



Avicenna Alliance Glossary

Terms for Computer Modelling and Simulation

Introductory Remark and Acknowledgments

There are occasional inconsistencies and differing interpretations in the use of certain in silico concepts within the literature, which may lead to misunderstandings. To enhance clarity, a group of academic and industry members of the Avicenna Alliance has developed a set of definitions for terms commonly used in the in silico domain. The definitions included in this glossary reflect a consensus among our members and aim to provide a shared understanding of the terminology used in our publications. We acknowledge that alternative definitions may exist and welcome feedback, as these definitions are expected to evolve over time.

This Glossary represents the fifth release, featuring an expanded list of terms, including an updated definition of Digital Evidence (i.e., In Silico Evidence). Additional concepts will continue to be introduced, and existing definitions may be refined in future updates. We therefore encourage the community to share comments or suggestions for improvement, supported by appropriate scientific justification, with Roberta Maggi, manager@avicenna-alliance.com.

Special thanks and recognition are extended to the following contributors, as well as many other Avicenna Alliance members, whose collective expertise has contributed to the development and continuous evolution of the Avicenna Glossary over the years.

While this fifth release builds upon the work carried out across previous editions, **we would like to express our particular appreciation to those who remained actively engaged in the ongoing review and enhancement of the glossary. Their continued support and dedication have been instrumental in ensuring that this resource reflects the latest developments and consensus within the *in silico* community:**

- Cécile Rousseau, Ph.D., Voisin Consulting Life Sciences
- Enrico Dall'Ara, University of Sheffield
- Marc Horner, Ph.D., Synopsys
- Roberta Maggi, Avicenna Alliance
- Thierry Marchal, Ansys, part of Synopsys
- Alexandre Serigado, Voisin Consulting Life Sciences
- Ani Amar, Consultant
- Claudio Capelli, University College London
- Daniele Tartarini, University of Sheffield
- Elaheh Elyasi, TwInsight
- Francesco Pappalardo, University of Catania, Co-founder of Mimesis
- Liesbet Geris, VPH Society
- Maria Cristina Jori, Mediolanum Cardio Research (MCR)
- Mathieu Rimaud, TwInsight
- Raphaëlle Lesage, Systems Pharmacology
- Shiny Martis B., Ph.D., Voisin Consulting Life Sciences
- Yoann Lafon, Université Gustave Eiffel.

Martha De Cunha Maluf-Burgman
Glossary Initiative Leader @ Avicenna Alliance
Director Regulatory Affairs - Digital Health,
Edwards Lifesciences

DEFINITIONS:

Absolute benefit

Difference between the rate or risk of event between the untreated / control individuals and the corresponding treated individuals in the same group or cohort. Instead of the event rate, it can also be the value of a marker.

Adequacy assessment

Process of evaluating the evidence in support of credibility of a computational model, for a given context of use, and making a determination on whether the evidence is sufficient.

Agent-Based models (ABM)

Computational representation of a physical reality that utilizes a large number of autonomous discrete particles (called Agents) that move in space and time, interact with each other and change their internal state according to a set of rules. ABMs are capable of re-creating macro-level phenomena by the actions and interactions of micro-level individual agents (emergence).

Example: “A multi-step and multi-scale bioinformatic protocol to investigate potential SARS-CoV-2 vaccine targets”, Briefings in Bioinformatics, Volume 23, Issue 1, January 2022, bbab403, <https://doi.org/10.1093/bib/bbab403>

Applicability

Relevance of the credibility assessment of the computational model (e.g. verification and validation activities, uncertainty quantification) for a given context of use. (Adapted from FDA, source “Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions - Draft Guidance for Industry and Food and Drug Administration Staff”, <https://www.fda.gov/media/154985/download>).

Assertion

Principal feature (e.g., Chemical or biological entities and their functional relation(s) between these entities) of a piece of knowledge (scientific extract, Figure, Table) that carries scientific information in the form of plain language that will be assembled into a Knowledge Model.

Assessment

Rigorous evaluation of the credibility evidence to confirm that the model is sufficiently accurate to support the decision.

Base model

Hypothetical, abstract representation of the object's properties, in particular, its behaviour, which is valid in all possible contexts, and describes all the object's facets. (H. Vangheluwe, McGill University, 2001).

Black-box model

It consists of a certain structure of which the parameters are determined by means of experimental results.

Known as data-driven models black box develops models based on process data, used for gaining insight into the overall (input-output) process behaviour.

