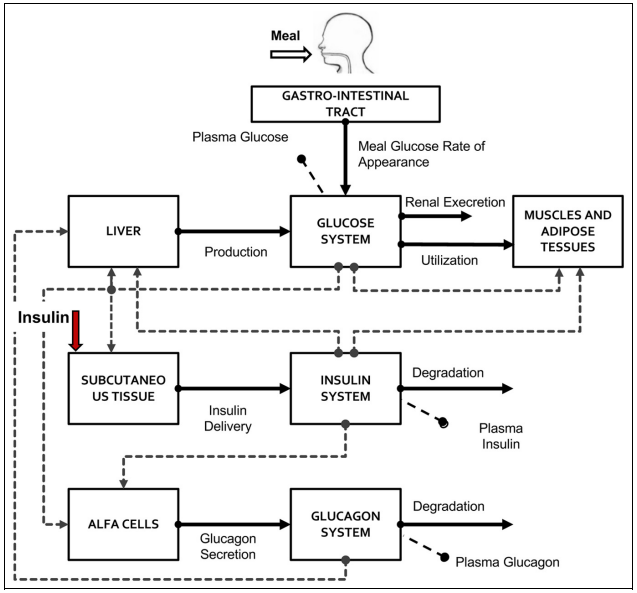
Britton OJ, *et al* PNAS 2013 110 (23) E2098-E2105

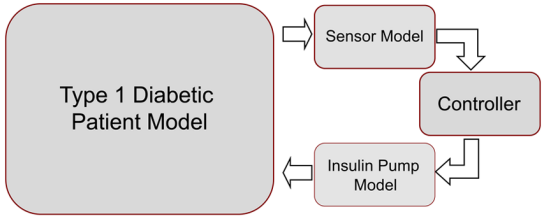
2019: FEops HEARTguide in silico tool for planning transcatheter aortic valve implantation is CE-marked

El Faquir N, *et al* Int J Cardiov Img 2019

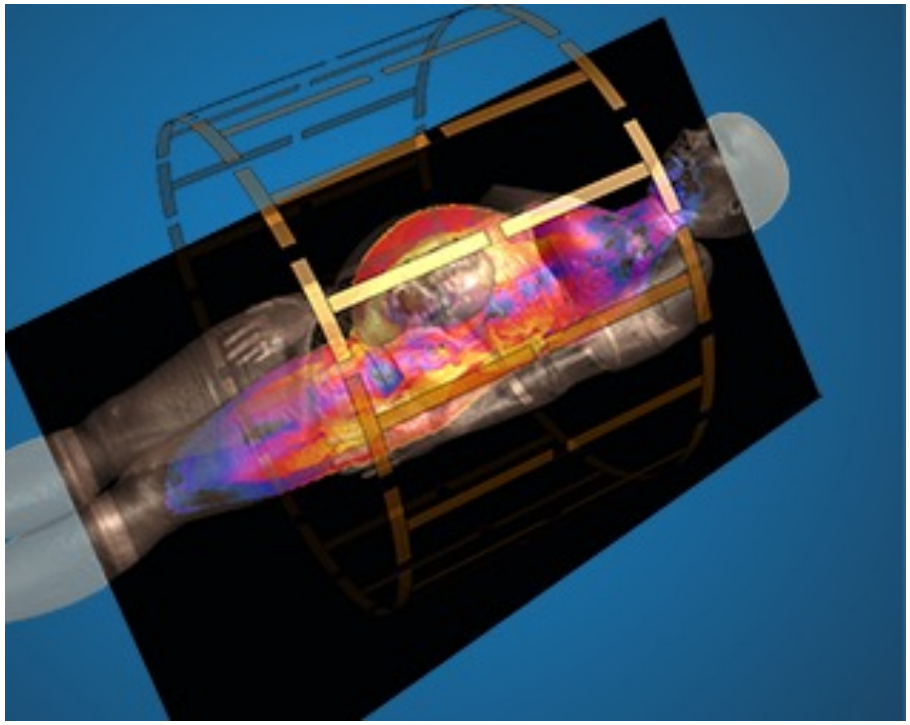
Replacement of animal experiments

- 2006: Juvenile Diabetes Research Foundation starts the Artificial Pancreas Project
- FDA requires algorithms to be tested on dogs before human trials are allowed
- UVA/Padua T1DM simulator virtual patient cohort includes 100 adults, 100 adolescents, and 100 children, spanning the variability of the T1DM population observed in vivo
- 2008: FDA approves investigational device exemption supported only by simulator results

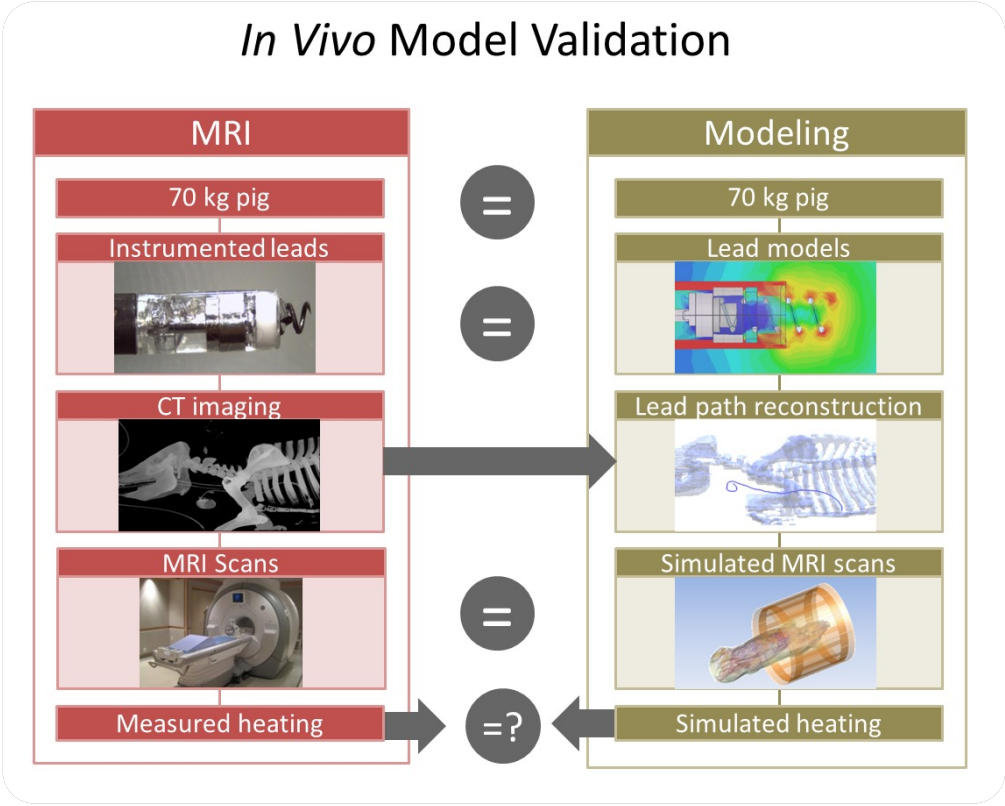




Replacement of animal experiments



Zurich MedTech Sim4Life platform



Reduction of human experiments

- In 2018 FDA accepts an in silico augmented clinical trial as evidence of low risk of fatigue fracture in Quad LV leads

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
2017, VOL. 27, NO. 6, 1089–1103
http://dx.doi.org/10.1080/10543406.2017.1300907

