How can we start with modeling?

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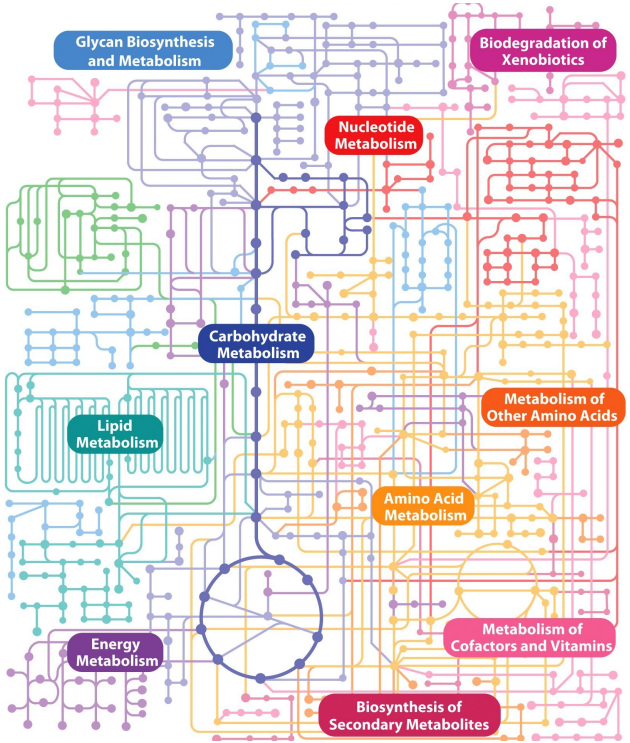
1. Define Model Scope

Biological networks can be large and complicated.

Scientists build models to answer biological questions.

Example: Under what conditions does the lac operon function?



genome.jp/kegg/

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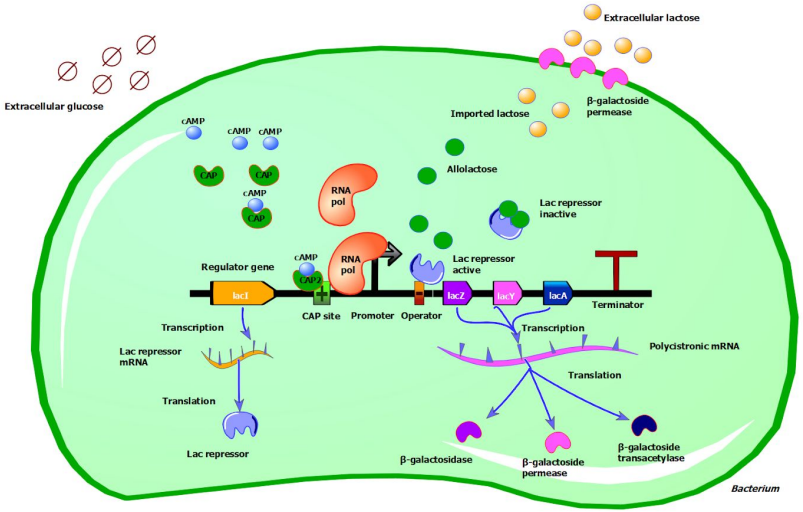
<u>Consider the Lac Operon:</u>

- What behavior(s) should the model exhibit?
- What components and relationships are required to elicit that behavior?



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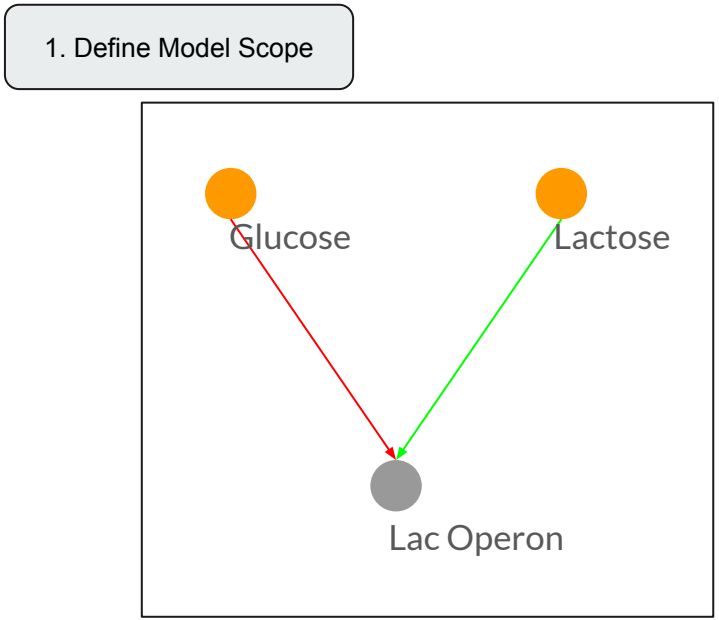

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2. Define Validation Criteria

Validation criteria can be thought of as relationships (qualitative or quantitative) between inputs and outputs.