The main properties of black-box models are the structure characteristics, which are: a) level of detail, b) degree of non-linearity, and c) the structural way in which dynamics are composed.

Reference: Based on Guidebook for successful development of process simulation projects, SimulateLive, and Avicenna Alliance paper: https://www.vph-institute.org/upload/ai-in-health-white-paper_6331c4e3c60cb.pdf
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8376137/>

Building Block

“A building block is a self-contained, interoperable, reusable and replaceable unit, encapsulating its internal structure and providing useful services or functionality to its environment through precisely defined interfaces.” (Verbraeck et al. 2002).

Reference: Design Guidelines for Simulation Building Blocks, Verbraeck and Valentin, <https://www.informs-sim.org/wsc08papers/111.pdf>

Calculation verification (i.e. solution verification)

The process of estimating the numerical error in the output of a computational model due to the use of numerical methods to solve the mathematical model (including the post-processing) specific to the context of use. It aims to estimate the magnitude of the numerical errors in the estimated solutions. (Based on M. Viceconti et. al.).

Calibration (Model) (i.e. tuning or fine-tuning)

The process in which a priori unknown and estimated parameters are refined through a numerical procedure in order to achieve a desired behavior of the model regarding given criteria.

Clinical outcome

Measurable change in patient’s health, function or quality of life at specific time point.

Clinical score

A standardized quantitative or qualitative indicator of the severity of a disease, or other variables for a particular patient, at a particular instant in time. The clinical score may be obtained on the basis of a series of clinical and/or biological and/or imaging and/or pathological factors.

Clinical submodel:

Part of the model that links the evolution of disease (components of disease model) to clinical outcome.

See also “Submodel”

Code verification

The process of ensuring the quality (including correctness, reproducibility and good standards practices) of the algorithm and its source code via minimization of weaknesses and errors, when translating the chosen mathematical model.

Comparator

Test data that are used for comparison with computational results as part of the validation, which may be data from bench testing or *in vitro*, *ex vivo*, *in silico*, and *in vivo* studies.

Compartment

Specific subsection or structure of a biological system in a computational model. The level of granularity depends on the Context of Use. Compartment may be also called “**part**” depending on the field of application.

Computational Fluid Dynamics (CFD) modelling

It is a branch of fluid mechanics that uses numerical analysis and data structures to analyse and solve problems that involve fluid flows and simulates their behaviour and thermomechanical dynamics properties.

A CFD model is a representation of the fluid dynamics in a specific application, which is solved using a numerical algorithm to obtain the flow velocity, the pressure and other engineering quantities of interest as a result.

Reference: AA definition

Computational model

A numerical representation of the mathematical model such that it can be executed on a computer.

Computational modelling

Numerical representation of the mathematical model performed by means of computational implementation in order to simulate and study complex systems. (Based on FDA: Frontiers in Medicine, September 2018, Volume 5, Article 241 by Tina Morrison (FDA) et. al.)

Computational modelling and simulation (CM&S) in healthcare

It is the use of mathematics, physics and computer science to create numerical representations of real-world (or conceptual) systems that can be used for example, to reduce, refine or replace experimental and clinical research).

Context of Use (CoU)

A statement that defines the specific role and scope of the computational model used to address the question of interest.

It should include a detailed statement of what will be modelled and how the outputs from the computational model will be used to answer or inform the question of interest. It is important to note that the CoU is distinct from the “indications for use” or “intended use” of a medical device, which are descriptions of how a device is intended to be used in clinical practice. [Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices V&V 40 – 2018. ASME, 2018. 60p. ISBN: 9780791872048.]

Credibility

Credibility is the trust, established through the collection of evidence, in the predictive capability of a computational model for a context of use. Trust can be established through the collection of evidence from credibility activities, which includes performing verification & validation (V&V) and then demonstrating the applicability of the V&V evidence to support the use of the computational model for the COU.

Credibility activities

Systematic, documented scientific activities (e.g., Computational Modelling and Simulations and bench testing) performed to establish and demonstrate that the digital evidence (i.e., in silico evidence) is sufficiently trustworthy and fit for purpose for the intended context of use.

Credibility goals

Predefined, decision-driven target(s) that specify the required level and scope for each credibility activity.

Decision consequence

The significance of an adverse outcome resulting from an incorrect decision concerning the question of interest, i.e., the severity of the adverse outcome if the decision based on the model is incorrect.

Descriptors

Descriptors are all the associated values (depending on research area), varying from one patient to another (e.g., that could be associated with model inputs or outputs).

