Computational Support for Systems Biology of Aging

Pat Langley

Computer Science and Engineering
Arizona State University
Tempe, Arizona, USA

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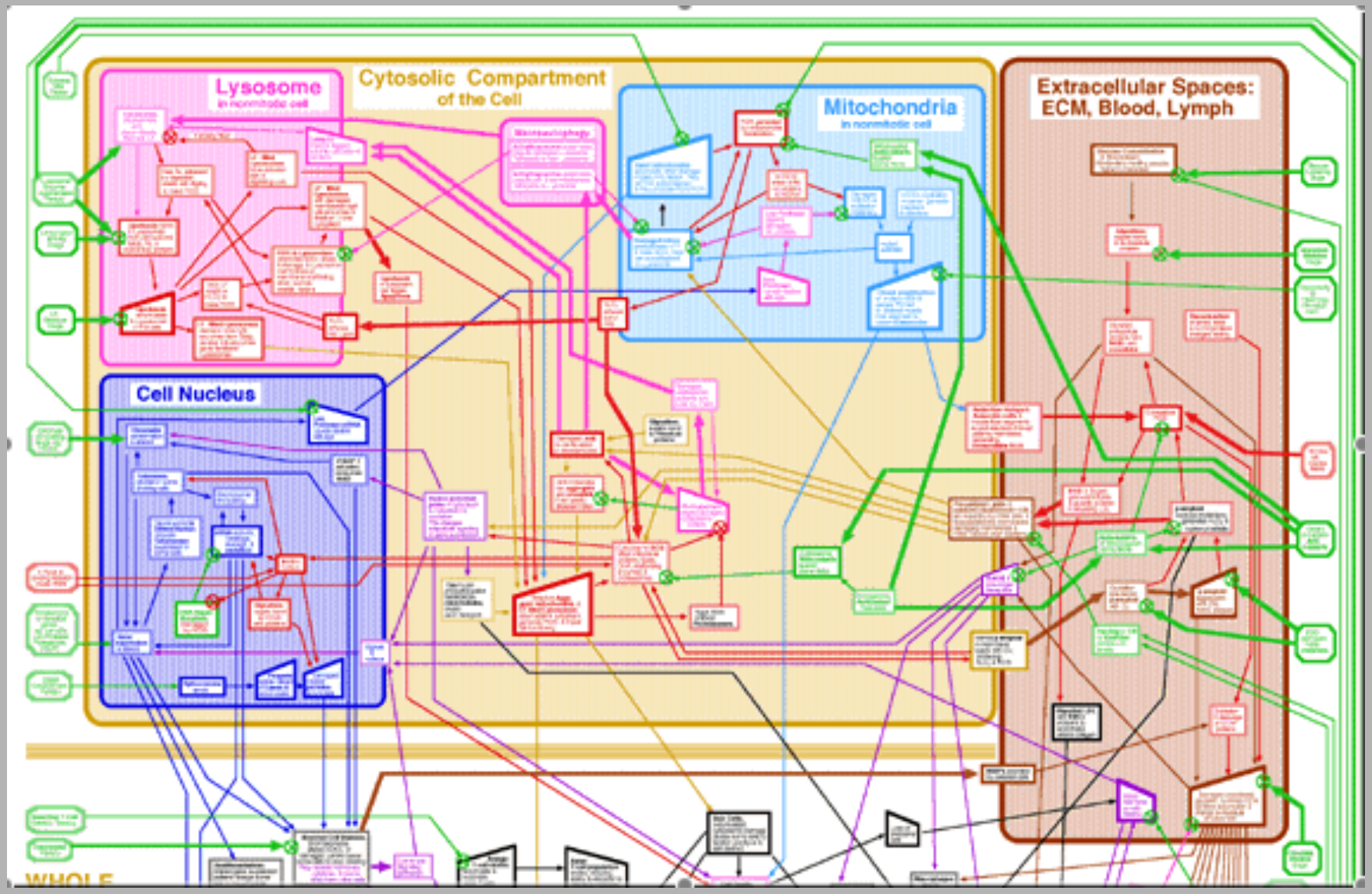
The Complexity of Human Aging

There is growing agreement that aging involves many interacting processes, including:

- Mutation of the mitochondrial DNA
- Accumulation of lipofuscin in the lysosomes
- Protein crosslinking in the extra-cellular matrix
- Shortening of telomeres in the nucleus

The daunting complexity of these and related processes suggests the need for computational assistance.

Furber's Network Diagram of Aging



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Challenges in Scientific Modeling

The creation of complex scientific models raises three separate but interrelated challenges:

1. The social nature of science requires use of *interpretable* formalisms that researchers can understand.
2. Science operates in a cumulative manner that *extends* and *revises* models by filling in technical details.
3. Science is concerned with *explaining observations* in terms of familiar concepts and mechanisms.

Software environments for scientific modeling must address each of these issues.

Today I will present such an environment for the biology of aging.

Challenge 1: Representing Models of Aging

We want a notation for models of aging that is *interpretable* by scientists yet precise enough for a digital computer.

Most traditional formalisms from computational biology will not suffice because our knowledge of aging is:

- *Localized* in describing changes in a variety of places
- *Entity-oriented* in specifying interactions among substances
- *Causal* in that interactions involve asymmetrical influences
- *Qualitative* in specifying only the directions of effects

These characteristics place constraints on our representation.

We also need a notation that makes close contact with biologists' ideas about aging.