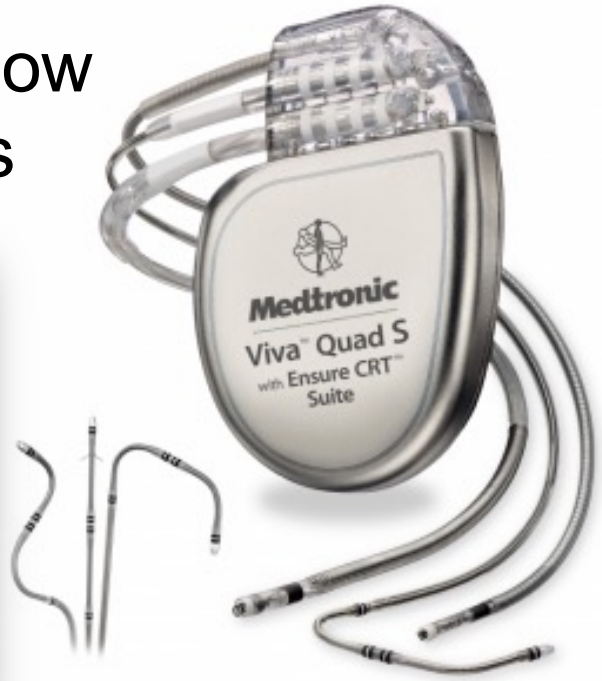
Taylor & Francis
Taylor & Francis Group

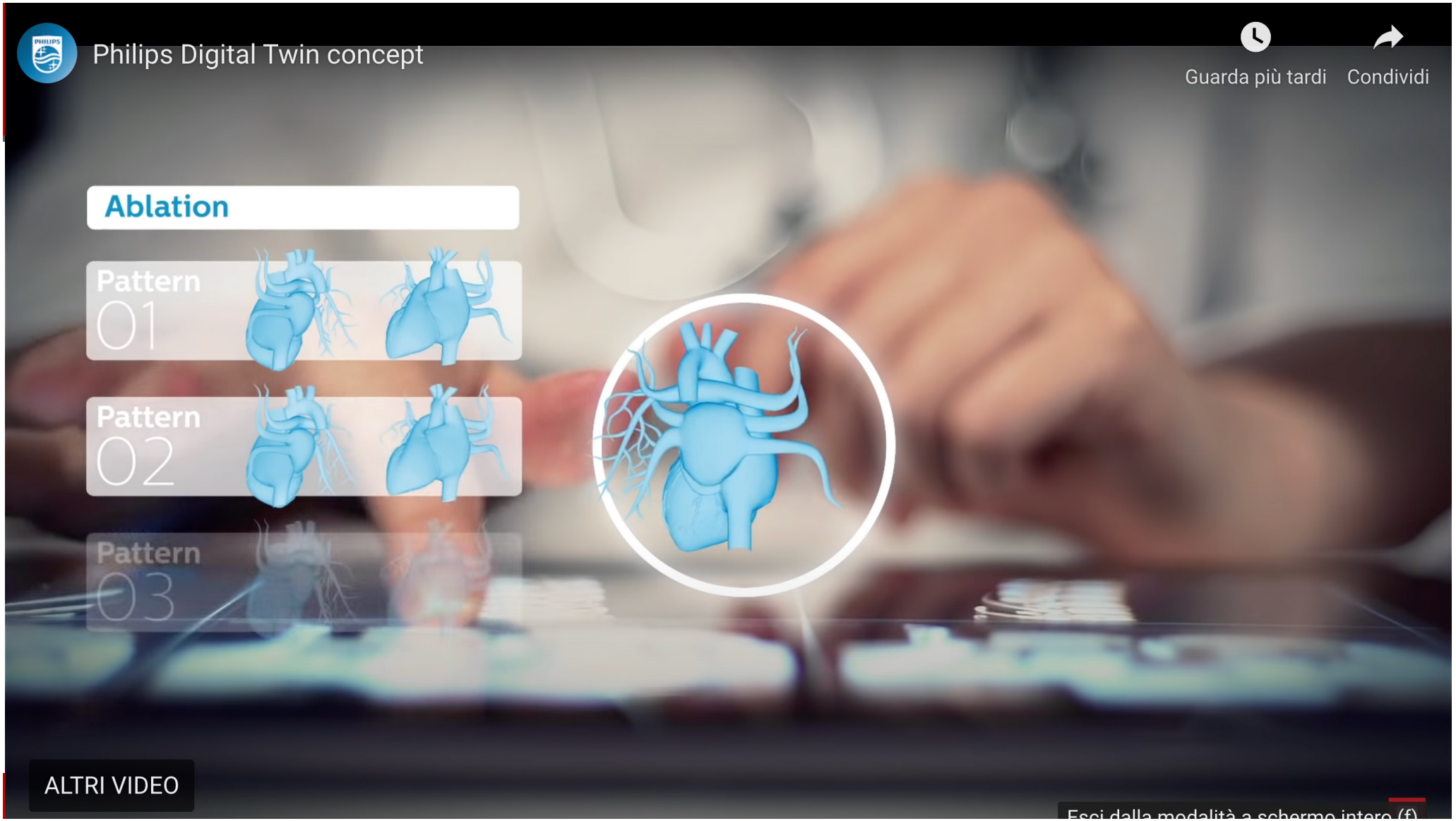
OPEN ACCESS

Incorporation of stochastic engineering models as prior information in Bayesian medical device trials

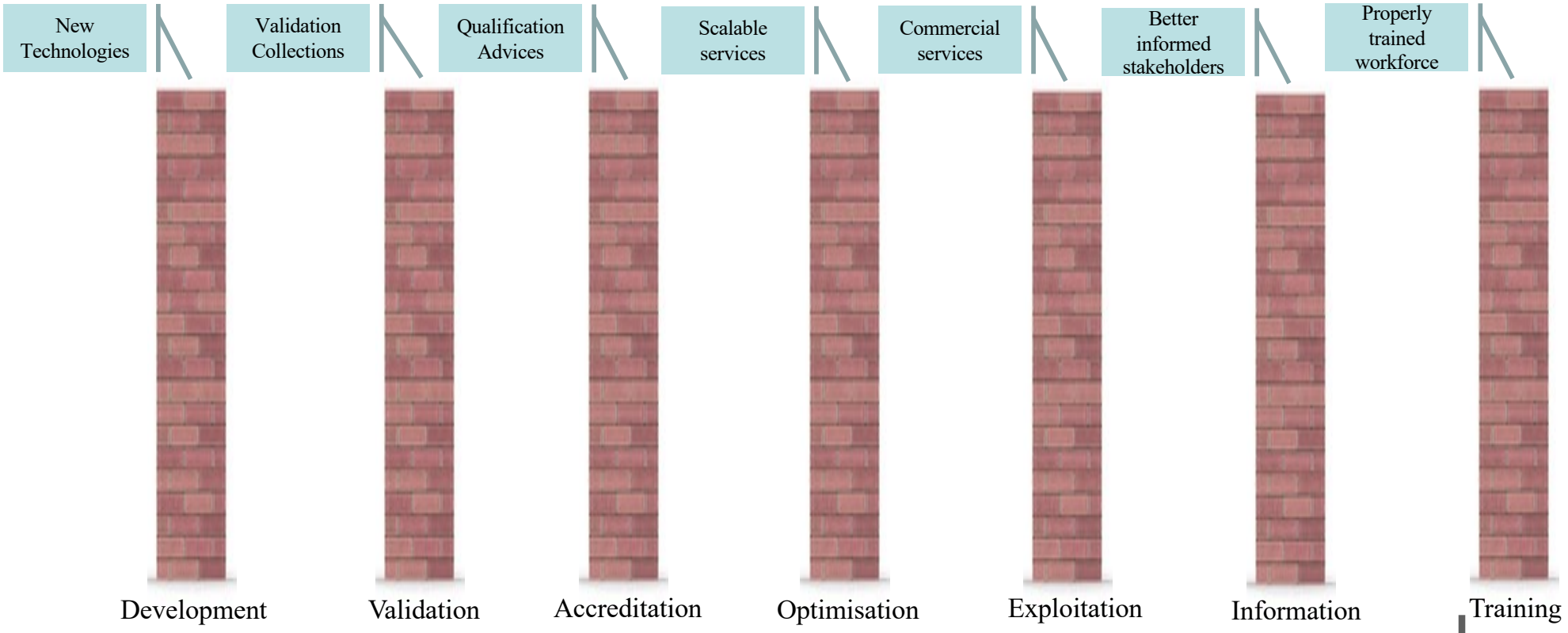
Tarek Haddad[a], Adam Himes[a], Laura Thompson[b], Telba Irony[b,c], Rajesh Nair[b]; and on Behalf of MDIC Computer Modeling and Simulation Working Group Participants[d,e]