Digital Evidence (i.e., in silico evidence)

Scientifically and clinically validated and documented evidence generated using computer-based models, simulations, or data-processing systems, intended to support regulatory, clinical, or safety decisions, and whose credibility is demonstrated through appropriate verification, validation, and uncertainty evaluation commensurate with its context of use. This definition excludes data generated by medical imaging devices, e.g., MRIs, CT scans.

Digital twin

A computational model of physical assets (or processes or systems) that learns and is updated from multiple sources, in real time or not, depending on the context of use. It acts as a bridge between the physical and virtual world, allowing analysis (e.g. simulations) that can help to anticipate problems and plan for the future.

Disease submodel:

Model of the (electro)physiology and/or pathophysiology and/or geometry of distinct sub-parts (cells, tissues, organs or processes) of biological system. It is connected to other submodels by its inputs and outputs.

See also “Submodel”.

Effect model law

The Effect Model Law states that a natural and systematic relationship exists between the frequency (or probability) of a clinical event occurring without treatment and the frequency (or probability) of the same event occurring with treatment. Effect Model Law is widely used concept in clinical pharmacology, biostatistics, and personalized medicine.

Empirical (data-based) models

Models built exclusively on statistical analysis of (real-world) observation data that describe relationships between variables without necessarily understanding the underlying processes driving those relationships.

Extrapolation model

It is the ‘extending information and conclusions available from studies based on initial correlation analysis of existing data.

For instance, extrapolation can be made on patient populations, the initial correlation analysis of the data from different patient cohorts or in related conditions or with related medicinal products, in order to make inferences for another subgroup of the population (target population), or condition or product.

Reference: Based on EMA/189724/2018. Reflection paper on the use of extrapolation in the development of medicines for paediatrics; and Annex 1 from Good Simulation Practices, VPH Institute, InSilico World and Avicenna Alliance).

Finite Element Analysis (FEA)

Finite element analysis is using FEM to simulate and predict the behaviour of any object under various physical conditions. (See FEM definition).

References: AA definition

Finite Element Methods

Finite Element Methods is a computational method that approximates the solution of differential equations describing a physical problem. These methods subdivide the geometry of the modelled object using a digital description of the geometry (e.g., CAD) into finite-sized elements of geometrically simple shapes. The collection of all these simple shapes constitutes the so-called finite-element mesh. Once the material properties of each component and the boundary conditions are provided, the object behaviour can be predicted by solving partial differential equations.

Finite Volume Method (FVM)

The finite volume method is a numerical method for solving differential equations based on conservation laws (e.g. heat and mass transfer). The numerical flux is conserved from one discretization cell to its neighbor. It may be used on arbitrary geometries, using structured or

unstructured meshes. The FVM is locally conservative because it is based on a balance approach: a local balance is written on each discretization cell (also called control volume)

The integral formulation of the fluxes over the boundary of the control volume is then obtained by the divergence formula.

REF: Robert Eymard, Thierry Gallouët, Raphaële Herbin. Finite Volume Methods. J. L. Lions; Philippe Ciarlet. Solution of Equation in (Part 3), Techniques of Scientific Computing (Part 3), 7, Elsevier, pp.713-1020, 2000, Handbook of Numerical Analysis, 9780444503503. 10.1016/S1570-8659(00)07005-8. hal-02100732v2

In silico

In silico means carried out in the computer (i.e., in the silica), which is analogous to *in vitro* (in the glass), *ex vivo* (outside the living organism), or *in vivo* (inside the living organism). References: Chiavaroli C, Rousseau CF, Voisin EM. *In Silico* Approach: From Computer To Patient? Advantages and Limits of Toxicology Prediction in the Current Regulatory Environment. Voisin Consulting Life Sciences 2017 White Paper.

***In silico* clinical trial (ISCT)**

Use of computational modelling and simulations to mimic the human experimentation required in the regulatory evaluation process of a medicinal (including medical devices) product or intervention, under well-defined conditions using verified and validated models. It requires the definition of virtual patients or virtual populations of patients.

Reference: “Use of disease models and virtual patients to run computer-simulated clinical trials” - Novartis definition

***In silico* evaluation**

Evaluation performed via computational modelling & simulation outside the traditional clinical settings; e.g. *in silico* evaluation can involve computational models to predict the behaviour of a molecule in a biological system, or to simulate the performance of a new material in various environmental conditions. This type of evaluation can be a cost-effective and time-efficient way to test and optimise new products, without the need for expensive and time-consuming physical experiments. These examples are not exhaustive.

