Mechanistic Models, Model Mechanisms, and Computational Models of Explanation for Biological Phenomena

C. Anthony Hunt[1], Ahmet Erdemir[2], Feilim MacGabhann[3], William W. Lytton[4], Edward A. Sander[5], Mark K. Transtrum[6], and Lealem Mulugeta[7]

[1] Bioengineering and Therapeutic Sciences, University of California, San Francisco, CA
[2] Biomedical Engineering and Computational Biomodeling Core, Lerner Research Institute, Cleveland Clinic, OH
[3] Biomedical Engineering and Institute for Computational Medicine Johns Hopkins University, Baltimore, MD
[4] Departments of Neurology, Physiology & Pharmacology, SUNY Downstate Medical Center, Brooklyn, NY
[5] Biomedical Engineering, University of Iowa, Iowa City, IA
[6] Physics and Astronomy, Brigham Young University, Provo, UT
[7] *InSilico* Labs LLC , Houston, TX

Problems

- The space of biological multiscale models is huge, complicated, and inaccessible to unaided thought.
- Important differences between published models are often difficult to identify easily, which can impact actual as well as perceived credibility.
- We lack informative descriptors to aid distinguishing among major model types.
- Ambiguous terminology limits credibility and acceptance of simulation evidence.

Objectives

- Offer alternatives to ambiguous terminology, such as "mechanistic model," and encourage their use.
- Suggest informative semantic descriptors that distinguish among major model types
- Provide a foundation for ontology to identify appropriate roles of terms such as "mechanistic" and "mechanism" for biology simulation research.
- Strengthen the credibility of simulation research in biology by improving semantic and methodological clarity.

Approach

- Mechanistic models of biological phenomena (with or without computation) are explanatory of underlying biology and phenomenological models are not [1].
- The context for this work: published reports that seek a mechanism-based explanation of a biological phenomenon.
- Adopt a definition for the word "mechanism" and use it to cluster published models of explanation into distinguishable types; link the definition of mechanism to "multiscaleness."
- Acknowledge and use workflows in determining types of models of explanation.

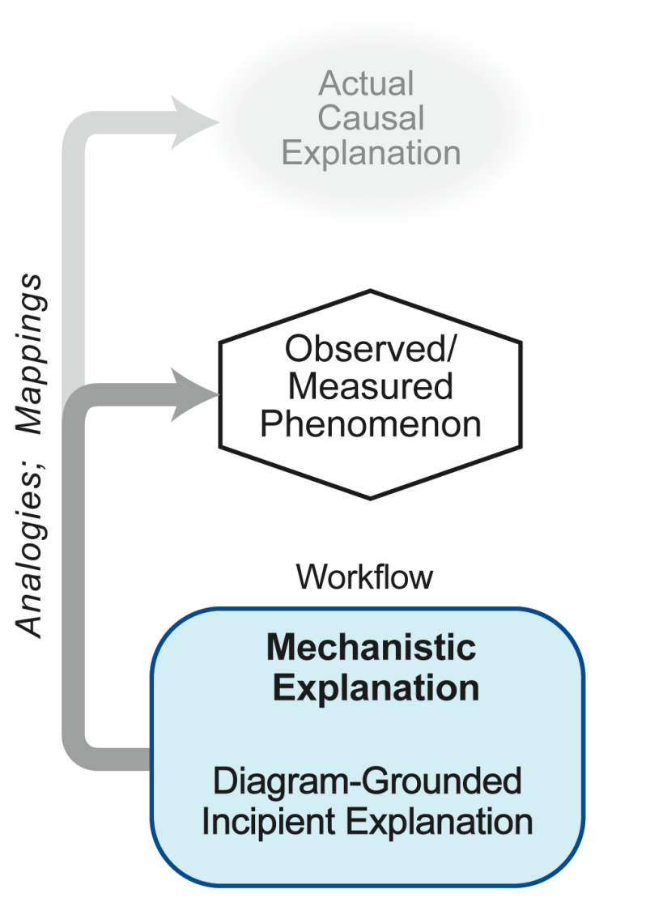
Mechanism n : 1) a structure or system (e.g., biological, mechanical, chemical, electrical, etc.) performing a function in virtue of its component parts, component operations, and their organization [2], where the function is responsible for the phenomenon to be explained;
2) entities and activities organized such that they exhibit the phenomenon to be explained [3];
3) entities and activities organized in such a way that they are responsible for the phenomenon to be explained [4]

Specification 1: in addition to a phenomenon, an explanatory mechanism exhibits four essential features [5]: 1) Components (e.g., entities and activities, modules); 2) Spatial arrangement of components; 3) Temporal aspects of components; and 4) Contextual locations (e.g., location within a hierarchy).

