Avicenna Alliance Glossary
Terms for Computer Modelling and Simulation

Introductory Remark and Acknowledgments

*There are occasional confusions and diverging opinions possibly leading to misunderstanding in the use of some in silico concepts in the literature. To clarify **our** message, a team of academic and industry members of the Avicenna Alliance is proposing a definition of words regularly used in the "in silico" literature. The definitions in this glossary, results of a consensus within our members, clarify the meaning of the terms we are using in our publications. We understand that different definitions may exist and we welcome any comment as these definitions may evolve.*

***This Glossary is a third release with an extended list of definitions**; more concepts will be defined and existing definitions may be adjusted in future updates/releases of this document. Therefore, comments and inputs are welcome to enrich this glossary. You are encouraged to share your comments or suggestions for modification with Roberta Maggi, manager@avicenna-alliance.com.*

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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.

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 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
Computational modelling and simulation (CM&S) makes use of programming languages, numerical methods, high-performance computing, to create numerical representations of first-principles equations, to reduce, refine or even replace experimental and clinical research.
(Reference: National Institute of Biomedical Imaging and Bioengineering (NIBIB). Computational Modeling. 2020 [cited 2020 12 Nov 2020]; Available from: https://www.nibib.nih.gov/science-education/science-topics/computational-modeling)

Context of Use (CoU)
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
Represents the belief in the predictive capability of the computational model for the context of use (COU) applying engineering judgement based on the available evidence. (Reference: ASME V&V 40 - 2018). See "Model credibility".

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)
Results of computational modelling and simulation submitted as part of a (regulatory) evaluation process provided in a prescribed format, that encompass *in silico* trials and *in silico* tests.

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".

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, Raphaèle 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., 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* trials (IST)**
Use of computational modelling and simulation (CM&S) for testing treatments (drugs and/or medical devices) to mimic both bench testing (in vitro, ex vivo) and animal / human experimentation (in vivo) with the goal of providing digital evidence for regulatory evaluation process, under well-defined conditions, ideally described in standard. Also known as *in silico* experiments.

The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product, medical device, or medical intervention - from a published article https://doi.org/10.1177/0954411917702931.

***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" - Novadiscovery 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.
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.

***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.

The three types of *in silico* evaluation methodologies considered here are:
○ *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))
○ *in silico* medicine refers to the use of individualised computational modelling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.
○ *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 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
Model aimed at describing causal relationships (i.e., carried by knowledge) based on scientific laws, typically simplified in terms of cause-effect actions, as opposed to a correlational, data driven model.

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

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
Model risk is the possibility that the use of a *in silico* method leads to a decision that results in patient harm and/or other undesirable outcomes. It reflects the risk the decision-maker incurs when using a computational model to support a decision.

References: ASME V&V 40 - 2018, Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices.
And,
Horner M, Reiterer M, Rousseau C.F. Ensuring the Quality of *in silico* Evidence: Application to Medical Devices. Avicenna Alliance 2021, Position Paper. http://avicenna-alliance.com/publications.html

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.

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

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 Pharmaco-Kinetics (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
It describes the specific question, decision or concern that is being addressed (at least in part) based on the results of a computational model. It is "*the calculated or measured result from a computational model or comparator, respectively*" (ASME V&V 40-2018).

Reference: Horner M, Reiterer M, Rousseau C.F. Ensuring the Quality of *in silico* Evidence: Application to Medical Devices. Avicenna Alliance 2021, Position Paper. http://avicenna-alliance.com/publications.html

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

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.

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
Activity demonstrating that the underlying mathematical model correctly represents the reality of interest within the Context of Use. "The process of determining the degree to which a model or a simulation is an accurate representation of the real world". See also "Model Falsification"
Reference: ASME V&V 40-2018

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 (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 all.

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.

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.compbiomed.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.compbiomed.2021.104802.

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.

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