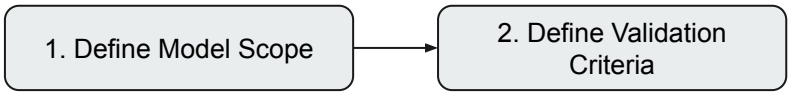

Table 1. Validation criteria for the modeled *lac* operon system.

	Glucose	Lactose	*lac* Operon transcription
Validation Criterion 1	present	absent	OFF
Validation Criterion 2	present	present	OFF
Validation Criterion 3	absent	present	ON
Validation Criterion 4	absent	absent	OFF

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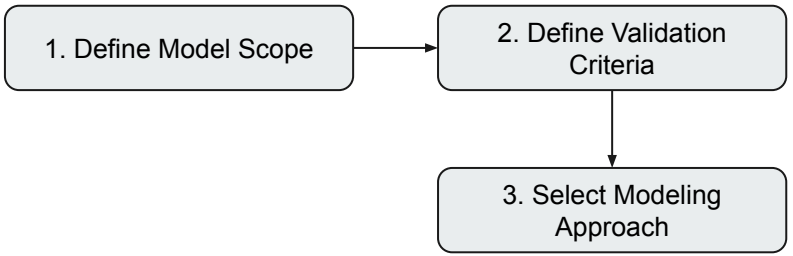
3. Select Modeling Approach

Many mathematical and computational frameworks are available:

<u>Examples:</u>

- Logical models
- Kinetic models
- Constraint-based models



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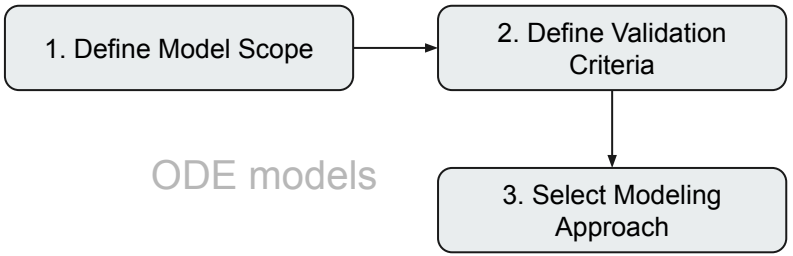

Interaction maps, Statistical mining, Graph theory

Bayesian networks, Discrete, Rule-based models

ODE models

Abstract

Large scale

High Detail

Specific

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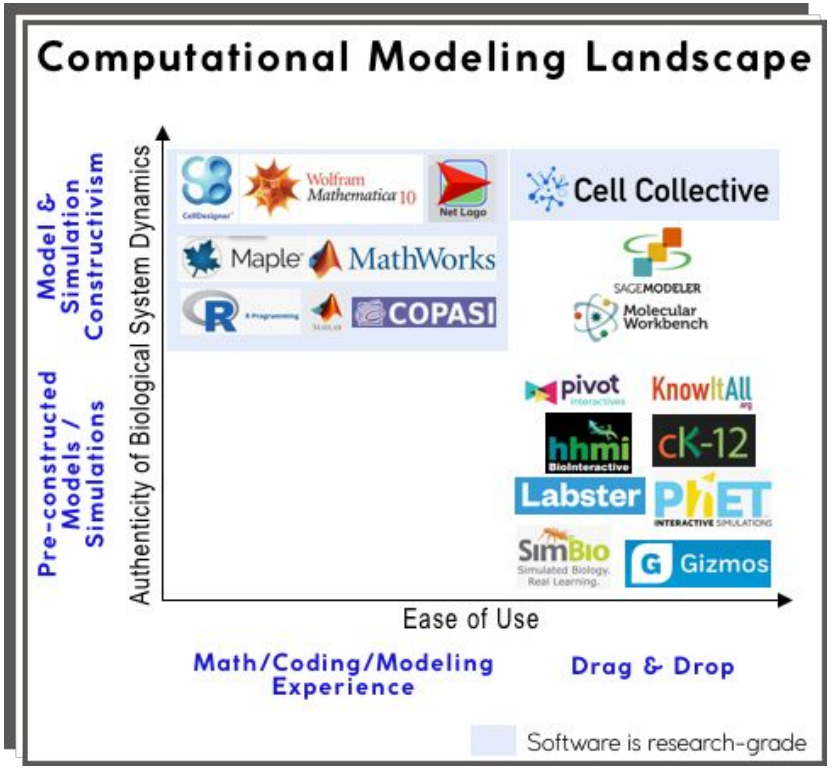