Specification 2: within biological mechanisms, inner layer phenomena are the entities and activities responsible for an outer layer phenomenon.

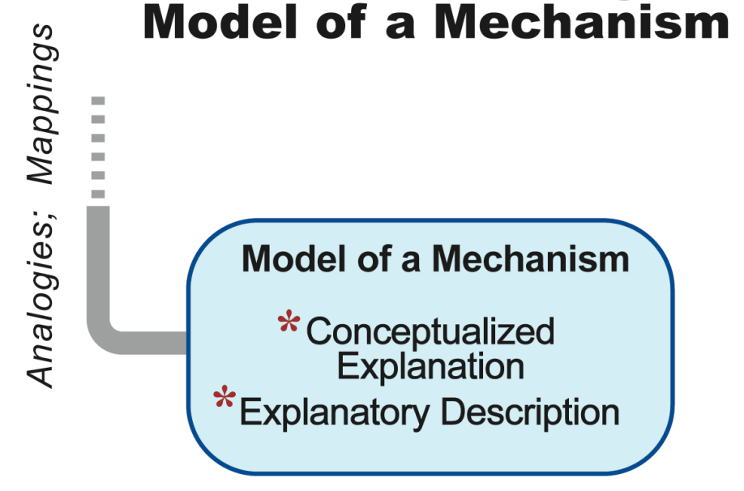
Categories of Models of Explanation

I. Mechanistic Explanation