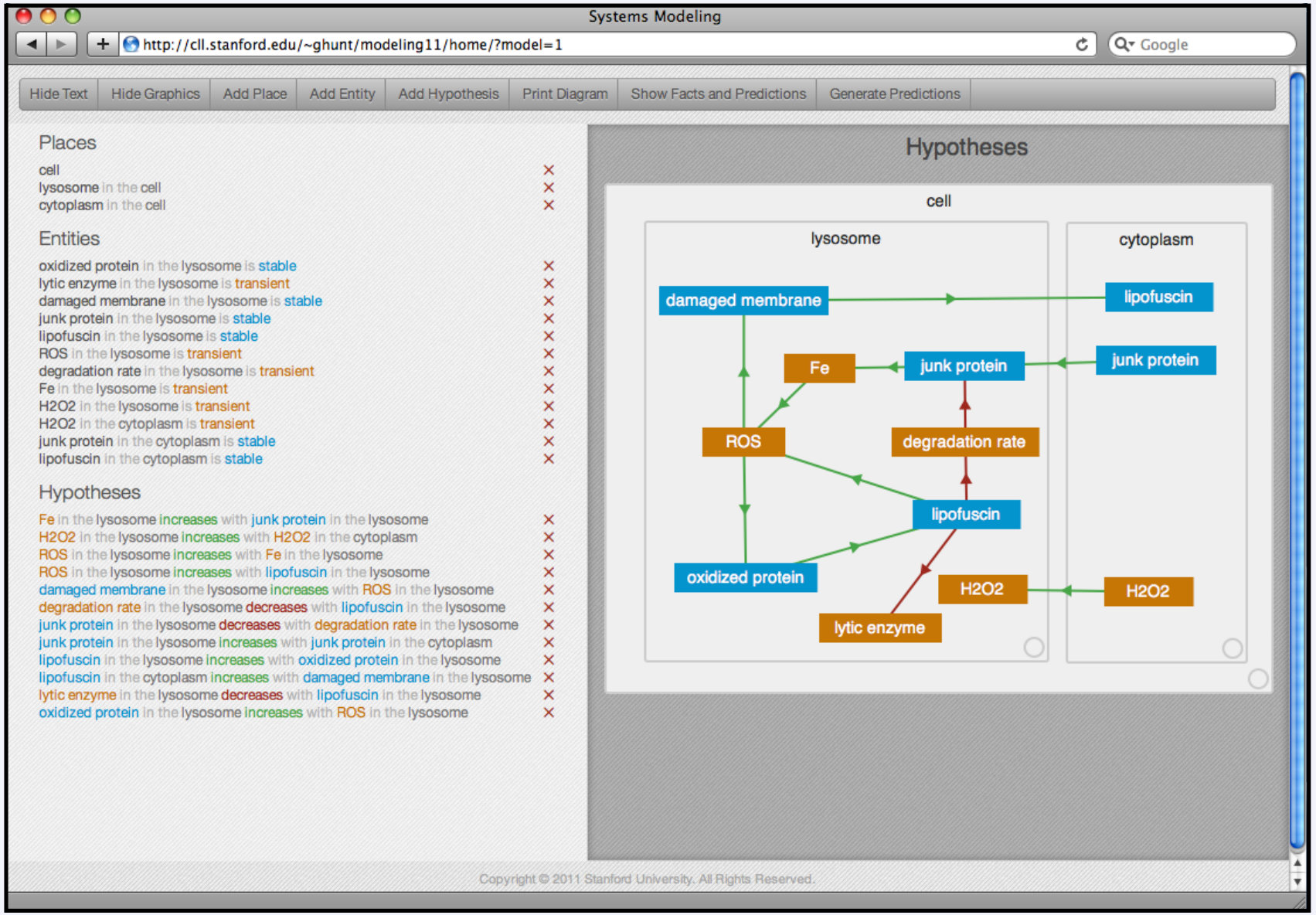
A Formalism for Models of Aging

We have developed a formalism for aging models that involves:

- *Places* in the cell (e.g., lysosome, cytoplasm)
- *Quantities* that are measured in a place
  - For *transient* entities or variables (e.g., ROS, Fe, rates)
  - For *stable* entities (e.g., oxidized proteins, lipofuscin)
- Hypothesized *causal influences* between quantities
  - Increase/decrease of one quantity with another
  - Dependent terms may be amounts or rates of change

Each hypothesis describes a *qualitative* causal link between two *quantitative* variables.