***In silico* medicine**

In silico medicine refers to the use of individualized computational modelling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.

***In silico* method (ISM)**

Are procedures to conduct experiment, evaluation or analysis, using computer-based tools. *In silico methods* comprise utilisation of mechanistic and phenomenological models.

***In silico* testing**

In silico testing (or experiment or study) refers to the execution of an *in vitro* or *ex vivo* experiment in the computational environment (Ref: Viceconti, M., A. Henney, and E. Morley-Fletcher, *In silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. Research and Technological Development Roadmap. 2016, Avicenna Consortium: Brussels (Chapter I, page 11)).

***In silico* trials (IST)**

The use of computational modeling and simulation (CM&S) for testing medical interventions, including drugs and medical devices, in both preclinical and clinical contexts. ISTs aim to provide digital evidence under well-defined conditions, ideally described in standards, thus supporting drug/device development including for regulatory approval processes.

Reference: Vasey, B., Nagendran, M., Campbell, B. et al. Reporting guideline for the early-stage clinical evaluation of decision support systems driven by artificial intelligence: DECIDE-AI. Nat Med 28, 924–933 (2022). <https://doi.org/10.1038/s41591-022-01772-9>.

The three types of *in silico* evaluation methodologies considered here are:

- o *in silico* test (or experiment or study) refers to the execution of an in vitro or ex vivo experiment in the computational environment

(Ref: Viceconti, M., A. Henney, and E. Morley-Fletcher, *In silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. Research and Technological Development Roadmap. 2016, Avicenna Consortium: Brussels (Chapter I, page 11))

- o *in silico* medicine refers to the use of individualised computational modelling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.

- o *in silico* trial (see above definition on “*In silico* Trial”)

Reference: Viceconti, M., et al., *In silico* trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods, 2020.

Knowledge gap

A phenomenon whose mechanism is not fully understood nor described to-date by any scientific consensus or proof-supported hypothesis.

Knowledge model

The founding literature describing the knowledge upon which the Formal Model is implemented. It includes assertions, data, the associated knowledge gaps, a graphical representation, and a list of model components.

Mathematical model

“The mathematical equations, boundary conditions, initial conditions, and modelling data needed to describe a conceptual model” (ASME V&V 40-2018).

Measurable variable

The variable of the model that can be quantified.

Mechanistic model

Models that describe causal relationships of a system based on scientific laws, e.g. mass and energy balances, or other equations that describe the behavior of a system or specific phenomena, e.g., blood flow in the heart, orthopedic implant performance, and protein folding. This is in contrast to empirical (data-based) models.

Medical Device

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used alone or in combination in humans for one or more of the following specified medical purposes:

- 1) the diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of a disease or other condition;
- 2) the investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;
- 3) the delivery of information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations.

A medical device does not achieve its primary intended action through pharmacological, immunological, or metabolic means, or chemical action in or on the human body.

Medical device submodel or Treatment

Describes the disposition and the action of a health product on its target(s) within the organism. In some cases, this may be simply represented by a change of parameter in the pathophysiological or disease submodel. For drugs, it may include a PK-PD model predicting the amount of drug at the site of action as well as its effect.

See also “Submodel”

Mesh Refinement Analysis

Mesh refinement Analysis is the process of resolving the model with successively finer meshes, comparing the results between these different meshes, gaining accuracy to solve the defined model until numerical conversion is reached. This comparison can be done by analysing the fields at one or more points in the model or by evaluating the integral of a field over some domains or boundaries. The mesh strategy should be justified when used to support regulatory submissions.

Reference: Multiphysics Cyclopedia, Physics, PDEs, and Numerical Modelling (February 21, 2017)

Model

A representation of a system that we observe, try to understand, and/or create. It may imply a simplification of a real system. (See “Base model”).

Model Block Development

Is the process of composing a few building blocks in a more complex one. (See Building Block)

Model credibility

Refers to the trust in the predictive capability of the computational modelling and simulation for the COU. Trust can be established through the collection of verification and validation (V&V) evidence and by demonstrating the applicability of the V&V activities to support the use of the computational model for the COU.

Reference: ASME V&V 40-2018.

To demonstrate the credibility, it is recommended to identify the credibility factors (e.g., goodness of fit, input parameters) for which it will be defined prospective credibility goals, (e.g., low/medium/high equivalency).

Reference : FDA draft guidance - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions>.

Model Extrapolation

A prediction from a model that is either a projection, extension, or expansion of an estimated model (e.g., regression equation, or Bayesian hierarchical model) and it is beyond the range of the data set used to fit the model.