[a]Medtronic, plc, Mounds View, Minnesota, USA; [b]Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [c]Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [d]Medical Device Innovation Consortium Clinical Trials Powered by Bench and Simulation Working Group; [e]See online supplement for a complete list of participants

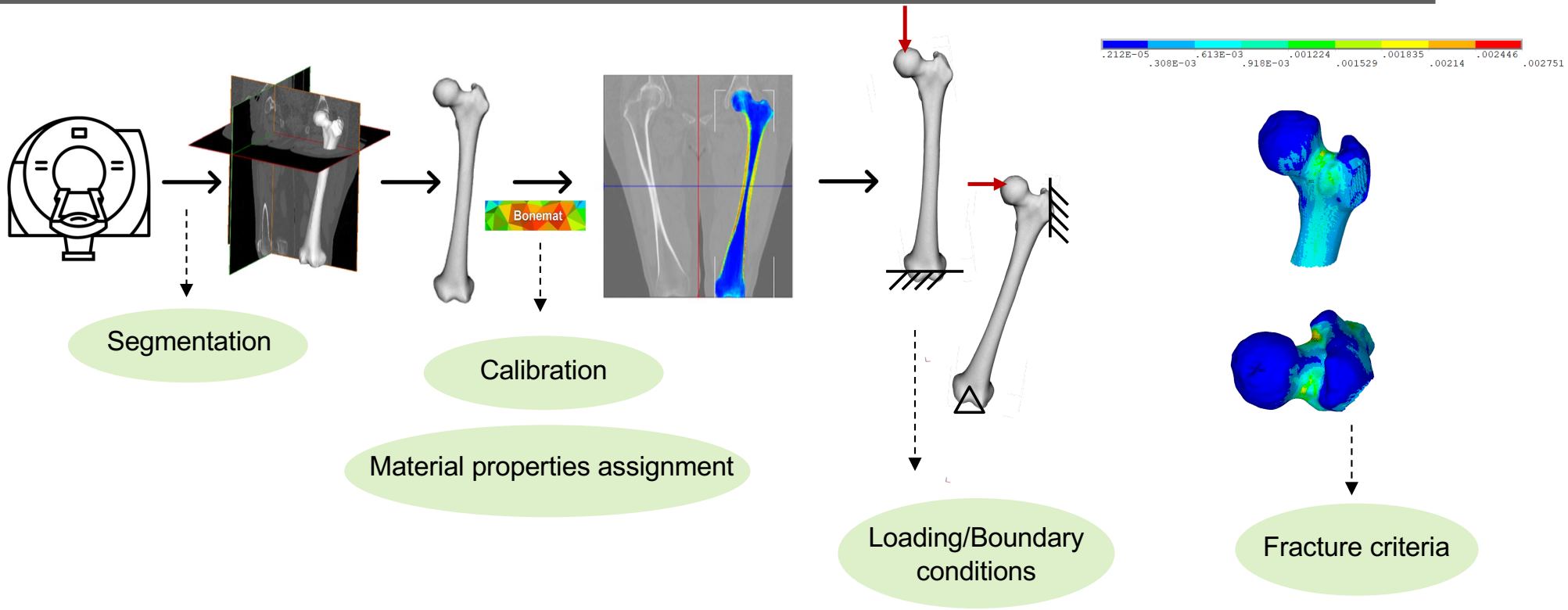



Philips Digital Twin concept
Guarda più tardi
Condividi
Ablation
Pattern
01
Pattern
02
Pattern
03
ALTRI VIDEO
Esci dalla modalità a schermo intero (f)

The barriers to adoption



BBCT: From CT to the model



Bologna Biomechanical Computed Tomography

First attempt of validation

Subject-specific finite element models of long bones: An in vitro evaluation of the overall accuracy

Fulvia Taddei[a,*], Luca Cristofolini[a,b], Saulo Martelli[a], H.S. Gill[c], Marco Viceconti[a]

[a]Laboratorio di Tecnologia Medica, Istituti Ortopedici Rizzoli, Italy
[b]D.I.E.M., Engineering Faculty, University of Bologna, Italy
[c]OOEC, Nuffield Department of Orthopaedic Surgery, University of Oxford, UK

Accepted 26 July 2005

- Comparison of stress and strains predicted by the CT based FE-model
- Reasonable agreement over stresses
- Over 40% error in the prediction of strain

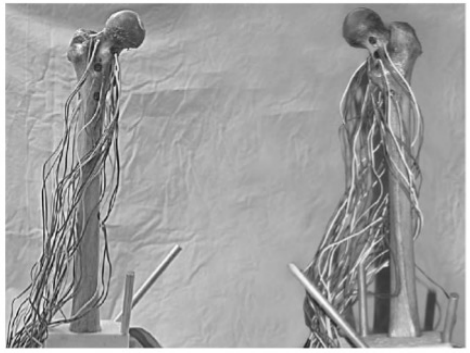


Fig. 1. An anterior (left) and posterior (right) view of the specimen, instrumented with the 13 strain gauges. The three aluminium rods embedded in the cement base used for the spatial registration are visible.

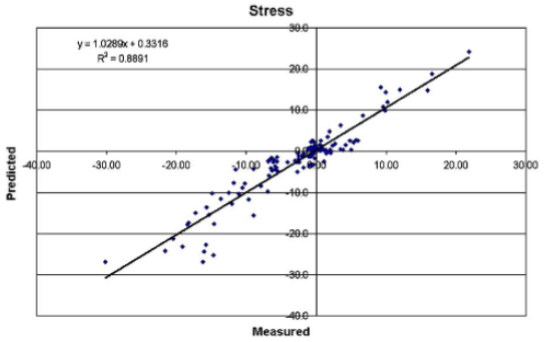


Fig. 6. Predicted vs. measured stresses (MPa) in the two-material homogeneous model.