A Modeling Environment



Stating a Lysosomal Model

Places

cell
lysosome in the cell
cytoplasm in the cell

Entities

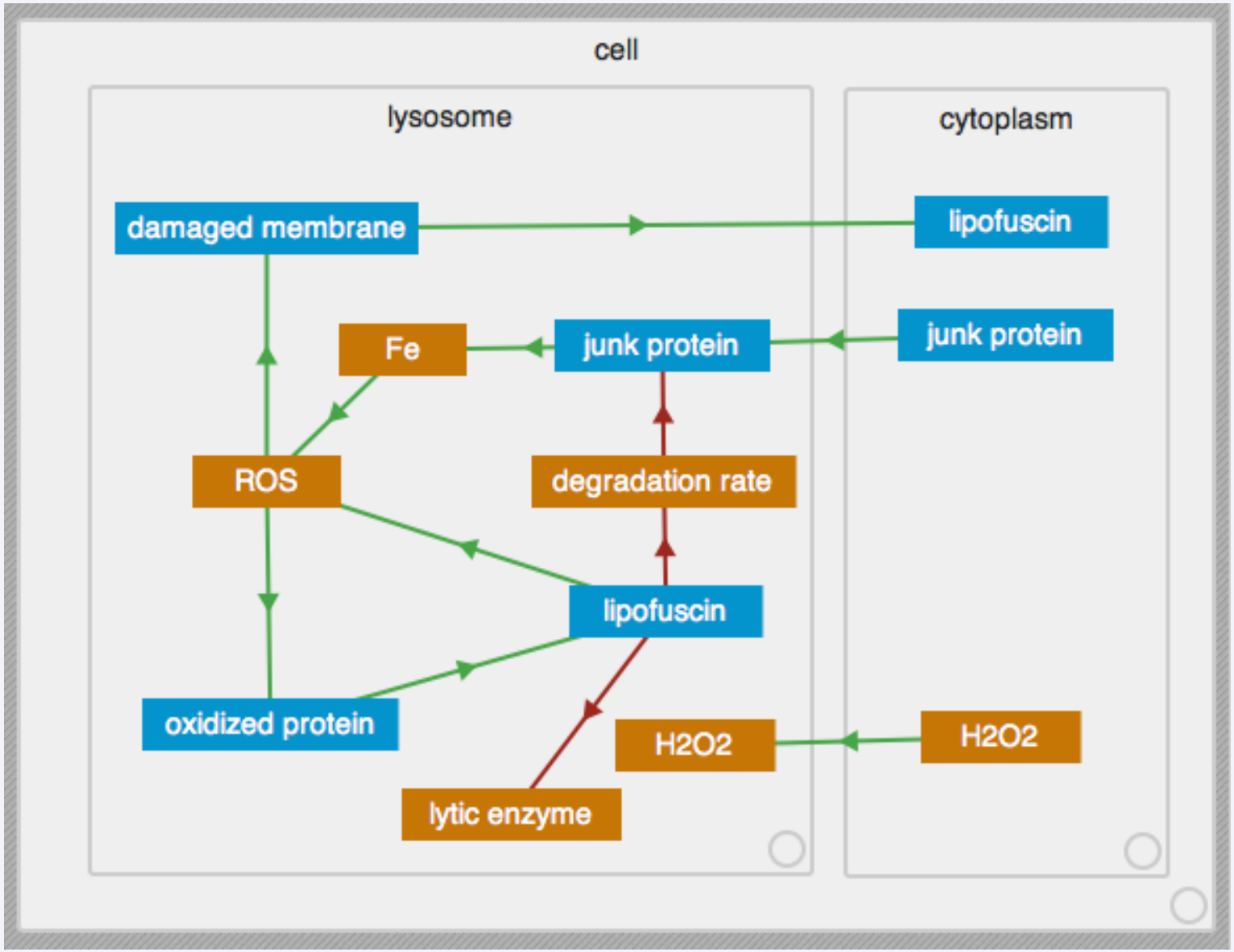
oxidized protein in the lysosome is stable
lytic enzyme in the lysosome is transient
damaged membrane in the lysosome is stable
junk protein in the lysosome is stable
lipofuscin in the lysosome is stable
ROS in the lysosome is transient
degradation rate in the lysosome is transient
Fe in the lysosome is transient
H2O2 in the lysosome is transient
H2O2 in the cytoplasm is transient
junk protein in the cytoplasm is stable
lipofuscin in the cytoplasm is stable

Stating a Lysosomal Model

Hypotheses

Fe in the lysosome increases with junk protein in the lysosome
H2O2 in the lysosome increases with H2O2 in the cytoplasm
ROS in the lysosome increases with Fe in the lysosome
ROS in the lysosome increases with lipofuscin in the lysosome
damaged membrane in the lysosome increases with ROS in the lysosome
degradation rate in the lysosome decreases with lipofuscin in the lysosome
junk protein in the lysosome decreases with degradation rate in the lysosome
junk protein in the lysosome increases with junk protein in the cytoplasm
lipofuscin in the lysosome increases with oxidized protein in the lysosome
lipofuscin in the cytoplasm increases with damaged membrane in the lysosome
lytic enzyme in the lysosome decreases with lipofuscin in the lysosome
oxidized protein in the lysosome increases with ROS in the lysosome