Reference: Based on “Bartley, Meridith L., et al. "Identifying and characterizing extrapolation in multivariate response data." PloS one 14.12 (2019): e0225715. doi: [10.1371/journal.pone.0225715](https://doi.org/10.1371/journal.pone.0225715)

Model falsification

Activity that challenges the validity of the model within its Context of Use. Once the model cannot be falsified after several independent attempts, the model can be considered valid within its Context of Use. Falsifiability is an important characteristic of the model that represents the capacity for the model to be proven wrong. See also “Validation”.

Model Geometry

Set of parameters describing shapes, sizes and volumes, for example, the shapes in geometric modelling are two or three dimensional (solid figures, computer-aided design and manufacturing, such as CAD/CAM), although many of its tools and principles can be applied to sets of any finite dimension.

Model influence

It is the contribution of the computational model to the decision, addressing the question of interest in relation to other available evidence.

Model Input

Data-knowledge describing parameters used in the model components, required for model execution. Input could be either a mathematical representation of a true physical or biological element.

References: Based on Riccardo Sacco, Giovanna Guidoboni, Aurelio Giancarlo Mauri, Chapter 3 - Elements of Computational Methods,
Editor(s): Riccardo Sacco, Giovanna Guidoboni, Aurelio Giancarlo Mauri, A Comprehensive Physically Based Approach to Modeling in Bioengineering and Life Sciences,
Academic Press, 2019, Pages 63-111, ISBN 9780128125182, <https://doi.org/10.1016/B978-0-12-812518-2.00011-1>.

Model Linearity

Is a property of a model that behaves linearly in a region of the input domain under study.

Model output

Describes the value (e.g., time series) of a model variable resulting from a simulation of the model provided with a set of model inputs.

Model Reference (Model Block)

A model reference is an instance of a model block.

Reference: Based on MathWorks' Model Reference Basics.

Model risk

Is the combination of the influence of the computational model (model influence) and the consequence of an adverse outcome resulting from an incorrect decision (decision consequence). Model influence is the contribution of the computational model relative to other contributing evidence in making a decision.

Decision consequence is the significance of an adverse outcome resulting from an incorrect decision. Consequences are typically considered in the context of potential harm to the patient. However, non-patient-related impacts may also be considered, such as delayed patient access to medical devices, impact on the clinician, financial loss, or increased time to market.

Model scope:

Extent of applicability of the model to biological/physiological/clinical systems, implied by the question of interest.

Model specifications

Qualitative or quantitative requirements (implicit or explicit) the model must meet.

Modelling

The process of representing a system with a specific computational tool.

Multiscale modelling (MSM)

Exercise of Computational models studying a system at multiple levels of time and/or biological organization, i.e., multiscale modelling. Models of how disease develops include molecular processes, cell to cell interactions, and how those changes affect tissues, organs, systems and bodies. Dimensional and temporal scales may be integrated.

Ordinary Differential Equation (ODE) model

It refers to *“a set of differential equations involving functions of only one independent variable and one or more of their derivatives with respect to that variable. ODEs are the most widespread formalism to model dynamical systems in science and engineering. In systems biology, many biological processes such as gene regulation and signal transduction can be modelled by reaction-rate equations expressing the rate of production of one species (e.g., protein, mRNA, metabolite, or small molecules) as a function of the concentration of other species in the system. ODE models provide a general framework to model such processes as continuous dynamic systems”*.

Reference: Ordinary Differential Equation (ODE), Model Encyclopedia of Systems Biology, 2013, ISBN : 978-1-4419-9862-0, Rui-Sheng Wang.

Parameter

A quantitative entity within a Formal Model whose value is set to remain constant in a particular given context. Its value might be derived from a piece of knowledge or adjusted during the Formal Model calibration phase.

Partial Differential Equation (PDE) model

“Sets of equations describing the evolution of a physical quantity, not only with time, but also according to a structure variable such as space”. PDE models “may be used for the physiological modelling of the evolution of a biological substance (e.g., a drug in an organism) submitted to changes, rather than ODE models (q.v.) when some physical or physiological knowledge of the medium containing it is available. Then derivatives are partial, meaning that they are calculated not only with respect to time but also with respect to a structure variable relevant to the representation of the medium”.