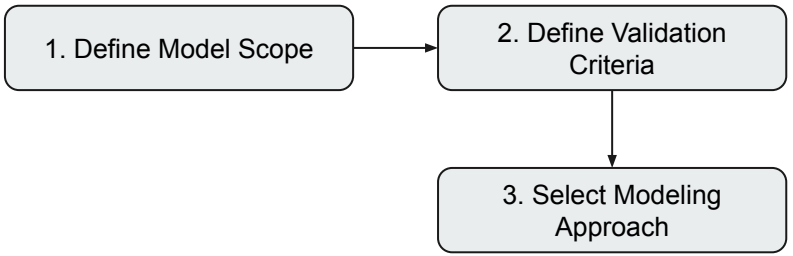

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4. Identify Components & Interactions, and Build a Draft Model

Determine the specific components that will be represented in the model and the relationship(s) between them.

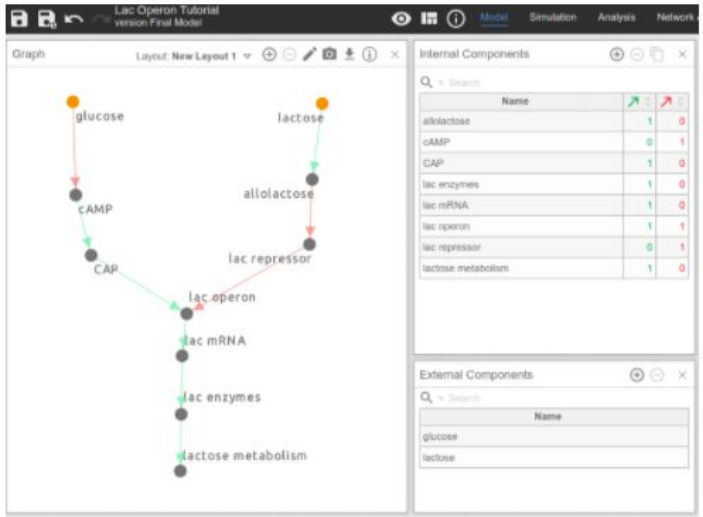
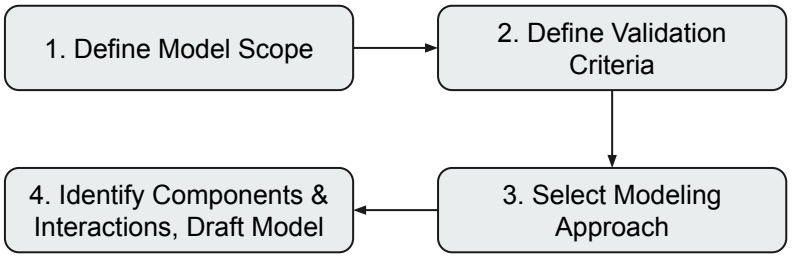


Figure 6. Fully connected network diagram of the *lac* operon model.



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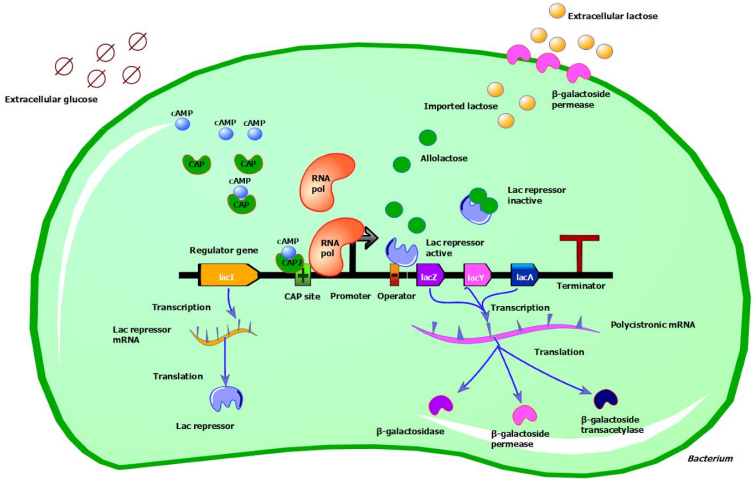