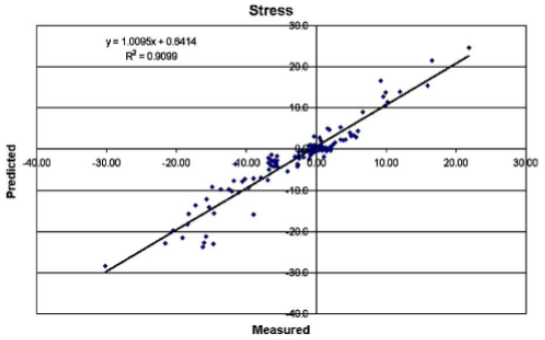
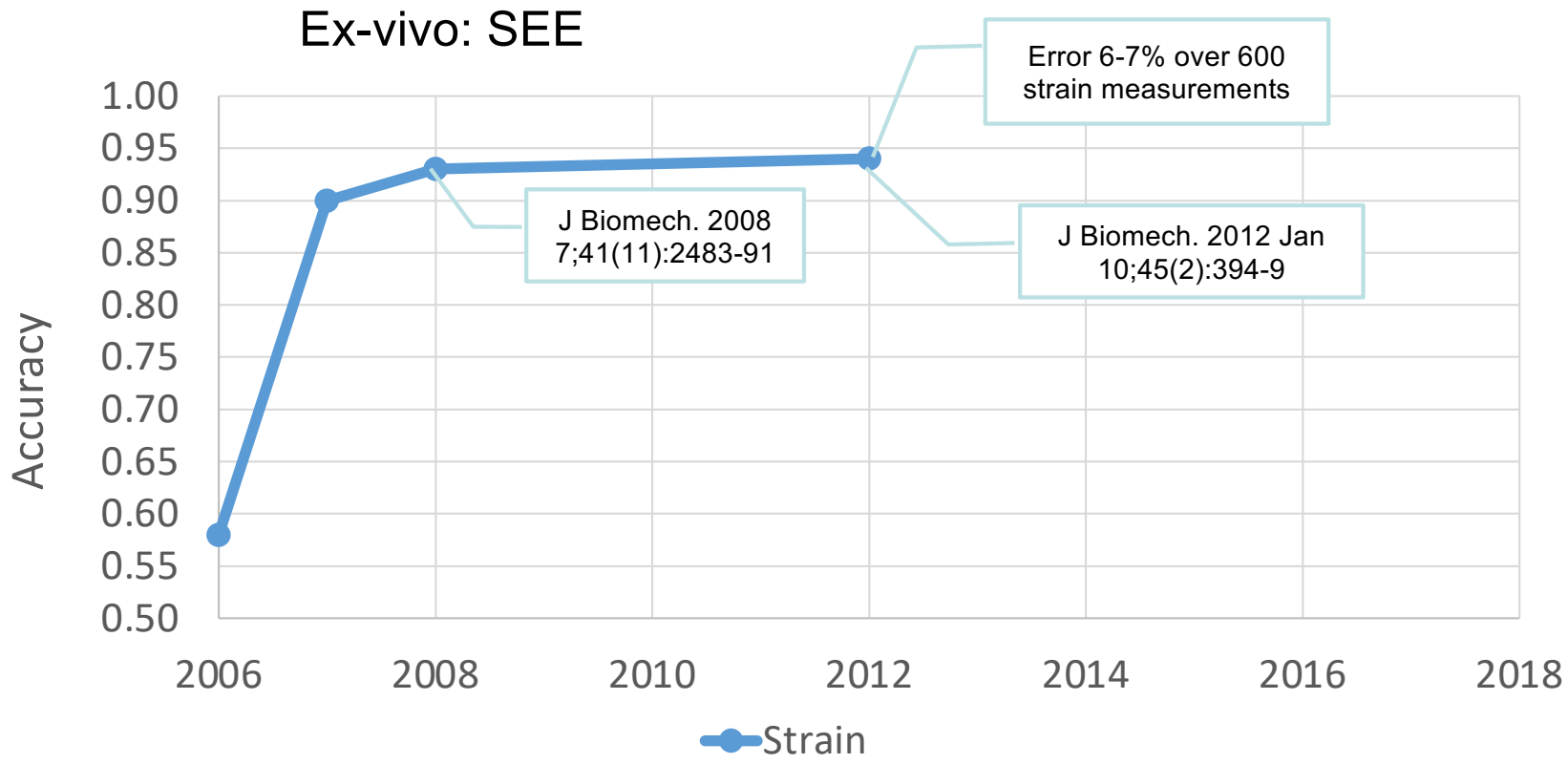


Fig. 7. Predicted vs. measured stresses (MPa) in the density-based inhomogeneous model.

Accurate prediction of strain



Predicting strength

Journal of Biomechanics 47 (2014) 3531–3538

Contents lists available at ScienceDirect

Journal of Biomechanics

journal homepage: www.elsevier.com/locate/jbiomech
www.JBiomech.com

To what extent can linear finite element models of human femora predict failure under stance and fall loading configurations?

Enrico Schileo [a,*], Luca Balistreri [b], Lorenzo Grassi [b], Luca Cristofolini [c], Fulvia Taddei [b]

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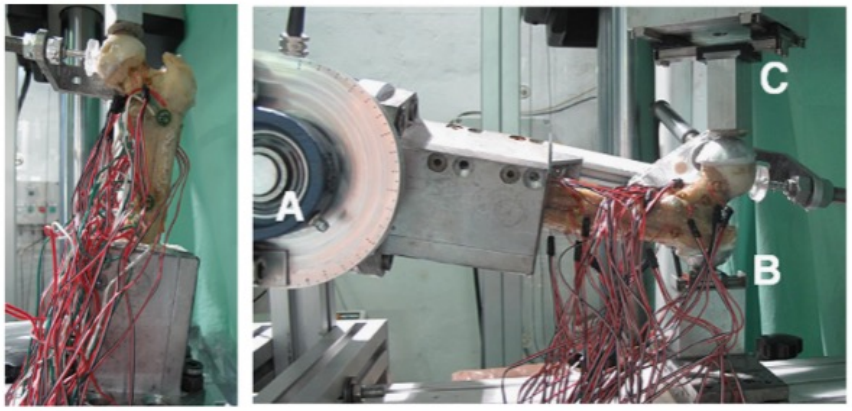
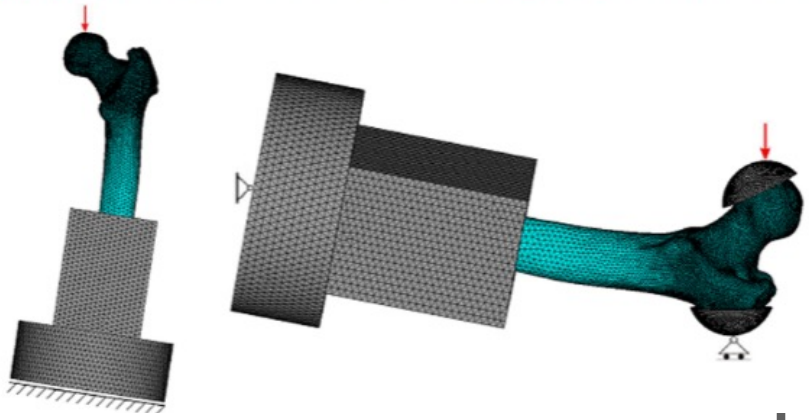
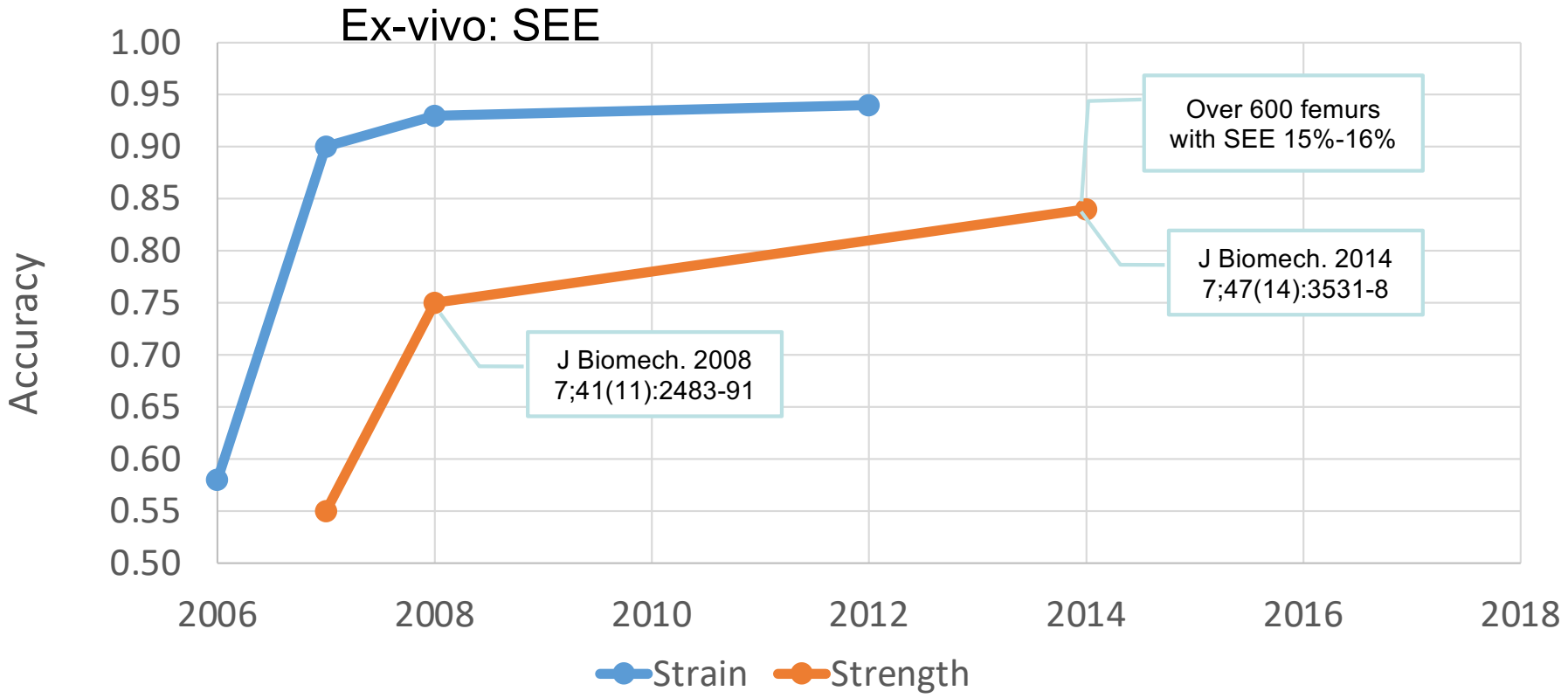
[b] Laboratorio di Tecnologia Medica, Istituto Ortopedico Rizzoli, Bologna, Italy
[c] Department of Industrial Engineering, University of Bologna, Bologna, Italy