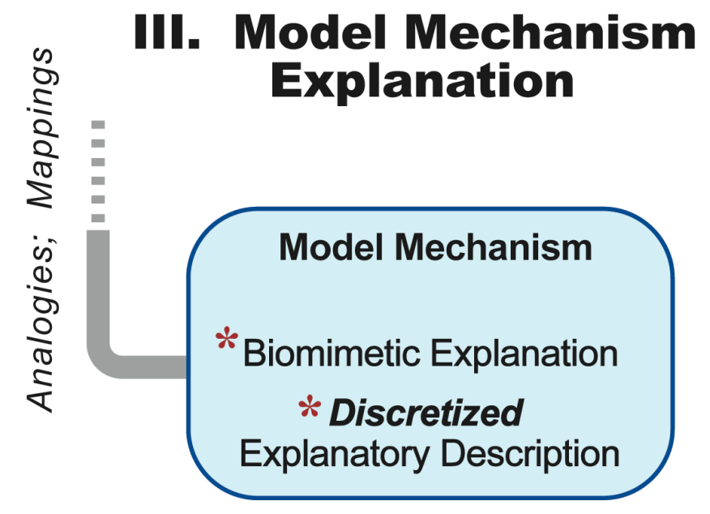


* Significant change from previous model of explanation

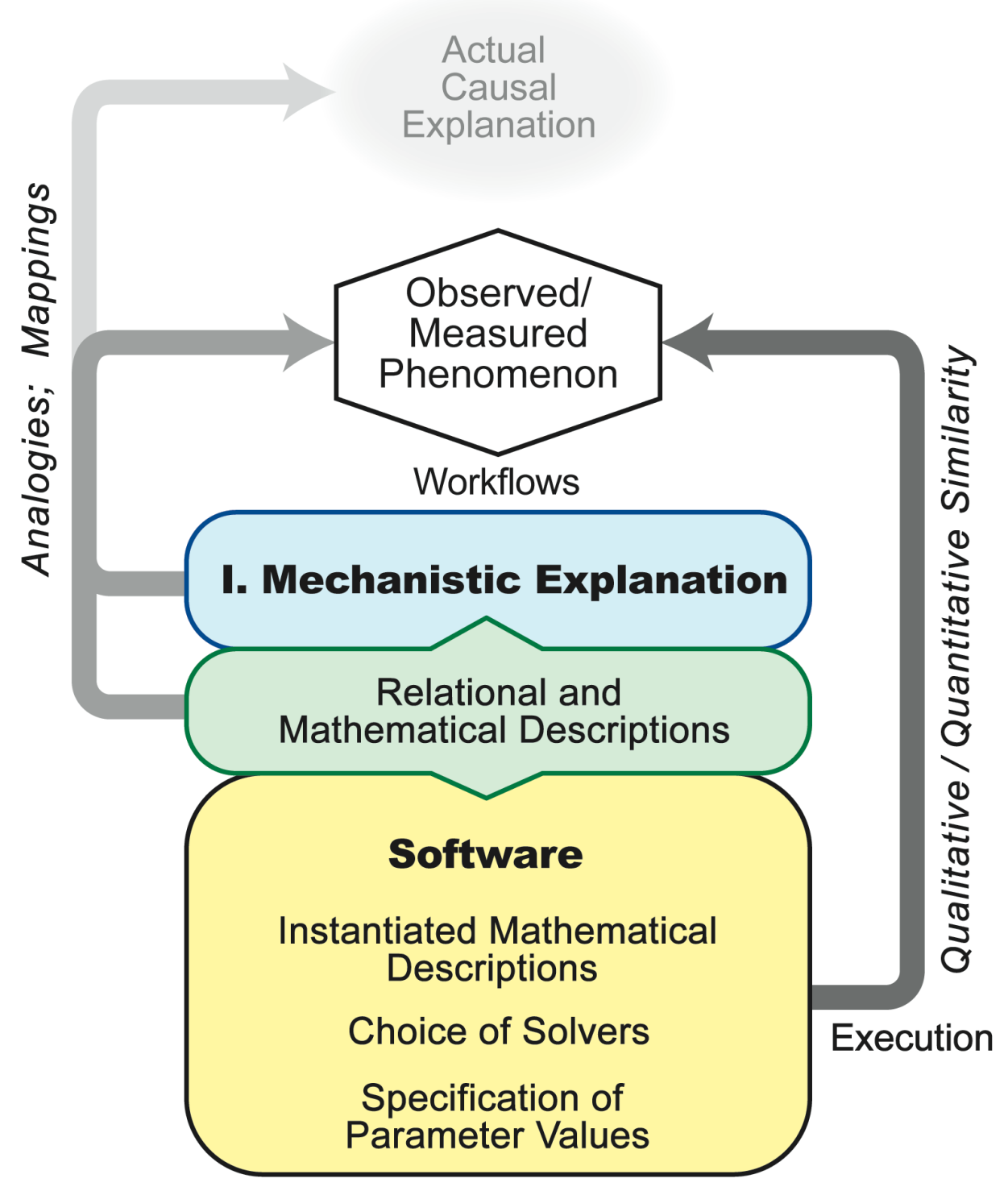
II. Explanatory Model of a Mechanism



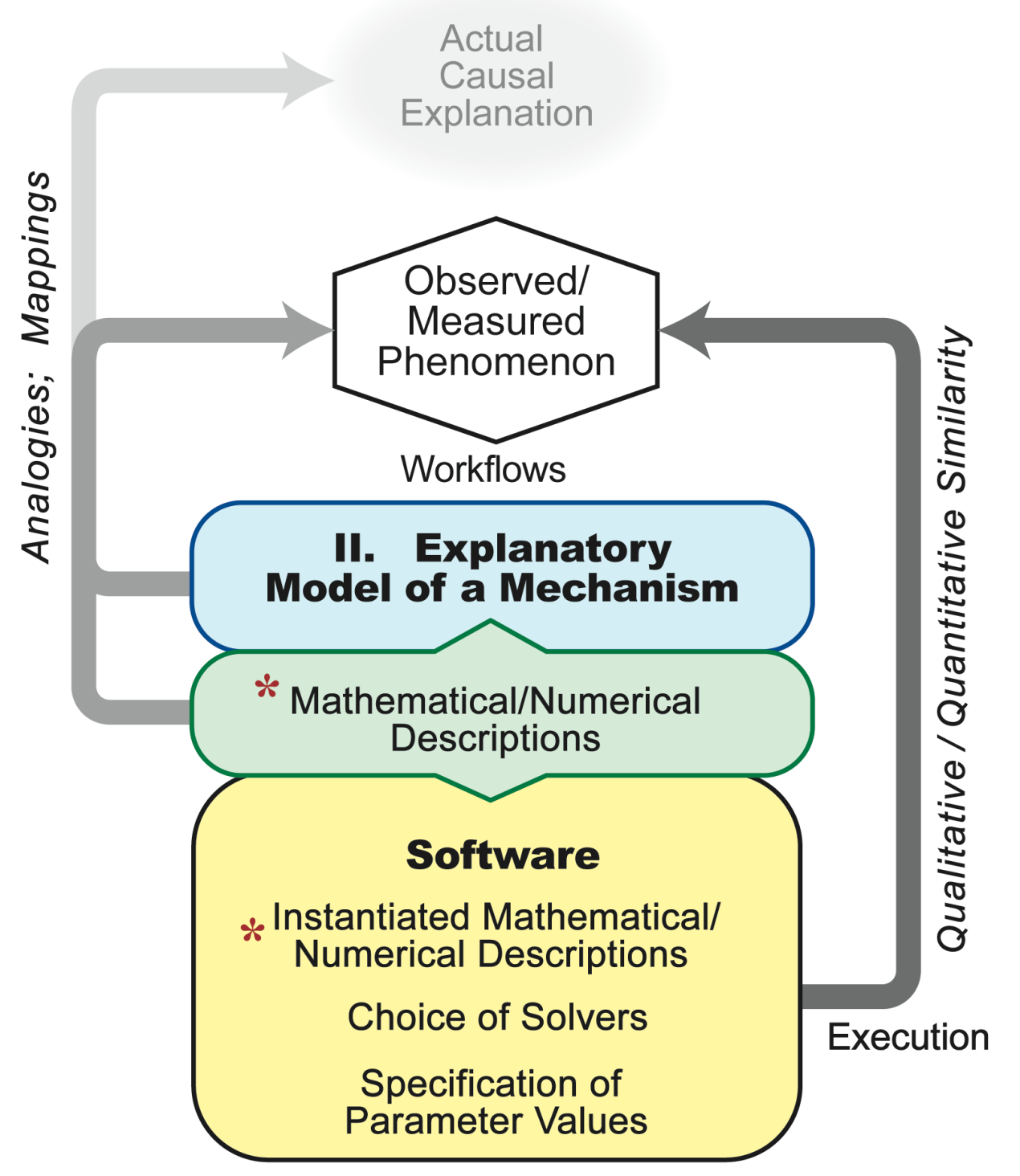
III. Model Mechanism Explanation



IV. Mechanistic Simulation