Reference: Based on Clairambault, J. (2013). Partial Differential Equation (PDE), Models. In: Dubitzky, W., Wolkenhauer, O., Cho, KH., Yokota, H. (eds) Encyclopedia of Systems Biology. Springer, New York, NY. https://doi.org/10.1007/978-1-4419-9863-7_694

Patient descriptor unknown

A modelling state in which one or more patient-specific attributes required to characterise an individual or subgroup are unavailable, unobserved, unmeasurable, or not credibly inferable, and are therefore explicitly treated as unknown within the computational model rather than assumed, fixed, or imputed without justification.

Personal Digital Avatar (PDA)

Digital twin of a specific human connected with its physical counterpart (physical twin) to regularly collect data about his/her evolution and predict likely evolution of his/her health.

Pharmacokinetic model

A simple and usually phenomenological mathematical model used for predicting the active concentration of a bioactive molecule at the site of action.

Physiologically Based Kinetic (PBK) model (Drug-chemicals)

Terminology used in OECD guidance where PBK models are used for chemical risk assessment as an alternative to animal testing. PBK models are the same as PBPK models; this is a more generic term that targets not only drug development, but also the safety assessment of chemical products.

References: Annex 1 from Good Simulation Practices, VPH Institute, InSilico World and Avicenna Alliance); and 'Physiologically Based Kinetic (PBK) models for regulatory purposes. Adopted April 2021. [Guidance document on the characterisation, validation and reporting of Physiologically Based Kinetic \(PBK\) models for regulatory purposes](#)

Physiologically Based Pharmacokinetics (PBPK) model

PBPK is defined as a mathematical model that simulates the concentration of a drug over time in tissue(s) and blood, by taking into account the rate of the drug's absorption into the body, distribution in tissues, metabolism and excretion (ADME) on the basis of interplay between physiological, physicochemical and biochemical determinants.

PBPK models integrate drug (substance) AND system (physiology) information into a mathematical modelling framework.

Reference: Based on EMA and FDA

Population pharmacokinetics (Pop-PK)

Pop-PK is *"the study of variability in drug concentrations between individuals (healthy volunteers or patients). It comprises the assessment of variability within the population, associated with patient characteristics such as age, renal function, or disease state."*

Reference: EMA, https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf

Prognostic model

Statistical or non-statistical mathematical model that predicts the probability of occurrence of a clinical event/outcome over time at the patient level as a function of the initial state of the patient (e.g., clinical, biological, physiological).

Quantitative structure-activity relationship (QSAR) models

Structure-activity relationship (SAR) and quantitative structure-activity relationship (QSAR) models - collectively referred to as (Q)SARs - are mathematical models that can be used to predict the physicochemical, biological and environmental fate properties of compounds from the knowledge of their chemical structure.

There are two types of QSAR models, classification or regression models. In drug discovery they are used to identify molecular structures with low non-specific activity and good inhibitory effects of specific targets; they are also used to estimate the octanol-water partition coefficient (logP), important information to evaluate how a substance behaves with respect to factors like bioavailability (drug likeness).

QSAR regression models relate a set of "predictor" variables (X) to the response (potency) variable (Y), while classification QSAR models relate the predictor variables to a categorical value of the response variable.

References: Annex 1 from Good Simulation Practices, VPH Institute, InSilico World and Avicenna Alliance).

[QSAR models - ECHA](#)

Question of interest

Describes the specific question, decision or concern that is being addressed (at least in part) based on the results of a computational model.

Real-world data

Is the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, e.g. electronic health records, claims and billing activities, and product and disease registries.

Real-world evidence

Is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Reference patient(s)

Real or Virtual patient(s) associated with reference scenario(s), expected behavior(s) and current behavior(s), intended to represent a class of patients within the population of interest exhibiting a similar qualitative behavior.

Responders

Subjects from a treated arm of a trial for whom the change in clinical endpoint value is above a predefined threshold, called response threshold.

Response threshold

Pre-defined value relative to the change in clinical endpoint from its baseline measured value, used to discriminate between "responders" and "non-responders" in a treated population.

Risk analysis

Analysis based on a combination of a model influence and decision consequence.

Sand box

A controlled environment to develop, validate or test innovative healthcare products. (Ref.: European Commission definition).

Scorings

Scorings are quantitative evaluations of closeness of an obtained behaviour to an expected behaviour of the model for a given set of input parameters. It is used during model calibration.

Sensitivity

Measure of the magnitude of influence of a given parameter, assumption, or variable on the model output/s. High sensitivity to a particular variable means a small change in that variable could lead to a substantial change in model output.

Simulation

Is the act of executing the model [for a specific set of input parameters].