Visualizing a Lysosomal Model



Stating a Mitochondrial Model

Places

cell, mitochondria in the cell, nucleus in the cell

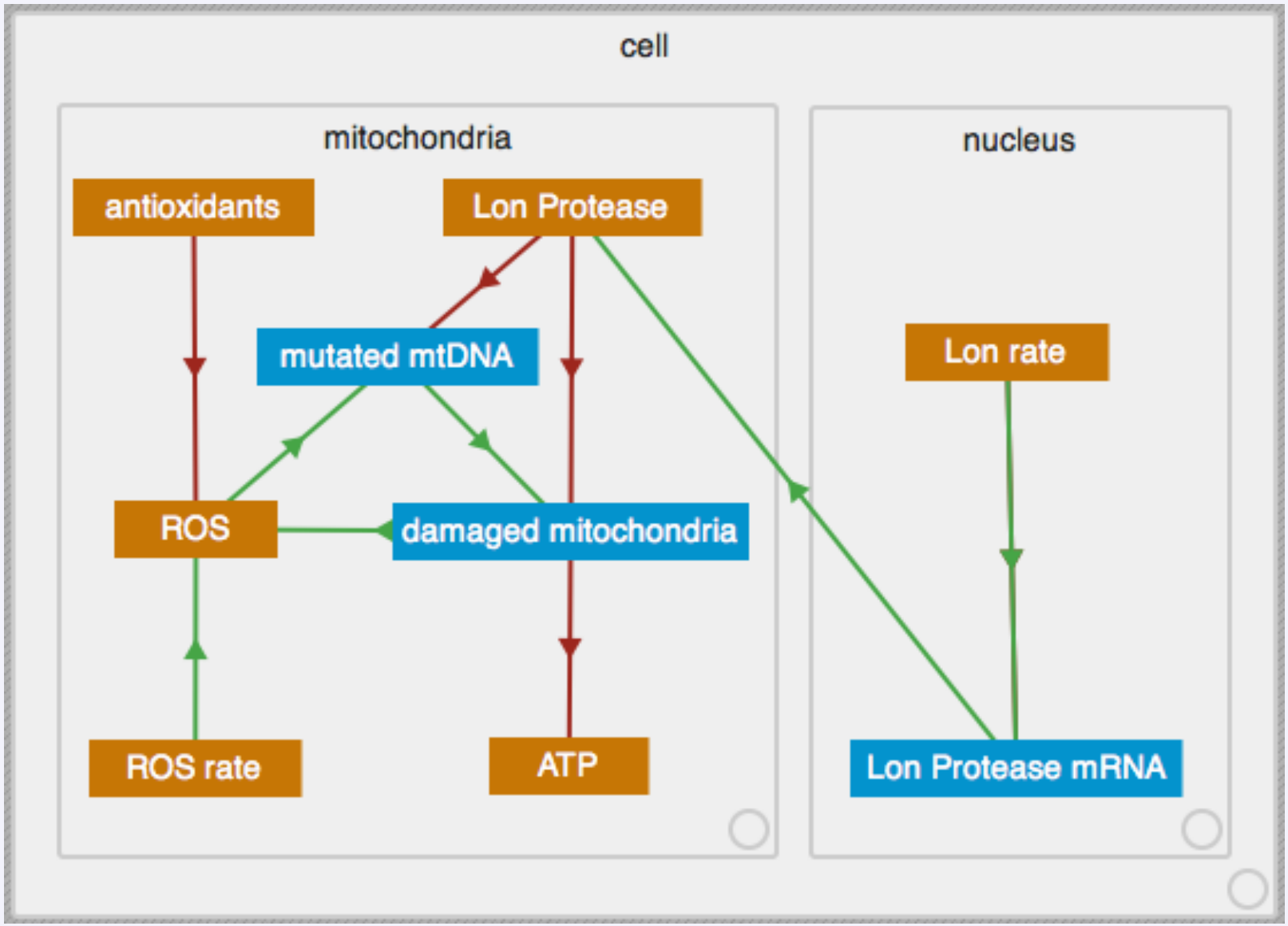
Entities

ROS rate, ROS, ATP, Lon Protease, mutated mtDNA, damaged mitochondria, antioxidants in the mitochondria, Lon rate, Lon Protease mRNA in the nucleus

Hypotheses

ROS in the mitochondria increases with ROS rate in the mitochondria
mutated mtDNA in the mitochondria increases with ROS in the mitochondria
Lon Protease mRNA in the nucleus decreases with Lon rate in the nucleus
Lon Protease in the mitochondria increases with Lon Protease mRNA in the nucleus
mutated mtDNA in the mitochondria decreases with Lon Protease . . .
damaged mitochondria in the mitochondria increases with mutated mtDNA . . .
damaged mitochondria in the mitochondria decreases with Lon Protease . . .
ROS in the mitochondria decreases with antioxidants in the mitochondria
ROS in the mitochondria increases with damaged mitochondria in the mitochondria
ATP in the mitochondria decreases with damaged mitochondria in the mitochondria

Visualizing a Mitochondrial Model



Encoding Empirical Facts

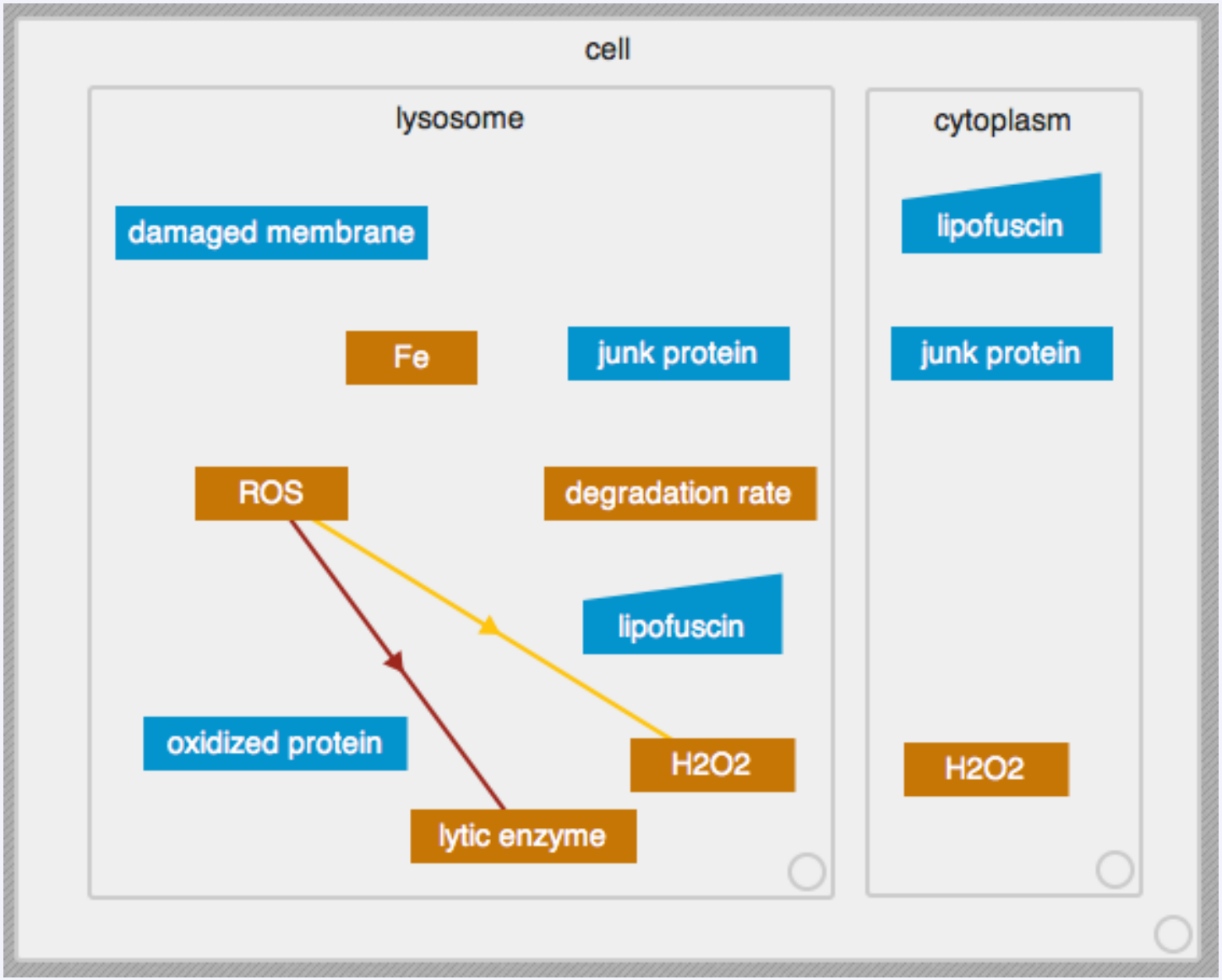
We must also represent *empirical* findings about aging; for this we use a notation similar to model hypotheses:

- A quantity increases (decreases) with another quantity
  - E.g., lipofuscin in the lysosome increases with time
  - E.g., lytic enzyme decreases with ROS in the lysosome
- A quantity does not change with another quantity
  - E.g., H2O2 does not vary with ROS in the lysosome

Each statement specifies, in constrained English, a pairwise relation between two quantities.

Note: *These describe phenomena that the model should aim to predict; they are not part of the model themselves.*

Visualizing Empirical Facts



Challenge 2: Extending Models of Aging

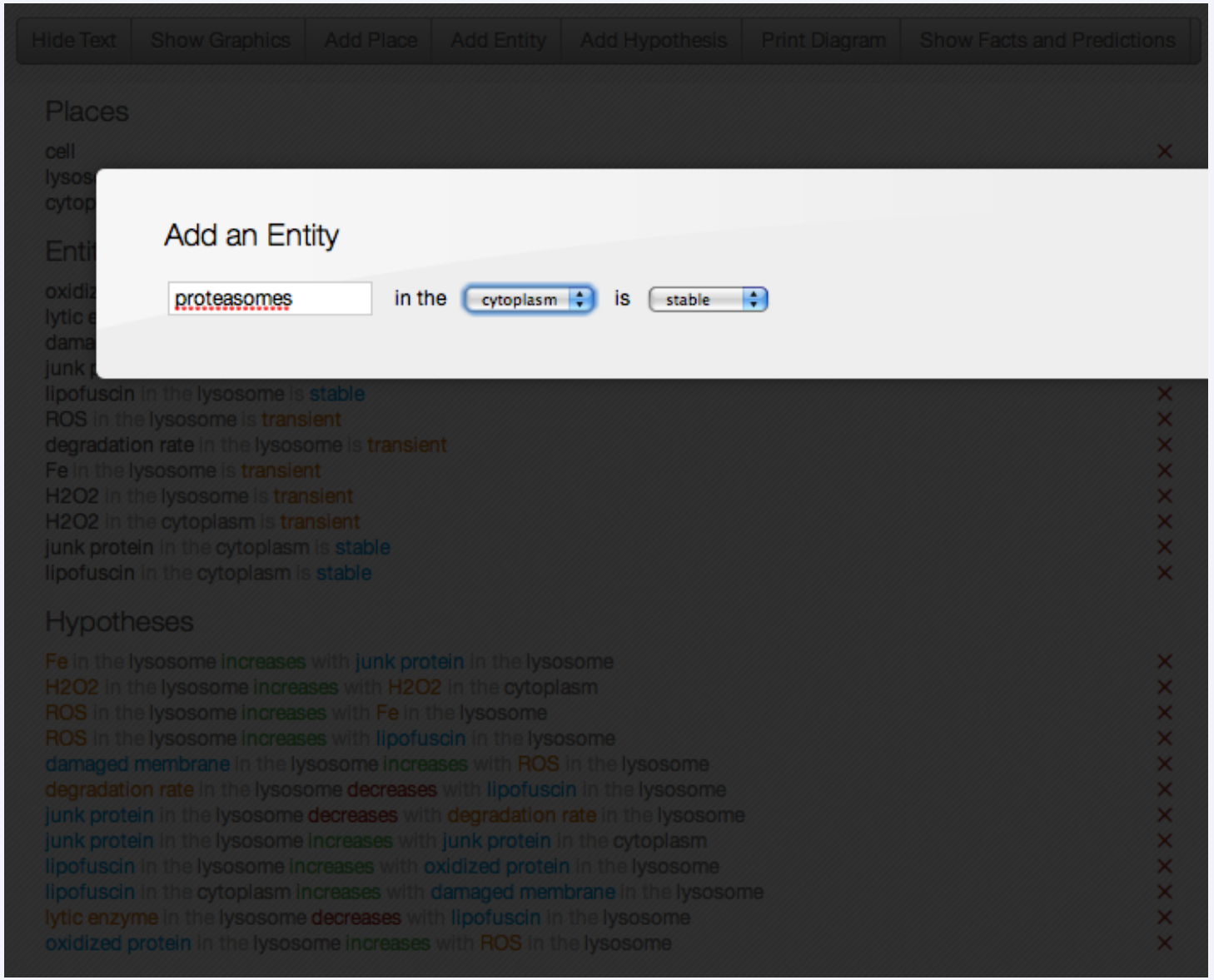
Biologists should be able to extend and revise models of aging easily and efficiently.