- Side-fall experiments are used to measured to force required to fracture a cadaver femur in a given pose
- Replicating the same boundary conditions the FE model predictions can be validated



Accurate prediction of strength



Clinical validation: the Sheffield cohort

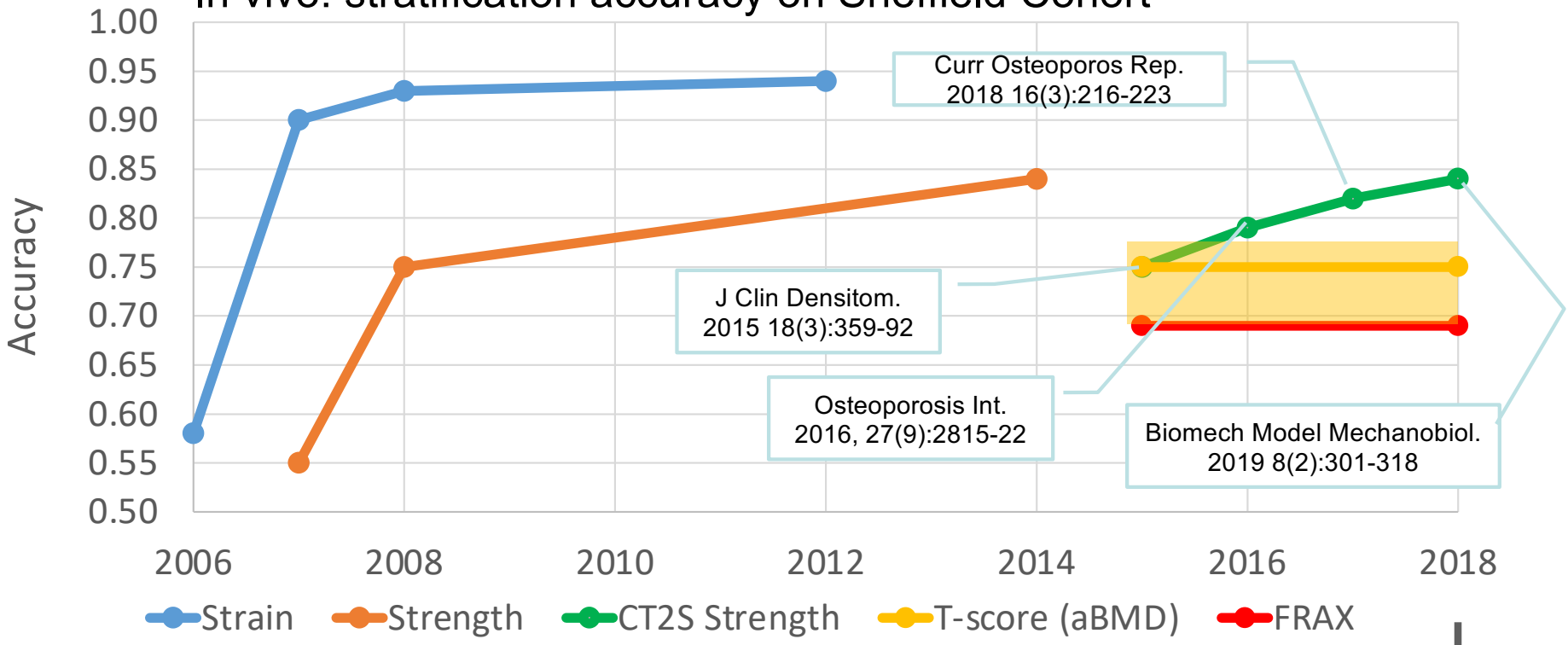
- 50 English women over 50 with acute hip fracture and no other diseases
- 50 women pair-matched for height, weight, and age with no fracture at the time of scan
- DXA, CT scan, FRAX risk, etc.

Yang L, Udall WJ, McCloskey EV, Eastell R. Osteoporos Int. 2014; 25:251-263

Is BBCT better than DXA?

Ex-vivo: SEE

In vivo: stratification accuracy on Sheffield Cohort



QCT-based models

Osteoporos Int
DOI 10.1007/s00198-016-3597-4

ORIGINAL ARTICLE

Patient-specific finite element estimated femur strength as a predictor of the risk of hip fracture: the effect of methodological determinants

M. Qasim[1,2] · G. Farinella[1,2] · J. Zhang[3] · X. Li[1,2] · L. Yang[2,4] · R. Eastell[2,4] · M. Viceconti[1,2]

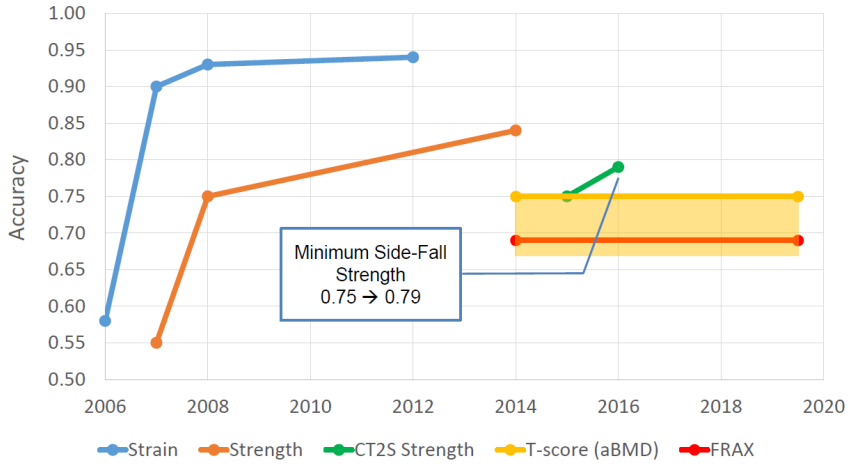


Fig. 2 Variation of load direction in the frontal and sagittal planes representing a sample of daily activities. Twelve different loading conditions were simulated

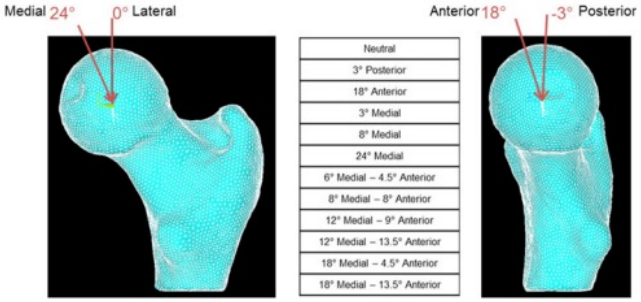
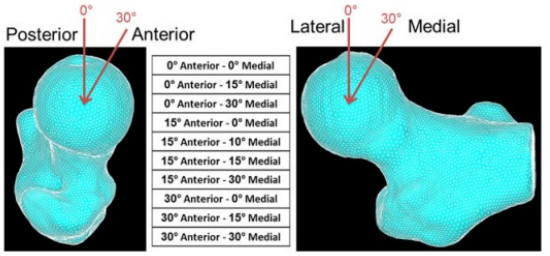