Strength of evidence:

Defines the confidence that can be put on the reliability of an assertion used in the model (or any evidence or knowledge).

Stress/strain Analysis

Stress/strain analysis is usually performed to determine the stresses and strains in materials and structures subjected to variations of their environment.

In continuum mechanics, stress is a physical quantity that expresses the internal forces that neighbouring particles of a continuous material exert on each other, while strain is the measure of the deformation of the material.

Reference: Based on “Characterization of Cardiovascular Implantable Devices, Ming H. Wu, Hengchu Cao, in Characterization of Biomaterials, 2013”, pages 355-417.

Submodel

A model may be divided into submodels during the model development process.

Submodels can be of the following types:

- **Disease submodel:** Model of the (electro)physiology and/or pathophysiology and/or geometry of distinct sub-parts (cells, tissues, organs or processes) of biological system. It is connected to other submodels by its inputs and outputs.
- **Clinical submodel:** Part of the model that links the evolution of disease (components of disease model) to clinical outcome.
- **Treatment or medical device submodel:** Describes the disposition and the action of a health product on its target(s) within the organism. In some cases, this may be simply represented by a change of parameter in the pathophysiological or disease submodel. For drugs, it may include a PK-PD model predicting the amount of drug at the site of action as well as its effect.

System

A well-defined object or group of objects (e.g., organs) in the real world that are joined together in some regular interaction or interdependence toward the accomplishment of some purpose, under specific conditions, only considering specific aspects of its/their structure and behaviour. (Reference: Based on H. Vangheluwe, McGill University, 2001; & A. Juan Perez, UOC, ISBN: 978-84-692-9597-7)

A system can be continuous or discrete depending on the time point under consideration.

Treatment or medical device submodel

Describes the disposition and the action of a health product on its target(s) within the organism. In some cases, this may be simply represented by a change of parameter in the pathophysiological or disease submodel. For drugs, it may include a PK-PD model predicting the amount of drug at the site of action as well as its effect.

See also “Submodel”

Uncertainty

Potential deficiencies in any phase or activity of modelling, computation, or experimentation process that is due to inherent stochasticity (aka aleatoric uncertainty), lack of knowledge or unreliable knowledge (aka epistemic uncertainty).

Reference: ASME V&V 40-2018

Uncertainty Quantification (UQ):

Activity to determine how the uncertainty in the model inputs (e.g., parameters, initial conditions) propagates into uncertainty in the model outputs; it is the process of identifying, characterising, and quantifying those factors that could affect the accuracy of computational results (based on FDA definitions in several guidances).

“The three sources of computational model uncertainty are uncertainties due to modelling assumptions and approximations, uncertainties resulting from the numerical solution of the governing equations, and uncertainties in the model input parameters.” (See “uncertainty”)

Reference: M. Viceconti et al.

Validation

The process of determining the suitability of a model by challenging it with independent test data and comparing the results against prespecified criteria. For quantitative models, validation involves confirming the calibration model’s performance with an independent data set. For instance, for target

identification libraries in drug discovery, validation involves analyzing samples (a.k.a. challenge samples) not represented in the library to demonstrate the discriminative ability of the library model.

Variability (Patient related)

Inter-individual differences between patients due to differences in diet, genetics or immune status or intra-individual differences in the same subject over time due to diurnal cycles and other rhythms, biological repair mechanisms, dietary variables, ageing, changes in environment, etc.

Reference: Inspired by “*Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility*”, Flora T. Musuamba et al., <https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.12669>.

Variables

Quantitative entity within a model, whose value depends on parameters/data on other variables and is expected to vary along the course of simulation.

Verification

The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modelling and simulation.

Verification (Calculation)

Calculation verification ensures the accurate reproducibility of the mathematical solutions of the model equations. It mainly aims at evaluating the approximation errors and ensuring the correctness of solving the equations, i.e., the quantification of the error caused by the approximated solution of the mathematical model, $vf(I)$.

Reference: Based on ASME V&V 40-2018 and M. Viceconti et al.

Verification (Code)

Code verification is essentially a quality assurance practice for the software we use to solve the model, and a stability check for the numerical algorithms it implements. Software quality assurance is done with methods typical of software engineering, such as regression tests, or unit tests. Numerical solvers implementations are tested to check their stability, their rates of convergence, their computational efficiency, etc. Commercial codes tend to have their own extensive code verification.