Our environment lets users alter the current model interactively in five basic ways:

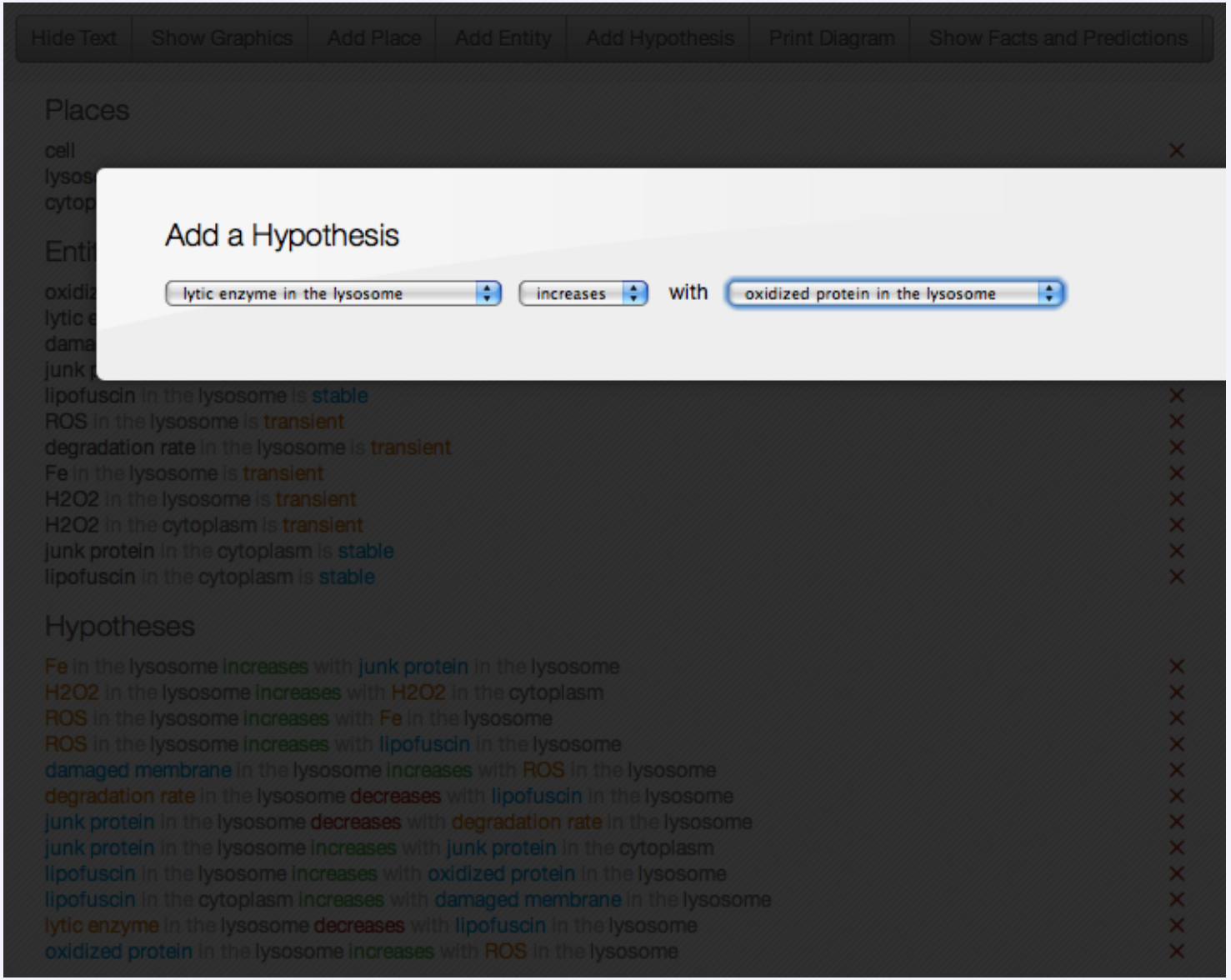
- Adding a place, entity, hypothesis, or empirical fact
- Adding a note (including URLs) to a hypothesis or fact
- Removing a place, entity, hypothesis, or fact
- Changing the graphical layout of places and entities
- Saving revisions to a file that can be loaded later

The modular character of models makes them straightforward to update and revise.

Adding a New Entity



Adding a New Causal Hypothesis



Challenge 3: Reasoning About Aging

We also want our models of aging to relate causal hypotheses to observable phenomena.

We would like the system to answer scientific questions like:

- What biological effects does the model predict?
- What observations/experiments does the model match?
- How does the model explain a given phenomenon?
- How would changes to the model alter its predictions?

Model complexity can make these difficult to do manually, but we can provide computational support for such reasoning.