Possible sources:

- Expert Knowledge
- Static Diagrams
- Published Literature

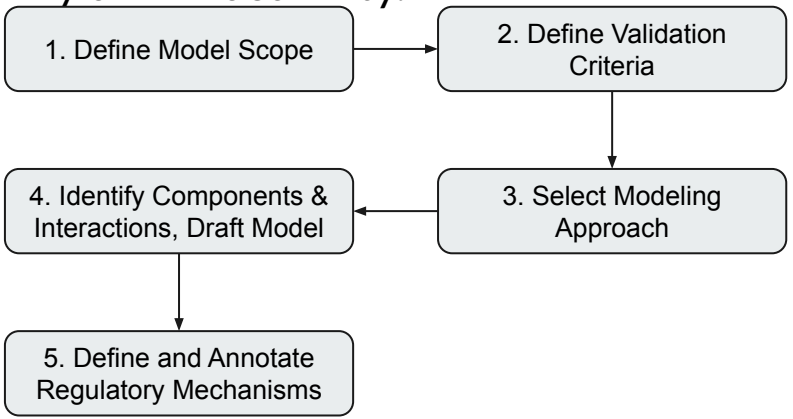
Cell Collective interprets the diagram so that it functions as a simulatable model.

5. Define and Annotate Regulatory Mechanisms

Well annotated models facilitate transparency and reusability.

<u>Levels of Annotation in Cell Collective:</u>

- Model
- Regulatory Mechanism



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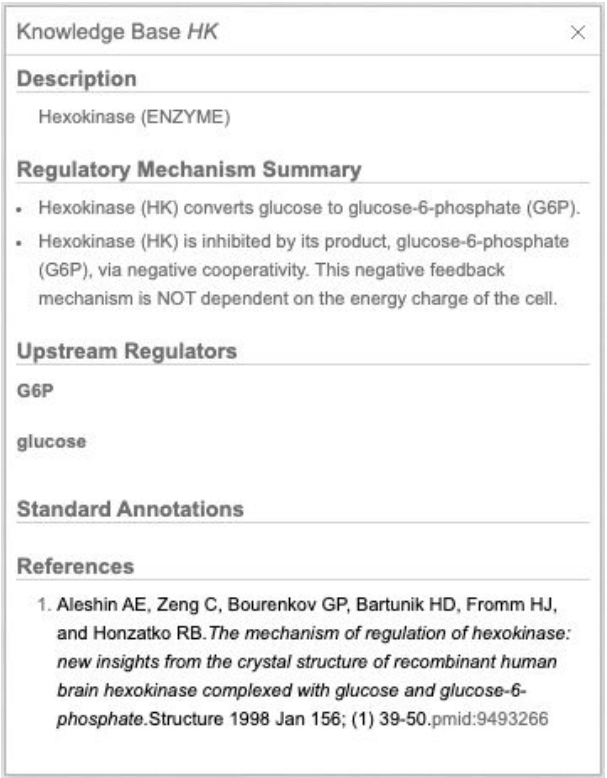
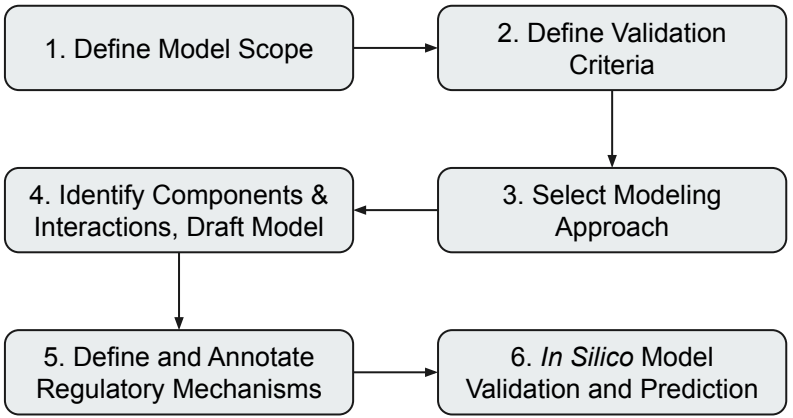


6. *In Silico* Model Validation and Prediction

Simulate the model to test whether it can reproduce the dynamics and behaviors defined in the validation criteria.