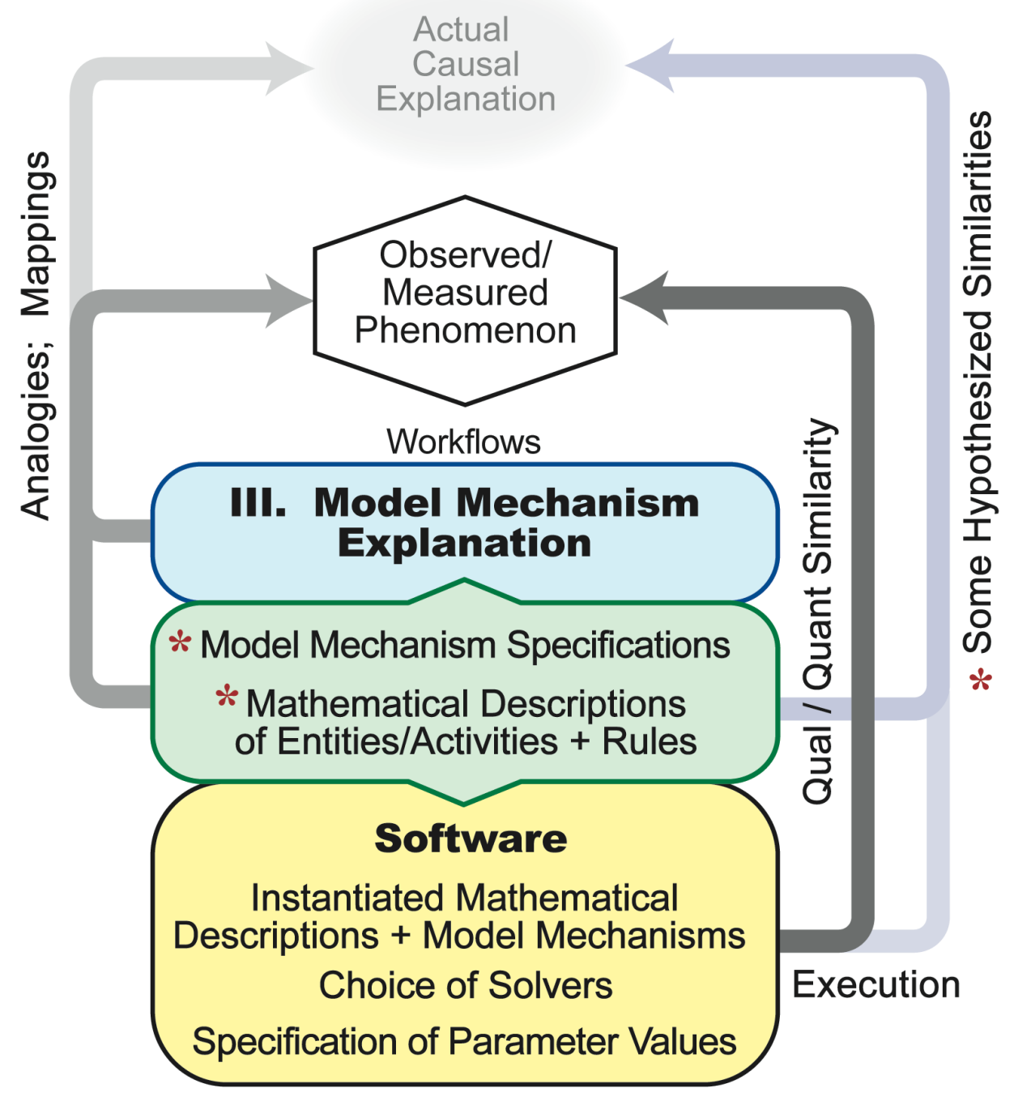


V. Simulation of a Model of a Mechanism



*Significant change from **IV**

VI. Model Mechanism Simulation



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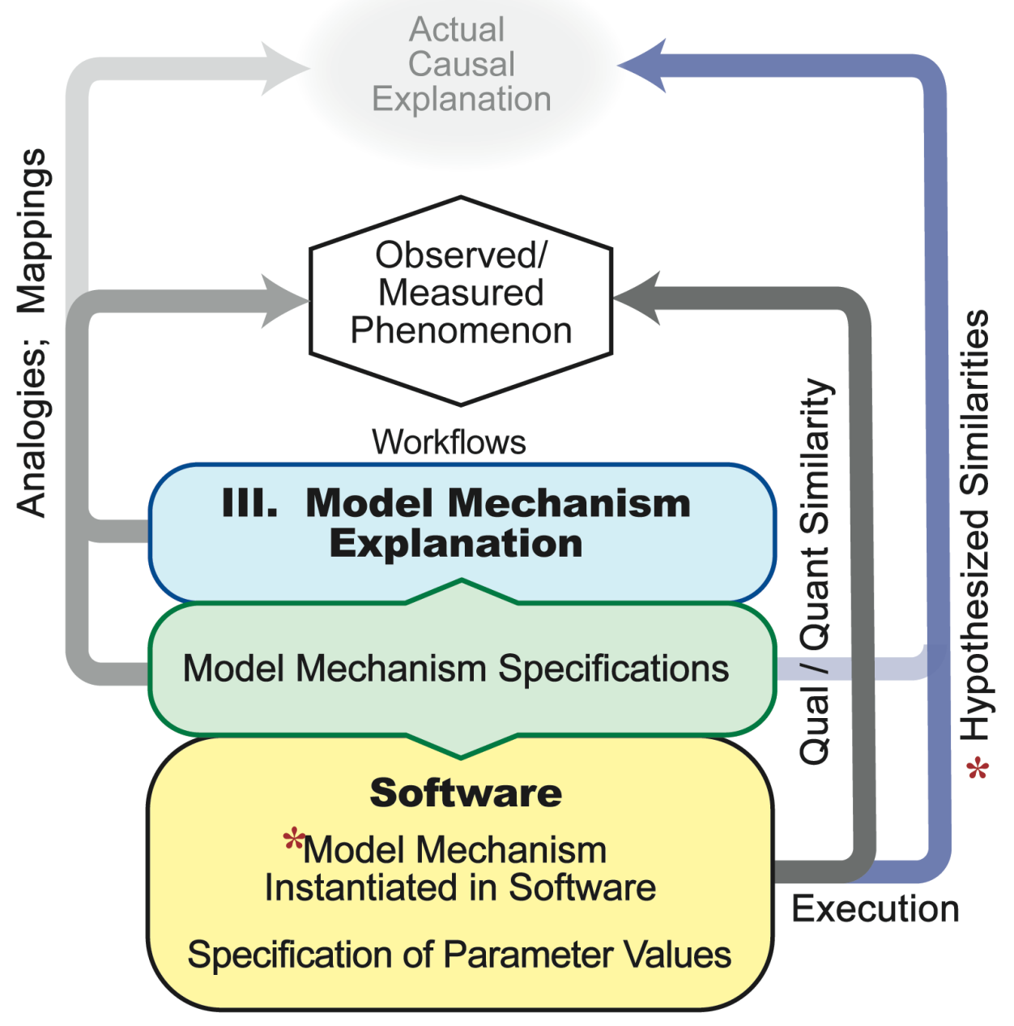
VII. Computational Model Mechanism



* Significant change from **VI**

I – Information about the phenomenon is **insufficient** to support a full mechanistic explanation, although some mechanistic features are included (well left of center on the **S1** spectrum).