Reference: M. Viceconti, M. A. Juárez, C. Curreli, M. Pennisi, G. Russo and F. Pappalardo, "Credibility of *In Silico* Trial Technologies—A Theoretical Framing," in *IEEE Journal of Biomedical and Health Informatics*, vol. 24, no. 1, pp. 4-13, Jan. 2020, [doi: 10.1109/JBHI.2019.2949888](https://doi.org/10.1109/JBHI.2019.2949888).

Verification (Model)

Model verification corresponds to the activity demonstrating the capability of solving the mathematical model correctly. It is usually separated into “code verification” and “calculation verification”. “*The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modelling and simulation*”.

Reference: Based on ASME V&V 40 - 2018) See “Code Verification” and “Calculation verification”.

Virtual cohorts

A library of multiple parameters (e.g., geometries) sets that represent a defined population under study for the context of use and the clinical intended population. It could be either statistical representation of the clinical intended population (e.g., epidemiology) or a subject-specific representation of patients. It may be used to support the development, and evaluation (i.e., the testing, the safety and/or efficacy) of new drugs or new medical devices."

Reference: Based on C. Miller et al, *In silico* trials for treatment of acute ischemic stroke: Design and implementation, <https://doi.org/10.1016/j.combiomed.2021.104802>; and F. Pappalardo, M.

Viceconti et al, *In silico* clinical trials: concepts and early adoptions, Briefings in Bioinformatics, Volume 20, Issue 5, <https://doi.org/10.1016/j.combiomed.2021.104802>.

Virtual Animal Twin (VAT) (for Animal testing & Veterinary)

Similar to Virtual Human Twin, the Virtual Animal Twin (VAT) (also known as Digital Animal Twin) is a multi-scale, multi-time, and multi-discipline digital representation of an animal, its health or disease state to provide animal-specific predictions. VAT's can include different levels of anatomy (cells, tissues, organs, or organ system) built using data-driven and knowledge-driven model, which are designed to mimic and predict the behaviour of their physical, physiological and pathological counterparts. VAT are used to complement or replace animal testing, and for animal care.

Virtual human twin (VHT)

Virtual Human Twin (VHT) (also known as Digital Human Twin) is a multi-scale, multi-time, and multi-discipline digital representation of a human, its health or disease state to provide patient-specific predictions. VHT's can include different levels of anatomy (cells, tissues, organs, or organ system) built using data-driven and knowledge-driven model, which are designed to mimic and predict the behaviour of their physical, physiological and pathological counterparts.

Virtual patient

A virtual patient can be considered as a computational model and simulation that represents the peculiar characteristics of one human subject (e.g., anatomy, (patho) physiology and/or lifestyle) and his/her interaction with the medicinal product of interest; and predicts (as opposed to measuring experimentally) quantities of interest necessary to support decision-making within a specific context of use.

Virtual patient can result from statistical process, for instance by using methodological heterogeneity assessments." (Reference: reference: Kononowicz AA, Woodham L, Georg C, Edelbring S, Stathakarou N, Davies D, Masiello I, Saxena N, Tudor Car L, Car J, Zary N. Virtual patient simulations for health professional education. Cochrane Database of Systematic Reviews 2016, Issue 5. Art. No.: CD012194. DOI: 10.1002/14651858.CD012194.)

Virtual population

Subset of plausible population generated based on the variability applied on subject descriptors.

Reference: "*Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models*", RJ Allen et al. 10.1002/psp4.12063.

Virtual population generation

Virtual patients are generated by drawing randomly a value for each parameter of the model from parameter distributions derived from available databases and literature or determined during the calibration process, in order to reproduce the characteristics of the population of interest.

The generation of a Virtual Population requires a list containing the disease model variables and parameters that vary within a population, as well as a thorough characterisation of these variables and parameters (mean values, type of distribution, parameters of distribution, multivariate distribution also called joint distribution).

Workflow (scientific)

"Typically, scientific workflow tasks are computational steps for scientific simulations or data analysis steps. Common elements or stages in scientific workflows are acquisition, integration, reduction, visualisation, and publication (e.g., in a shared database) of scientific data. The tasks of a scientific workflow are organised (at design time) and orchestrated (at runtime) according to dataflow and possibly other dependencies as specified by the workflow designer. Workflows can be designed visually, e.g., using block diagrams, or textually using a domain-specific language."

Reference:

Ludäscher, B., Bowers, S., McPhillips, T. (2009). Scientific Workflows. In: LIU, L., ÖZSU, M.T. (eds) Encyclopedia of Database Systems. Springer, Boston, MA. https://doi.org/10.1007/978-0-387-39940-9_1471