Fig. 3 Variation of load direction in the frontal and transverse planes representing a sample of side fall loading scenarios. Ten different loading conditions were simulated



QCT-based models

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Clinical Biomechanics

journal homepage: www.elsevier.com/locate/clinbiomech

The effect of boundary and loading conditions on patient classification using finite element predicted risk of fracture

Zainab Altai[a,b], Muhammad Qasim[c], Xinshan Li[a,b,*], Marco Viceconti[d,e]

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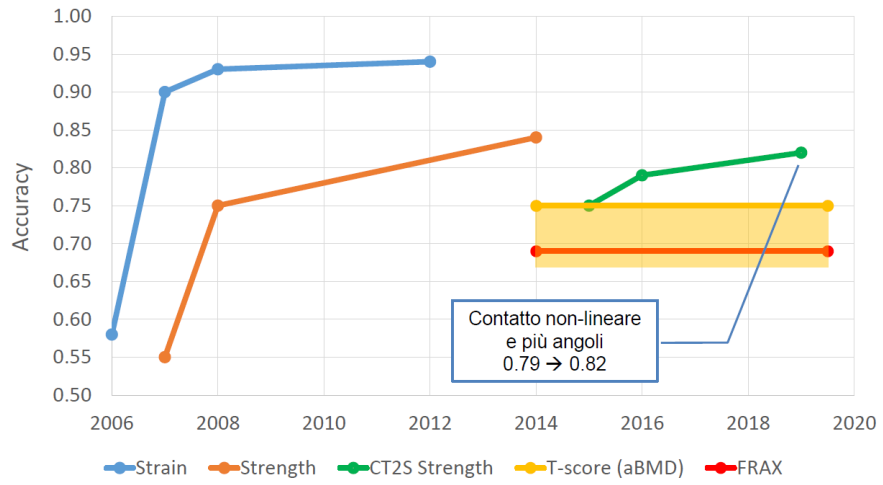
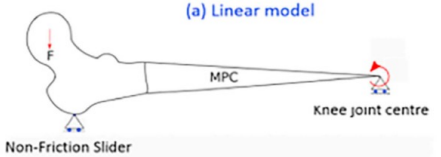
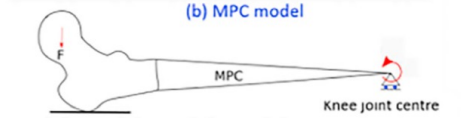
[b] INSIGNEO Institute for in silico Medicine, University of Sheffield, Sheffield, UK
[c] Faculty of Health, Education, Medicine and Social Care, Medical Technology Research Centre, Anglia Ruskin University, Chelmsford, UK
[d] Department of Industrial Engineering, Alma Mater Studiorum - University of Bologna, Italy
[e] Laboratorio di Tecnologia Medica, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy



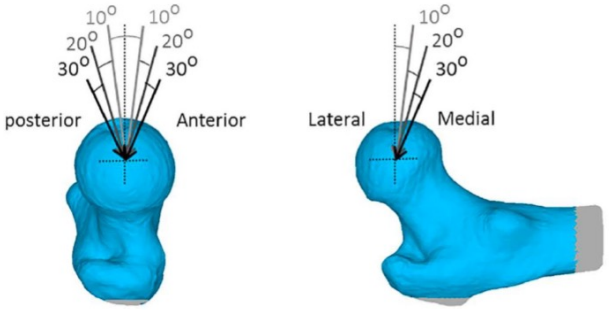
(a) Linear model



(b) MPC model



(c) Contact model



QCT-based models

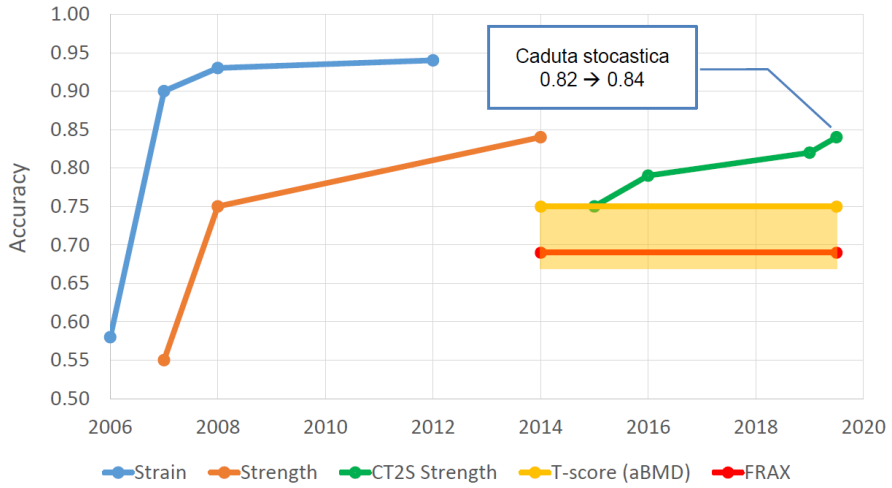
Biomechanics and Modeling in Mechanobiology (2019) 18:301–318
https://doi.org/10.1007/s10237-018-1081-0

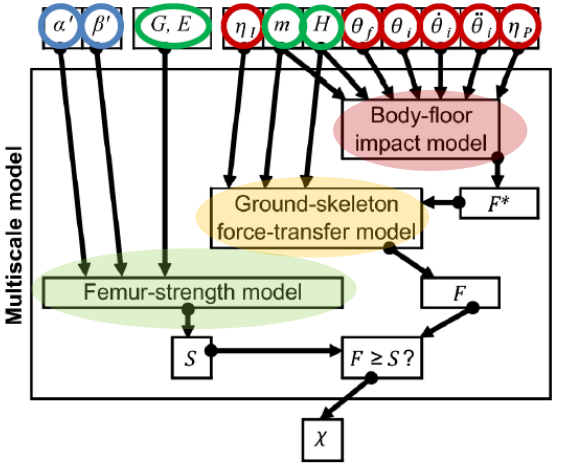
ORIGINAL PAPER

A multiscale model to predict current absolute risk of femoral fracture in a postmenopausal population

Pinaki Bhattacharya[1,2] · Zainab Altai[1,2] · Muhammad Qasim[1,2] · Marco Viceconti[1,2]

Received: 24 February 2018 / Accepted: 24 September 2018 / Published online: 1 October 2018





6 stochastic variables (impact force)

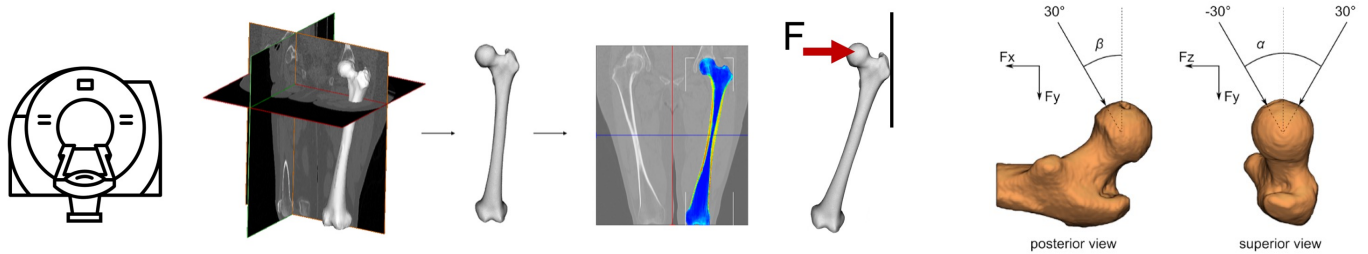
28 impact direction (load to failure)