II – Information about the phenomenon is **insufficient** to support a mechanistic explanation.

- This may be a non-biological model of using a mechanism analogy based on engineering principles, continuum mechanics, chemistry, electronics, etc.
- Model measures match the target phenomenon reasonably well.
- Such a model can be *explanatory*, but not mechanistic with spatial arrangements, temporal aspects, and/or components that do not have biological counterparts.

III – Information about the phenomenon **is sufficient** to create a biomimetic model mechanism (central to center-right location on the **S1** spectrum).

- Location on the **S2** spectrum is central or center-right.
- Permits characterization of the four essential features of an explanatory mechanism (see blue text) during execution with mappings between these four features and biological counterparts.
- Enables producing a detailed animation showing how the model's underlying entities and activities are responsible for the phenomenon.
- Model measures closely match experimental measurements quantitatively.

A ***Mechanistic Simulation*** builds upon a ***Mechanistic Explanation*** (**I**) during three workflow activities.

1. Relational and continuum mathematical descriptions (typically left of center on the S3 spectrum) are developed of the mechanistic explanation.
2. Those descriptions are instantiated in software and verified.
3. Qualitative and quantitative similarity is achieved between simulation output and measurements of the target phenomenon.

- Reliance on off-the-shelf (OTS) software is typical.
- Use of standardized software may increases credibility, reliability and reproducibility .

The workflow to build a ***Simulation of a Model of a Mechanism*** starts with an ***Explanatory Model of a Mechanism*** (**II**). The goal is to translate that knowledge into simulation output.

- Many mechanism-oriented MSMs, fit reasonably well under this descriptor.
- Computational mechanisms are not intended to have anything in common with referent mechanisms.
- Workflow activities often differ from those in **IV** in two important ways.

1. The modeler creates mathematical descriptions (continuum, usually ODEs & PDEs; left of center on the **S4** Spectrum) of the model of a mechanism in operation. Some descriptions may require numerical analysis techniques.
2. Mathematics are instantiated in software; user features are added; solvers are selected; and the implementation is verified.

- As in **IV**, the modeler strives to achieve qualitative and quantitative similarity between simulation output and measurements of the target phenomenon within some tolerance.
- Integration between OTS and custom software is typical.

Building a ***Model Mechanism Simulation*** starts with a ***Model Mechanism Explanation*** (**III**). The goal is to build an executable concretized software version of that model mechanism.

- Workflow activities (light green box) differ from those in **V** by endeavoring to exhibit three more stringent features.

1. Mappings can be provided between discretized descriptions of features of the software model mechanism and their biological counterparts.
2. The working hypothesis is that similarities will exist between some features the software model mechanism during execution and corresponding features of the actual causal explanation (light blue arrow).
3. Measurements taken during simulations are qualitatively and quantitatively similar to measurements of the target phenomenon.

- An accurate descriptor of the work product is simulation of a model mechanism.
- To achieve the above features, implementations (yellow boxes) require increased fidelity of biomimesis (right of center on the S5 spectrum).
- However, to achieve computational efficiencies and/or fine grain details, some model mechanism entities and activities are often described using a combination of rules and continuous mathematics, as in **V**. Doing so can cause the software mechanisms during execution to fall short of our definition of mechanism.
- Integration between custom and OTS software is typical.

