In Silico Trials: current status and future perspectives

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Too little information
Information overflow

5 concepts top!!
Population models
Subject-specific models
Seeding the EuroPhysiome: A Roadmap to the Virtual Physiological Human

“We zijn nog niet aan denieuwe patatjes”
“We are not at the new potatoes yet”

“Adparent rari nantes in gurgite vasto”
“Only the few swim in a rough sea”

http://www.vph-institute.org/documents.html
2007: PWC report

- PWC identifies 7 major trends:
  - The burden of chronic disease is soaring.
  - Healthcare policy-makers and payers are increasingly mandating what doctors can prescribe.
  - Pay-for-performance is on the rise.
  - The boundaries between different forms of healthcare are blurring.
  - The markets of the developing world, where demand for medicines is likely to grow most rapidly over the next 12 years, are highly varied.
  - Many governments are beginning to focus on prevention rather than treatment, although they are not yet investing very much in pre-emptive measures.
  - The regulators are becoming more risk-averse.
- Recommendation: “Greater use of new technologies to “virtualise” the research process and accelerate clinical development”
2011 green paper: Who are the End Users?

DIGITAL PATIENT
Subject-specific predictions for decision-support, diagnosis, treatment-planning, stratification
FOR THE DOCTOR

IN SILICO TRIALS
Virtual patient cohorts for 3R, surrogate outcomes, augmented clinical trials
FOR THE INDUSTRY

PERSONAL HEALTH FORECASTING
Subject-specific predictive models for mobile and digital health and wellness
FOR THE PATIENT - CITIZEN

http://www.vph-institute.org/documents.html
HeartFlow: FFRCT

Coronary CT Angiography

La Barbera M. Noninvasive Cardiac Imaging: Coronary CT Angiography
https://www.clinicalcorrelations.org/?p=679

HeartFlow FFRCT. Courtesy of HeartFlow Inc.
VASCOPS: first EC DP-SaMD

• Early screening of abdominal aortic aneurysm (AAA) patients
• Patient-specific risk assessment
• Automatic measuring device
• Translation of individual patients with respect to mean population data
• Certified as Class IIb medical device by PMG (Austria) (owned by Graz University of Technology)
FEOPS Heart-Guide

FEops HEARTguide™ obtained CE marking

Transcatheter Aortic Valve Implantation

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From CT to Bone Strength

On Diagnostics, USA

Insigneo CT2S Service, UK

Simfini Fracture Risk

PERISIMIO, Israel
Digital Twins

DIGITAL TWINS FOR BETTER HEALTH
Better diagnosis – Better care – Better life
Certification of predictive SaMD

- **Ab Initio** Molecular Dynamics
  - e.g. affinity binding
- **Mechanistic models**
  - Based on physics, chemistry, physiology
- **Grey-box models**
  - e.g. NARMAX, PBPK
- **AI Analytics**
- **Statistical models**
2016: Avicenna roadmap

“The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/intervention"

http://www.vph-institute.org/documents.html
Cost to Develop New Drug > $2.5b

Source: Tufts Center for the Study of Drug Development, USA - 2014
M&S in drug testing

• There is a robust experience around the use of M&S in drug testing, for very specific applications:
  – MD in drug design/ opt
  – Pharmaco-kinetics/ -dynamics
  – Physiology-based PK
Recommendations to regulators

16 July 2015

“the Committee urges FDA to engage with device and drug sponsors to explore greater use, where appropriate, of In Silico trials for advancing new devices and drug therapy applications”. Senate Fiscal Year 2016 FDA Appropriations Bill (S. 1800) & Report (S. Rept. 114-82)

10 March 2016

“advances in alternative testing require the creation of a regulatory framework […] including for example the recognition and evaluation of modelling and simulation technologies”. EU Parliament amendment to Regulation (EC) No 726/2004
FDA Guidance on M&S use

- **Context of use** of the CM&S study including a clear identification of the quantity(s) of interest (QOI) (e.g., to determine the maximum stress value(s) and location(s))

- **Scope of the analysis** (e.g., for a device that has multiple sizes and/or configurations, specify which sizes and/or configurations were modeled, and how the computational model relates to the intended patient population)

- **Type of analysis** (e.g., fluid dynamics and mass transport, solid mechanics, electromagnetics and optics, ultrasound, heat transfer)

- **Conduct Verification, Validation & Uncertainty Quantification**

- **Conclusions** with respect to the context of use
ASME Committee V&V-40

- Scope: Verification and validation in computational modeling of medical devices

- Charter of V&V40: Coordinate, promote, and foster the development of standards that provide procedures for assessing and quantifying the accuracy and credibility of computational models and simulations

Approved Nov 2018
AVOID CLINICAL TRIAL
ADVISA SR APPROVAL CRT-D MRI, 3T MRI

**In Vivo Model Validation**

- MRI
  - 70 kg pig
  - Instrumented leads
  - CT imaging
  - MRI Scans
  - Measured heating

- Modeling
  - 70 kg pig
  - Lead models
  - Lead path reconstruction
  - Simulated MRI scans
  - Simulated heating

Significant cost and time savings due to clinical trial avoidance leading to valuable incremental revenue gain and earlier patient access.

- Advisa SR approved with no clinical
- No clinical required for CRT-D MRI, 3T MRI, and future MRI programs

Credit: CRHF MRI
EMA Qualification process

- Novel Methodology validation plan
- Scientific advice (ITF)
- Interventional clinical trial
- Qualified Methodology
- Technical validation
- Briefing Book
- Qualification advice (SAWP)
- Observation al clinical trial
- Qualification Opinion (CHMP)
- Regulatory Plan
STriTuVaD

- Universal Immune System Simulator (UISS), U. of Catania
- UISS-TB to be used to reduce duration and cohort size of clinical trials of new therapeutic vaccines
Qualification of UISS-TB

Observed disease progression of $P_x$

Predicted disease progression of $P_x$

Validated patient-specific model of disease progression
Qualification of UISS-TB /2

\[ I_{Py} = [HLA, \text{Age}, \text{gender}, \ldots] \]

\[ t_0 \quad t_1 \quad t_2 \]

Observed disease progression of Py (treated)

Predicted disease progression of Py (treated)

Validated patient-specific model of treatment response
Simplest use: time extrapolation

- Physical Patients
- Virtual Patients

Validation

Prediction
Conclusions

• *In Silico* Medicine should be neutral with respect to the modelling method used (statistical, machine learning, grey-box, mechanistic)

• *Digital Patients* applications have a clear regulatory pathway and starting to appear in the hospitals

• *In Silico* Trials is a reality for medical devices in USA, but still to be demonstrated for drugs

• In Silico Medicine will become standard medical technologies such as imaging, with a florid industry behind

• Still, the growth of In Silico Medicine will be driven by our ability to develop reliable and accurate predictive models of physiology, disease, and therapeutic processes (Funding!)
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