Patient-specific height and weight

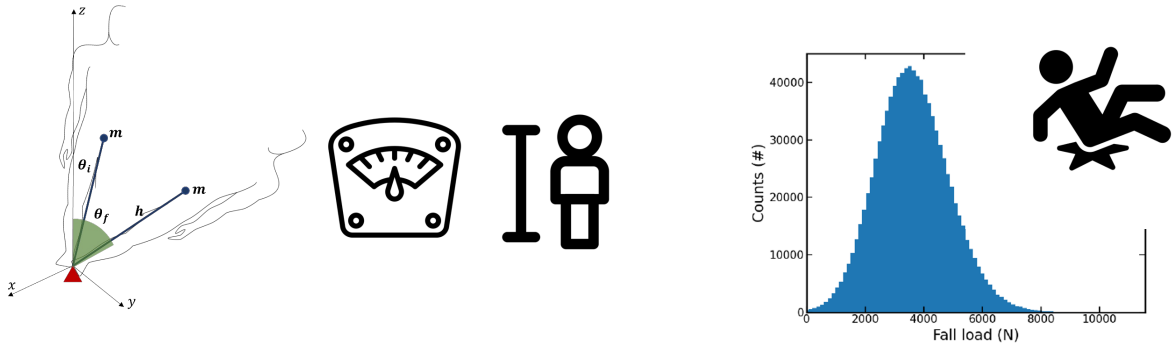
Patient's CT images

QCT-based models

QCT-based patient-specific **load to failure**



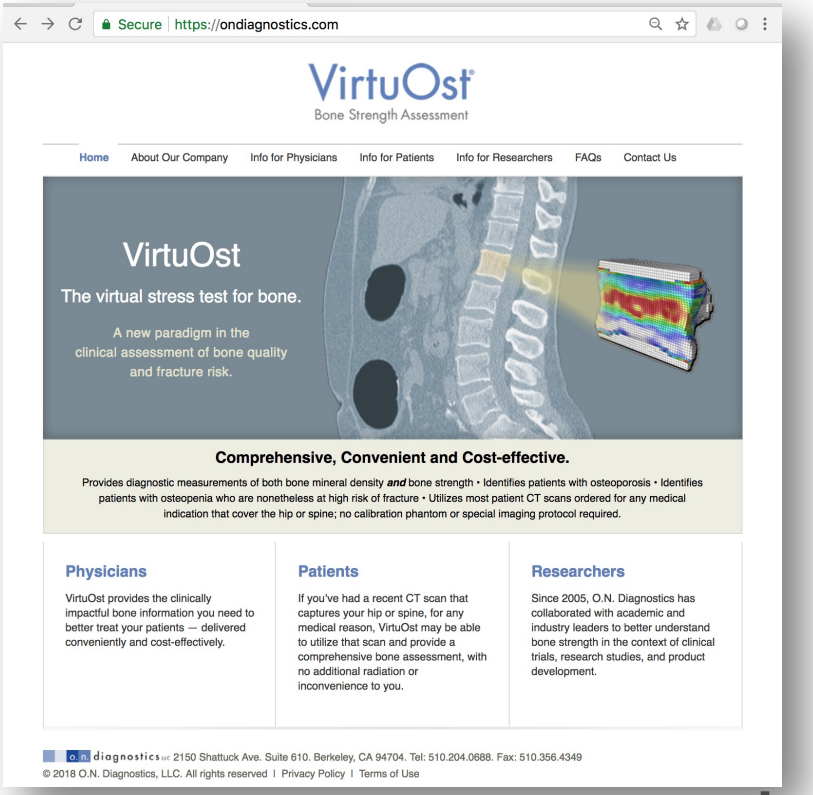
Falls simulation to predict **impact loads**



Fracture Risk (ARF0)