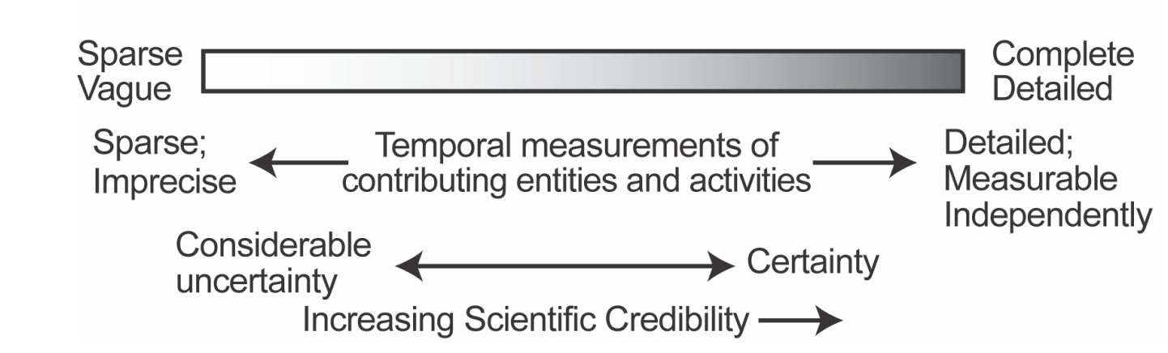
The workflow to build a ***Computational Model Mechanism*** starts with a ***Model Mechanism Explanation*** (**III**). The goal is the same as in **VI**.

- The workflow activities (light green box) are more stringent than those in **VI** in three ways.

1. Evidence supports that the four features of the software model mechanism have biological counterparts.
2. Features of the software model mechanism during execution meet the definitions of mechanism.
3. The working hypothesis is that similarities exist between the software model mechanism during execution and the actual causal explanation (darker blue arrow).

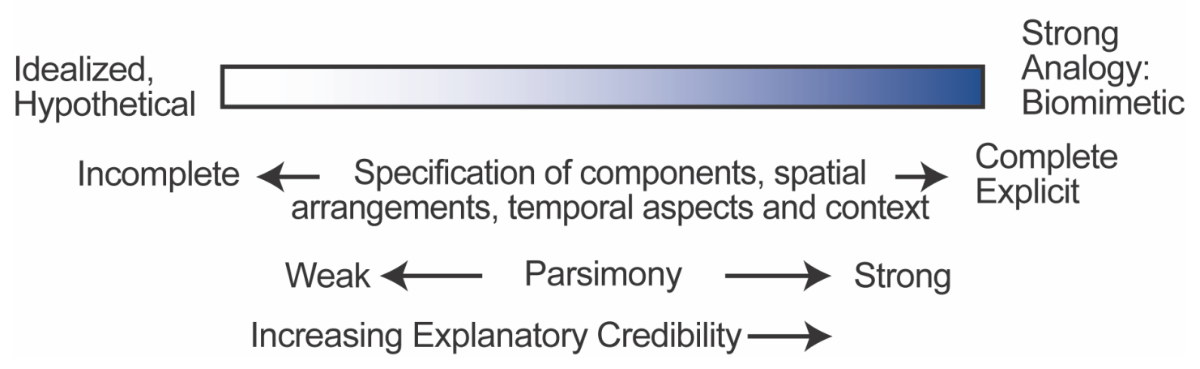
- To achieve the above features, implementations (yellow boxes) require increased fidelity of biomimesis (right of center on the **S5** spectrum).
- Examples of this type of model of explanation can be used to help design mechanism-based therapeutic interventions in disease.
- The framework integrates custom software with OTS software and tools.

S1 Knowledge about Phenomenon



Relevant information about the phenomenon of interest and how it may be generated. Making that information explicit and providing provenance increases credibility. Having available unbiased assessments of uncertainties further enhances credibility.

S2 Explanatory Description

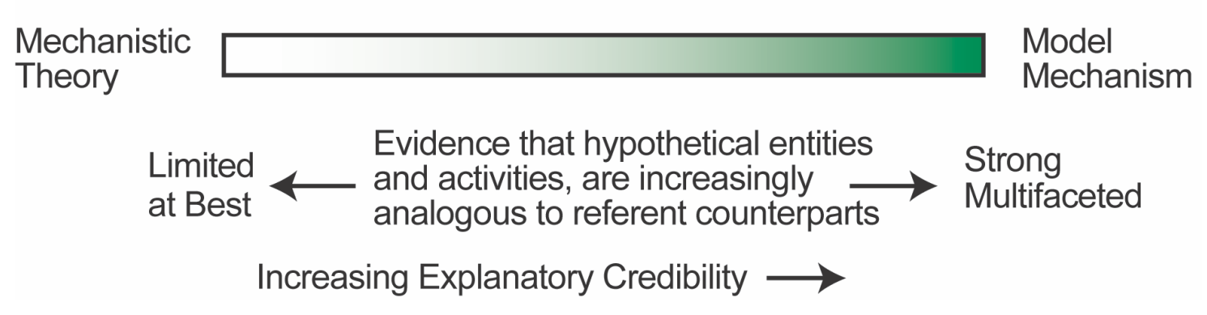


Identifies what is currently known, and hypotheses about generative components, spatial arrangements, temporal aspects, and their contextual location. Left-of-center, information is insufficient to offer a mechanistic explanation.