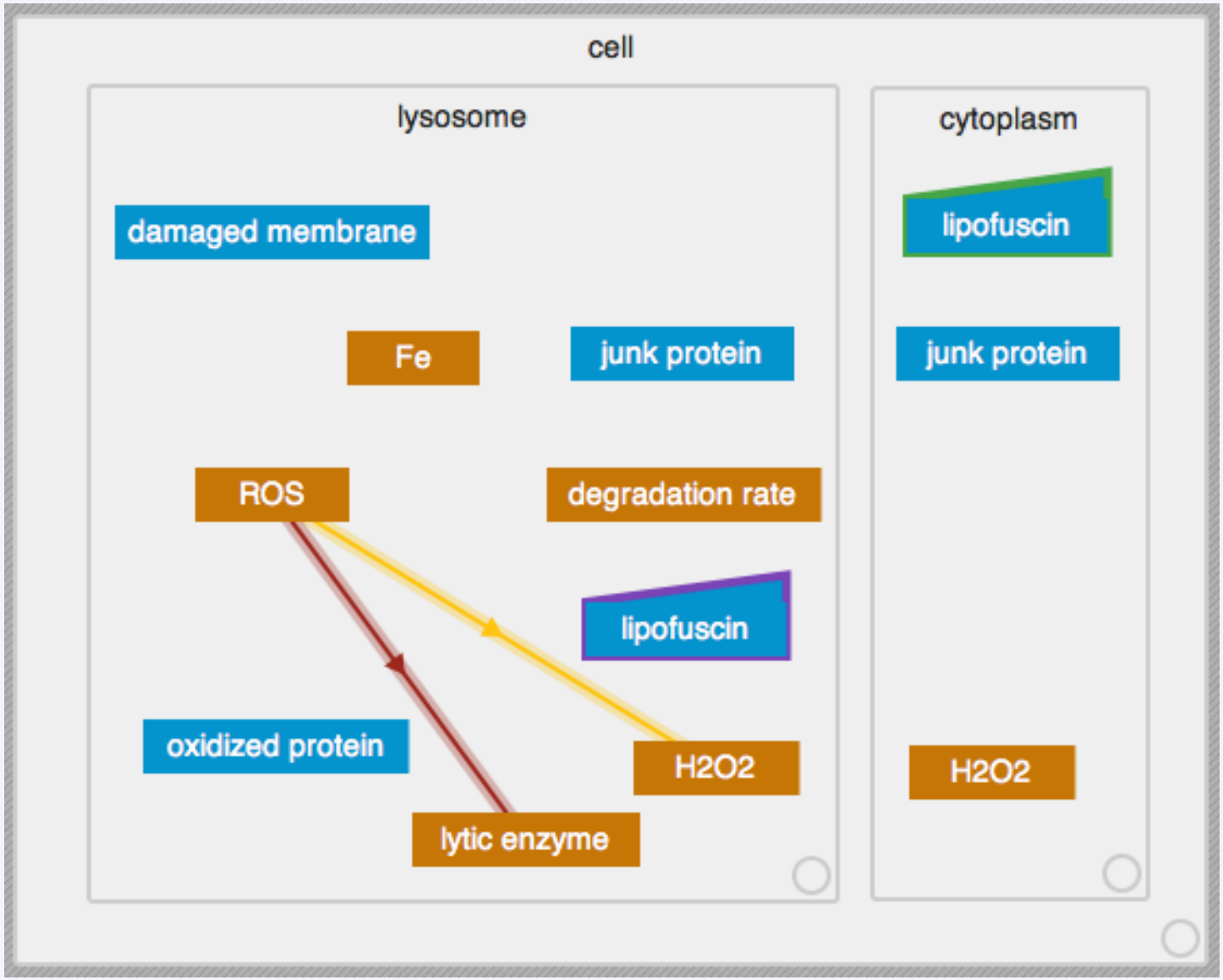
Simplifying Assumptions

Our approach to prediction makes five modeling assumptions:

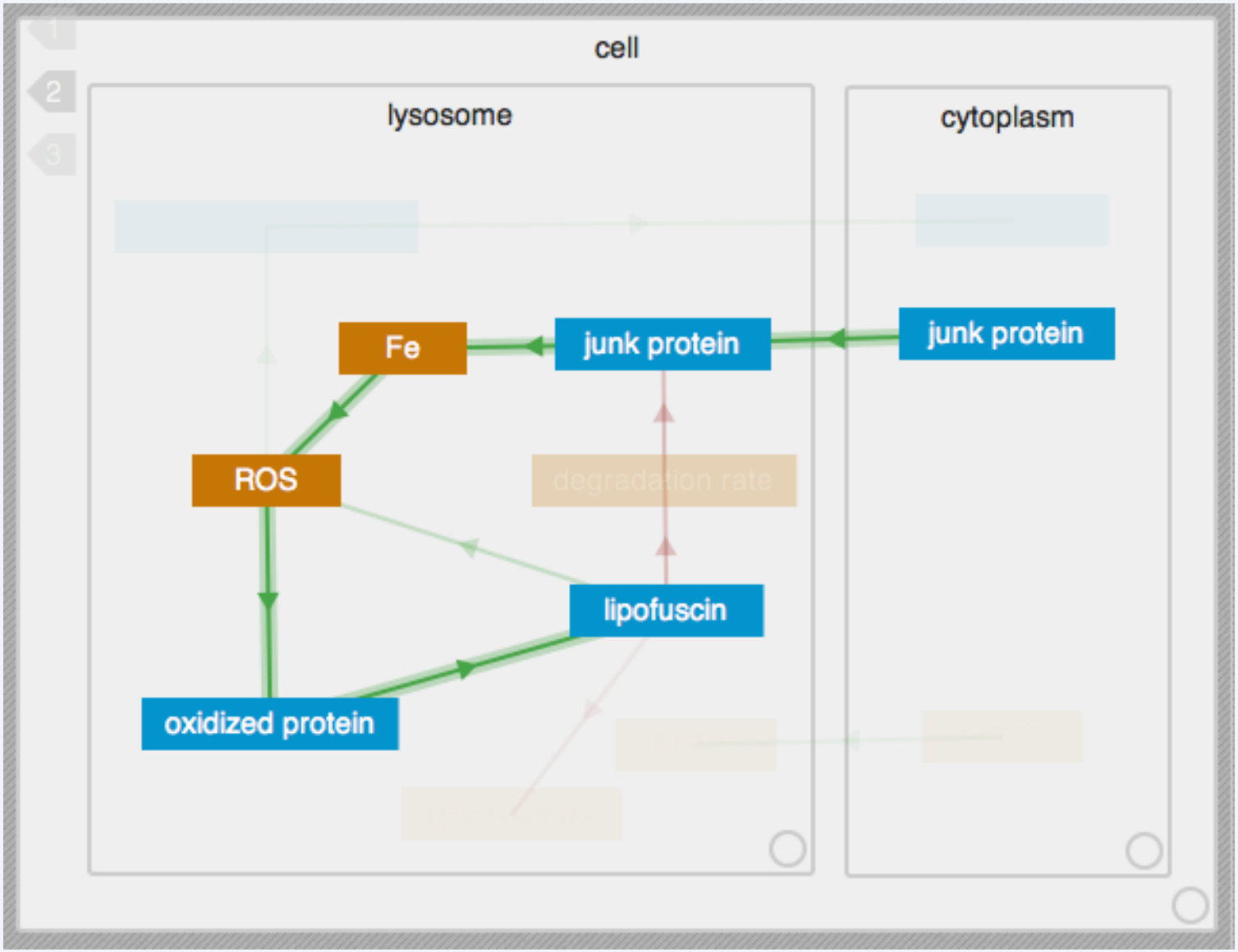
- All quantities are positive, including those describing rates
- The system being modeled exists in a single qualitative state
- If nothing influences a quantity, then it has a constant value
- Stable quantities accumulate effects on them over time
- Transient quantities do not accumulate effects over time

These assumptions seem appropriate for aging and age-related disease, but not for all biological problems.