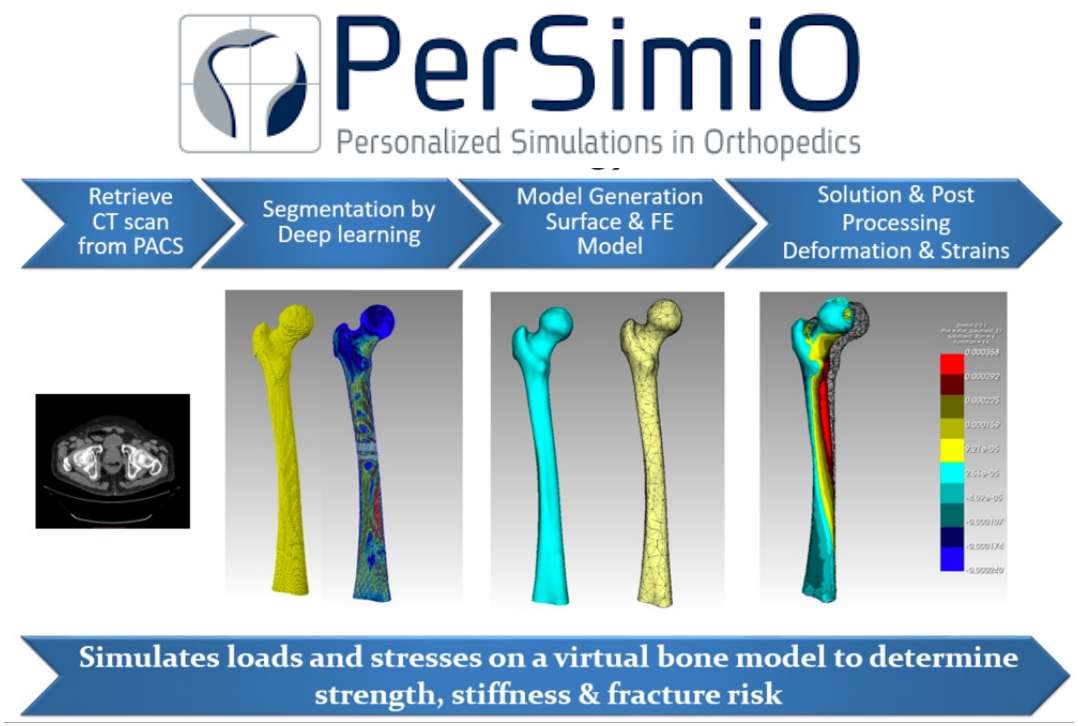
O.N. Diagnostic

- Secondary use of abdominal CT
- FDA- approved in 2018



PerSimiO

- Simfini-OSTEO
- CE marking in 2019

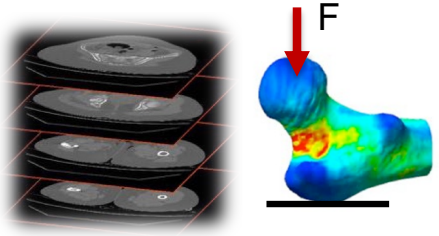


EMA qualification advice

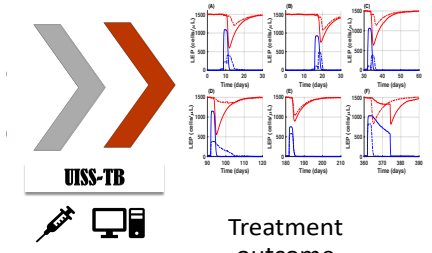
Qualification Advices

Accreditation

BBCT solution started regulatory process



UISS-TB solution started regulatory process



EMA Qualification advice on BBCT

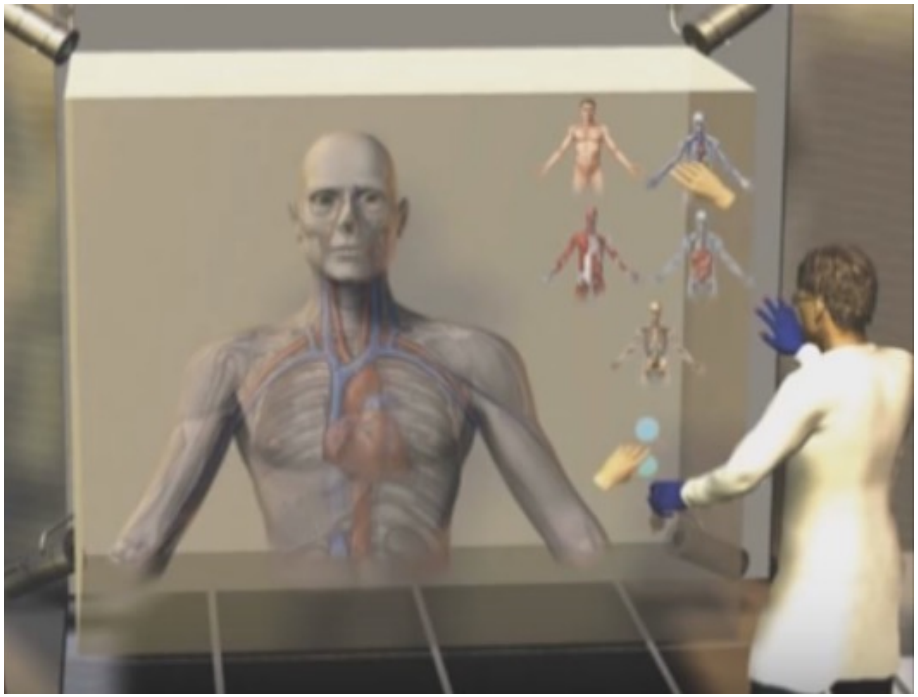
- Question the use of DXA as endpoint, claims osteoporosis drugs can only be shown effective by showing reduction of fractures
- Challenge a validation done on 100 cases, suggest much larger (1000?) cohort
- Suggest to compare with vBMD and epidemiology models (a la FRAX) in addition to aBMD
- This level of validation is clearly beyond the capacities of a research group
- There might not be a viable business model that would justify such study for a company

Digital Twins in healthcare

- Technical, regulatory, and cultural barriers are slowing down the adoption
- Low hanging fruits have been exploited, now only difficult staff is left
- Most problems require complex multiscale modelling
- So what?

At the beginning of this story …

- When the VPH was introduced many understood it as a model to predict everything in human pathophysiology
- This was clearly impossible, so we made an effort to dispel this perception
- But in doing so we lost sight of the holistic element in the original idea



Enter the Human Digital Twin

A model of everything fed with sparse data → **Impossible!!**

Data about everything that feed specialised models → **Possible?**

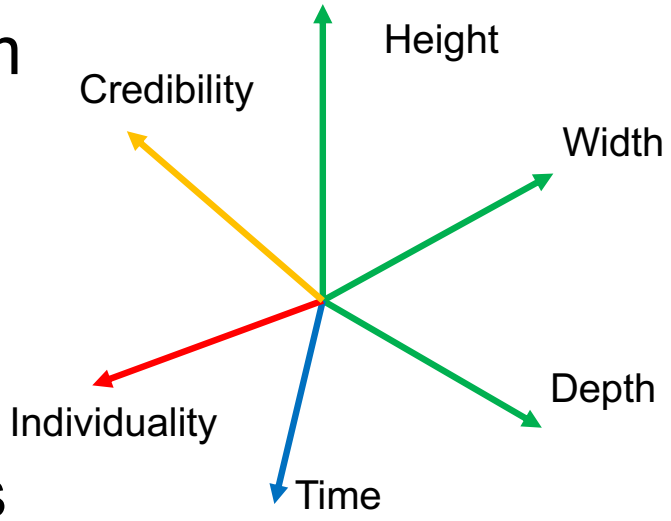
Most barriers are data-related

- Hard to develop good models without good data
- Validation is always limited by the availability of validation data collections
- Development and validation of multiscale models require multiscale data collections
- The development of data-driven (e.g. Deep Learning) predictors and surrogate models requires huge volume of data

Human Digital Twin

HDT – 6-dimensional reference frame

- Height, Width, and Depth range from the smallest to the largest human body
- Time ranges from Birth to Death
- Individuality ranges from Each Individual to Homo Sapiens Sapiens
- Credibility ranges from Speculative Predicted to Fully Certified Experimental



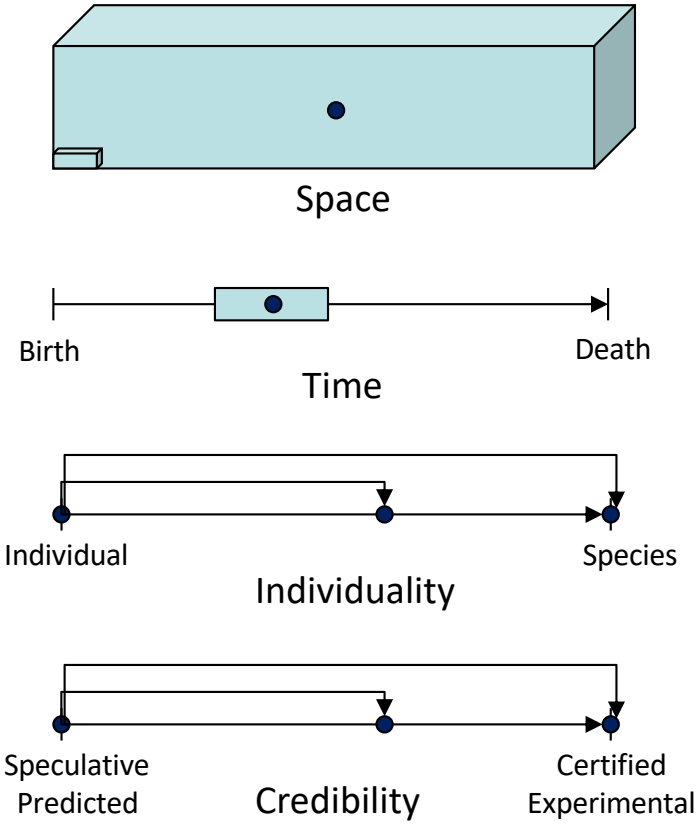
HDT – a recursive data storage

- The 6D reference frame has infinite resolution; in it we can recursively store datasets, each with its own grain and range:
  - A body scan with range 10^{0}m and grain 10^{-3}m
    - In it a femur with range 10^{-1}m and grain 10^{-4}m
      - In it an osteon with range 10^{-2}m and grain 10^{-5}m
        - » In it a lamellae with range 10^{-3}m and grain 10^{-6}m
          - » ….
- The HDT can be seen as a 6-dimensional, recursive lattice (hyper-scaffold), each cell containing n-instances of a specific type of data object

HDT – Recursion propagates

- Scale recursion is obvious for space and time dimensions
- But it propagates also to Individuality and Credibility dimensions:
  - You can cluster individuals and average their properties data at different space-time scale
  - Credibility might varies across space-time scales

For each new type of dataset



Origin (relative), Origin (template), Range and Grain

Origin (relative), Origin (template), Range and Grain

Species template, clustering and averaging operators

Credibility assessment rules, credibility enhancing operators

HDT – Models as automata

- A model is defined as the function $\hat{O} = f(I)$, a **relation between data cells** (between the *I* data cells (inputs) and $\hat{O}$ data cells (outputs, estimate of the true value *O*)
  - A model can be defined in single space-time scale, or link multiple ones (multiscale model)
  - Multiscale models can also be built as orchestrations of single scale models that use the HDT data hyper-scaffold to manage the data flow
  - A model can be defined in single Individuality level (subject-specific or population-based), or link multiple levels

6D Transformations

- Homogenisation and particularisation models transform physical properties from one space-time scale to another
- Statistical operators (average, variance) transform along the Individuality axis
- Proofs of the falsification / validation / certification transforms along the Credibility axis

HDT: Definition

- The Human Digital Twin is a 6-dimensional, recursive **data hyper-scaffold** where:
  - experimental data are stored, annotated, homogenised, and clustered
  - Predicted data are generated by models defined as relations between data cells
  - Access to data and models can be granted using Open Access, Collaborative, or Commercial licenses

What will you do with the HDT?

- Accumulate your data with other's to achieve statistically significant validation collections
- Form validation collections that provide an independent validation benchmark for competing models
- Simplify the development, validation and uncertainty quantification of single- and multi-scale models
- Simplify the transition from mechanistic to data-driven surrogate models
- Simplify the development of grey-box (partially data-driven partially mechanistic) models
- … and many other things we have not thought yet

Conclusions

- Digital Twins in healthcare are an industrial reality, but their development and validation is still too slow
- The creation of a Human Digital Twin infrastructure could accelerate the development and certification of new DT solutions

Thank You!

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