	Characterization	Descriptive			Requires Computation		
		Mechanistic description of phenomenon generation	Description of an explanatory *continuum* model of a mechanism [1]	Description of an explanatory *discretized* model mechanism	During execution, output of solvers are [2] predicted values of the phenomenon	Observable biomimetic entities and activities during execution	During execution, measurements of entities and activities are used to compute values of the phenomenon
I	Mechanistic Explanation	▨					
II	Description of a Model of a Mechanism		▨				
III	Explanatory Model Mechanism			▨			
IV	Mechanistic Simulation	▨			▨		
V	Simulation of a Model of a Mechanism		▨		▨		
VI	Model Mechanism Simulation			▨	▨	▨	
VII	Computational Model Mechanism			▨		▨	▨

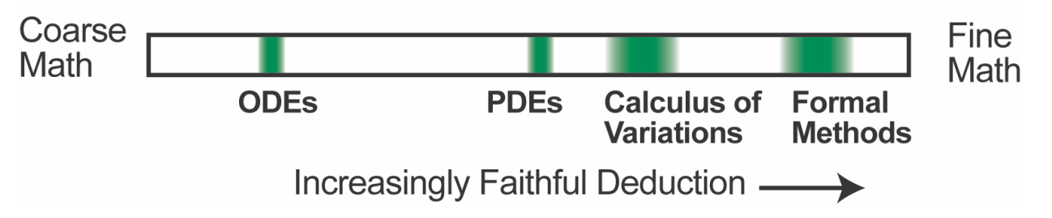
[1] An important subset of those mathematical descriptions, e.g., finite element analysis, goes beyond continuum mathematical descriptions because they also require numerical analysis techniques.
[2] In some cases, solver output may be used to compute predicted values of the phenomenon.

S3 Mathematical Description



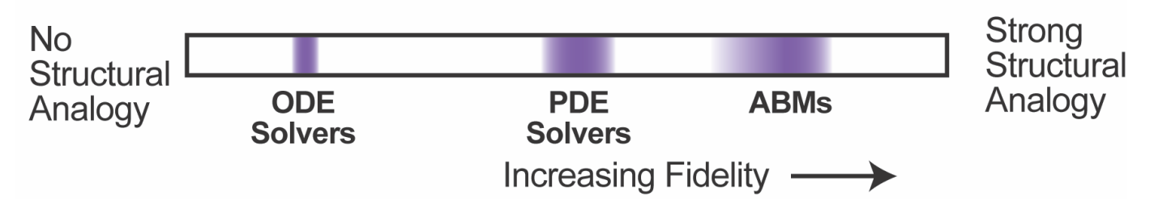
Location on this spectrum brings into focus characteristics of methods and approach that help distinguish among IV–VII. Relationship between explanations in I–III and mathematical description (light green box) in IV–VII must be clear.

S4 Transformation of S3



Expanding a computational model of explanation and/or combining it with others can improve explanatory power. It can also change model type. The choice of mathematical description used for expansion or combination can influence faithfulness of deductive transformations, and the degrees to which the simulation meets characterization IV–VII. Some mathematical model types cannot be easily modified and remain faithful to model-to-target phenomenon mappings while preserving the original meaning(s) provided in the explanatory descriptions.

S5 Implementation, Solvers, Simulation



This spectrum illustrates that implementation decisions (within the yellow boxes) influence the fidelity of biomimesis that can be built into the simulations during execution. Stronger analogies between the biology and implemented mechanisms during execution are expected to improve scientific clarity and credibility.

Conclusion

The scientific usefulness of biology simulations will become more evident to the larger community as more, credible multi-phenomena explanations become available. Achieving credible multi-phenomena explanations requires moving right on spectra S1-S5, but doing so requires increasing support from the larger biology community. Improving semantic clarity is a necessary and essential small step to achieving increased support when significant amount of information needs to be inferable from a simple term describing the model type. By characterizing four different types of computational models of explanation—IV–VII, we demonstrate how semantic clarity can be improved even as the complexity of those models of explanation increases.

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