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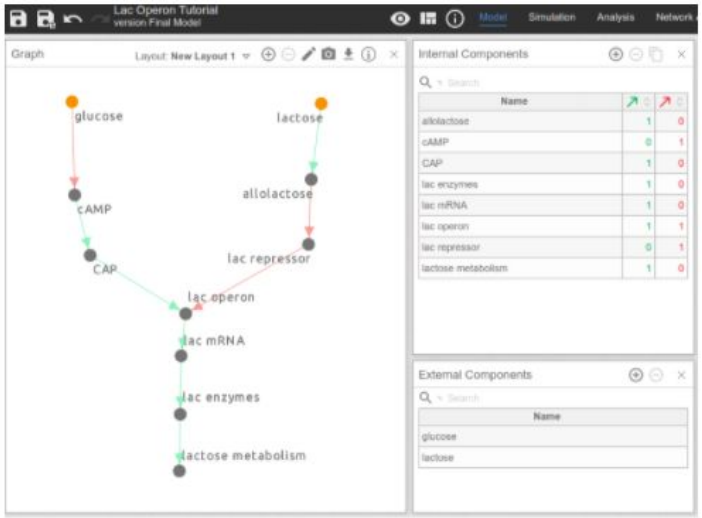

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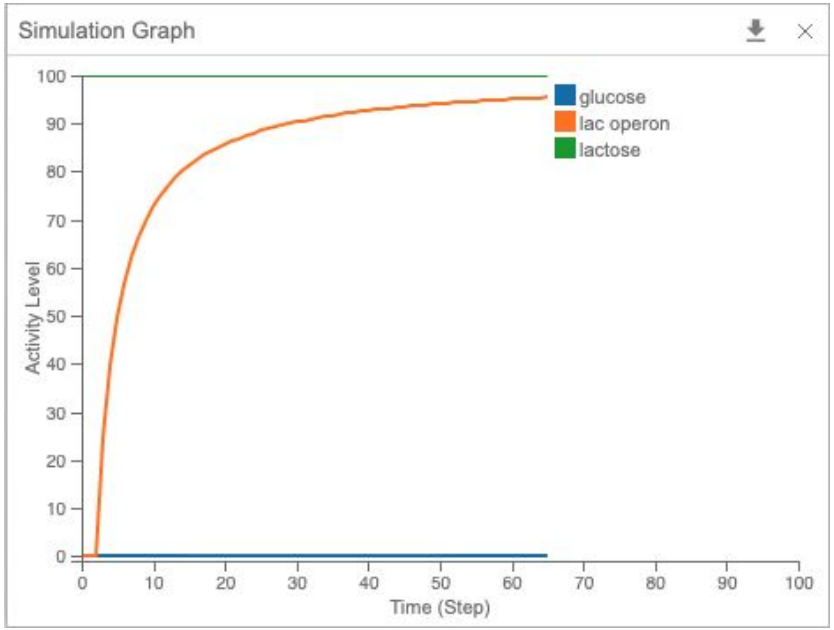

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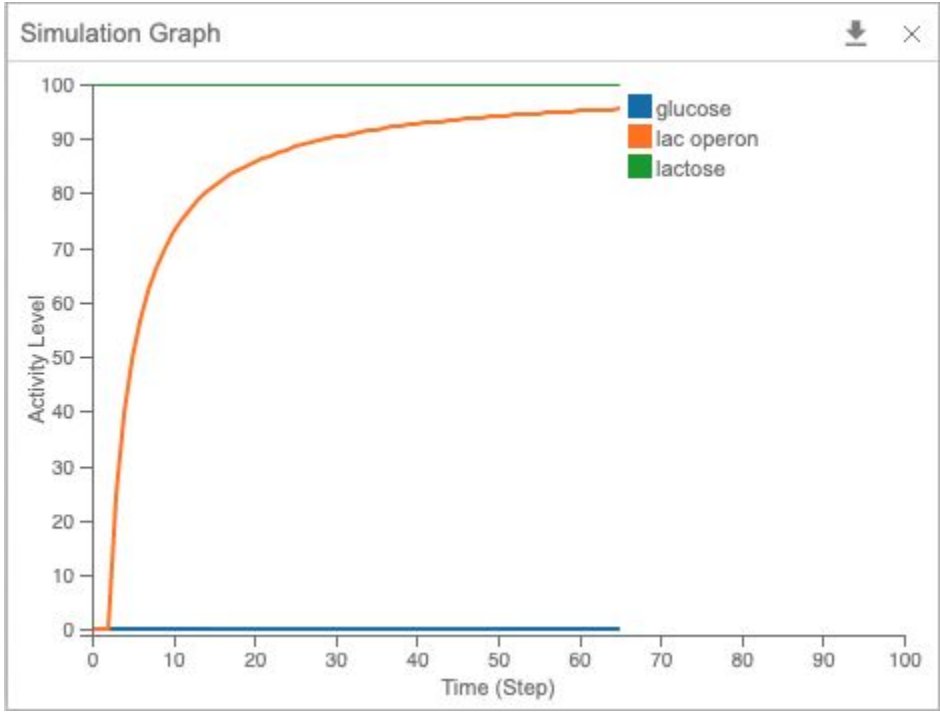


With a validated model, we can test:

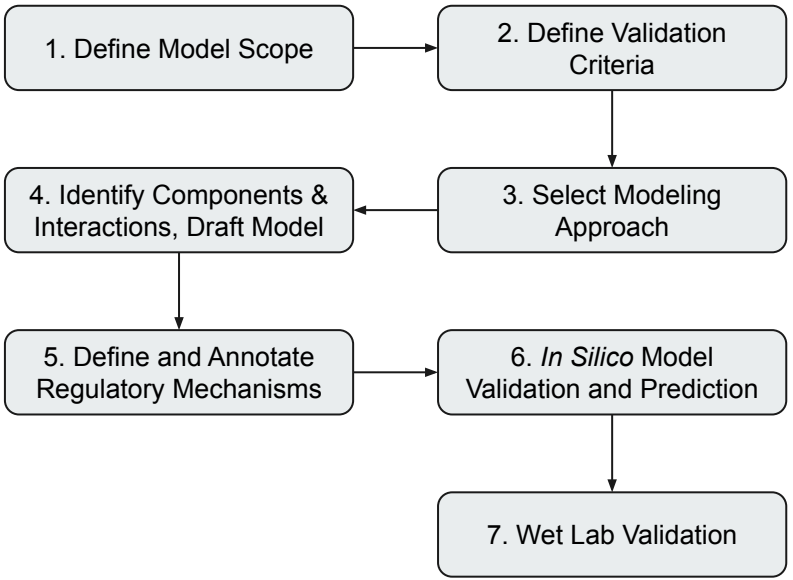
- *In silico* knock-outs
- Over-expressions
- Combinations of the above
- Dose-response
- Identify optimal intervention points

7. Wet Lab Validation

Hypotheses generated using a model can be validated experimentally.

<u>Benefits of Computational Modeling:</u>

- Identify experiments likely to succeed
- Saves Resources
- Saves Time



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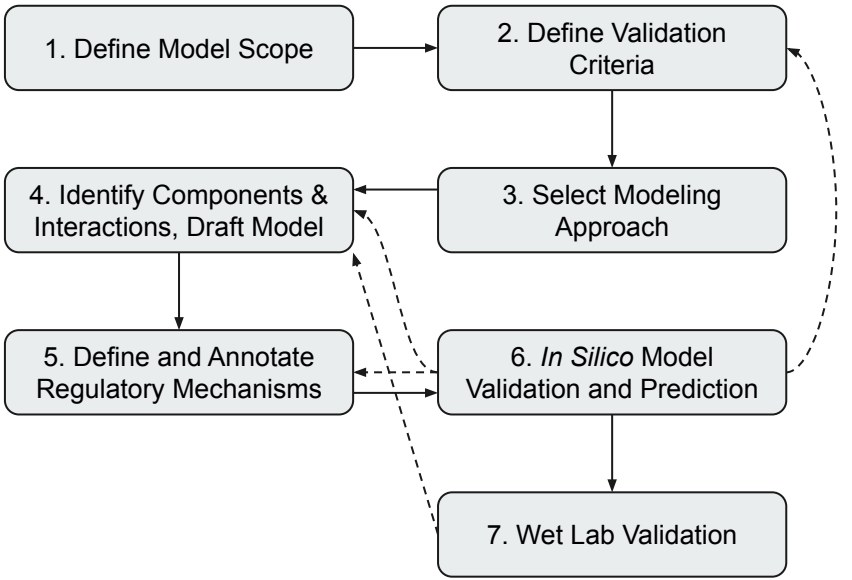
8. Possible Needs for Revision

Like the scientific process, modeling is iterative with multiple points that may require revision.



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Your Turn!!

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