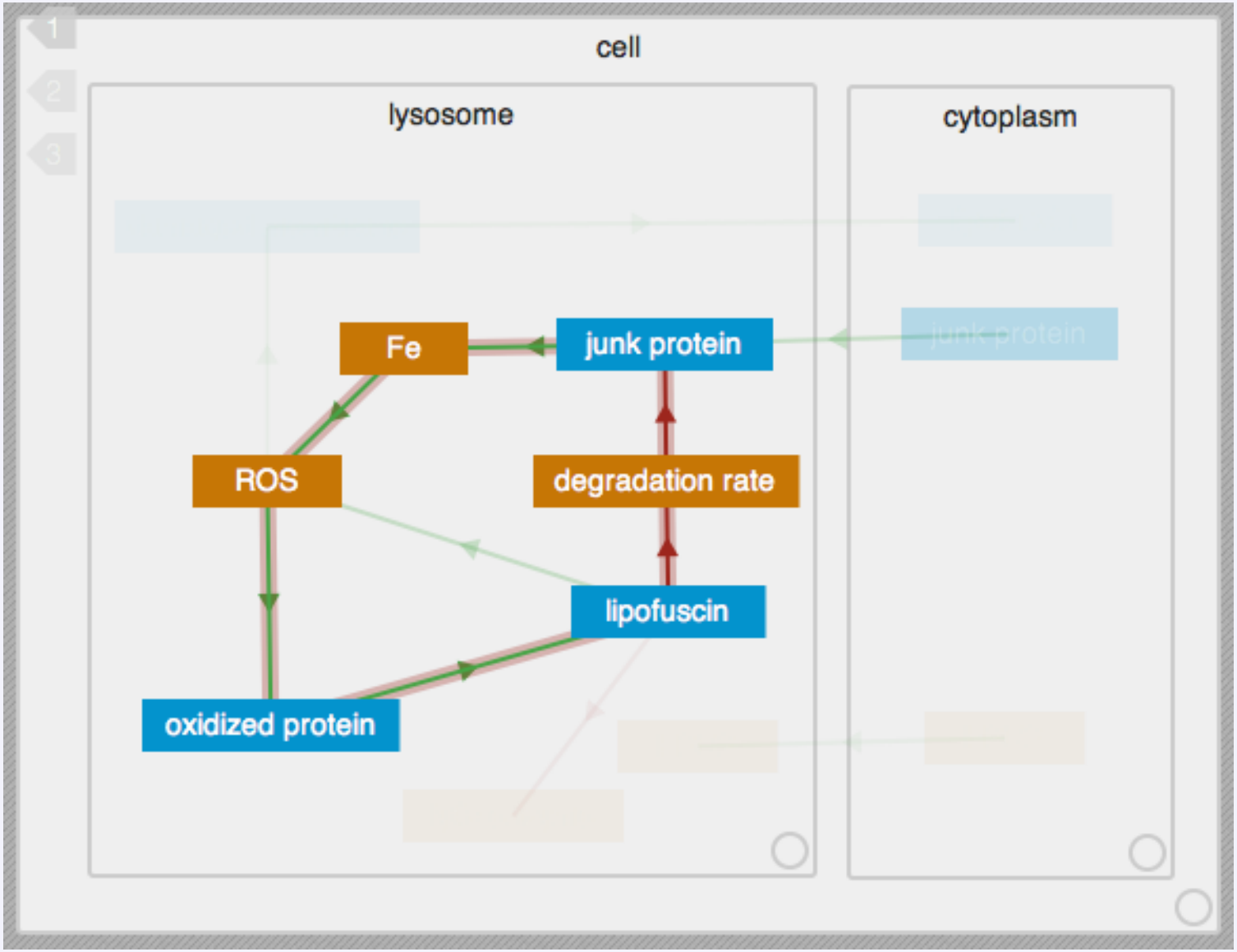
Visualizing Model Predictions



Visualizing an Explanatory Pathway



Visualizing an Alternative Explanation



Status of the Modeling Environment

Our modeling environment is still under development, but the system already lets users:

- Load, examine, and visualize a qualitative model of aging
- Extend, revise, and save the modified model
- Compare the model's predictions to empirical facts
- Examine the explanations that support each prediction

These provide the basic machinery to support models of aging.

We have initial versions the lysosomal, nuclear, mitochondrial, and extracellular portions of Furber's diagram.

Web Access to Models of Aging

The modeling environment and its initial models are available on the World Wide Web:

- The front end, which runs in Javascript on user's machine:
  - Handles both textual and graphical displays
  - Accepts user queries and changes to models
- The back end, which runs in Lisp on a Web server:
  - Stores model content and layout information
  - Generates predictions and associated explanations

The ability to access, utilize, and modify models on the Web opens the way to community-based model development.

See http://cll.stanford.edu/~ghunt/modeling11/

Directions for Future Research

Our effort is still in its early stages, and we need further work to:

- Provide additional content about mechanisms of aging
- Augment system to group causal influences into *processes*
- Support methods for *hiding content* in large, complex models
- Extend notation to include *contextual* and *arithmetic conditions*
- Evaluate the software's usability for biogerontologists
- Support *community-based development* of aging models

Such an extended system could aid SENS researchers by letting them codify knowledge and identify candidates for intervention.

Intellectual Debts

Our approach to computational biological aides incorporates ideas from many traditions:

- Formalizations of biological knowledge (e.g., EcoCyc, 2003)
- Qualitative reasoning and simulation (e.g., Forbus, 1984)
- Scientific simulation environments (e.g., STELLA, PROMETHEUS)
- Web-based tools for biological visualization (e.g., KEGG)
- Interactive for biological processing (e.g., BioBike, 2007)

However, it combines these ideas in novel ways to assist in the construction of system-level models of aging.

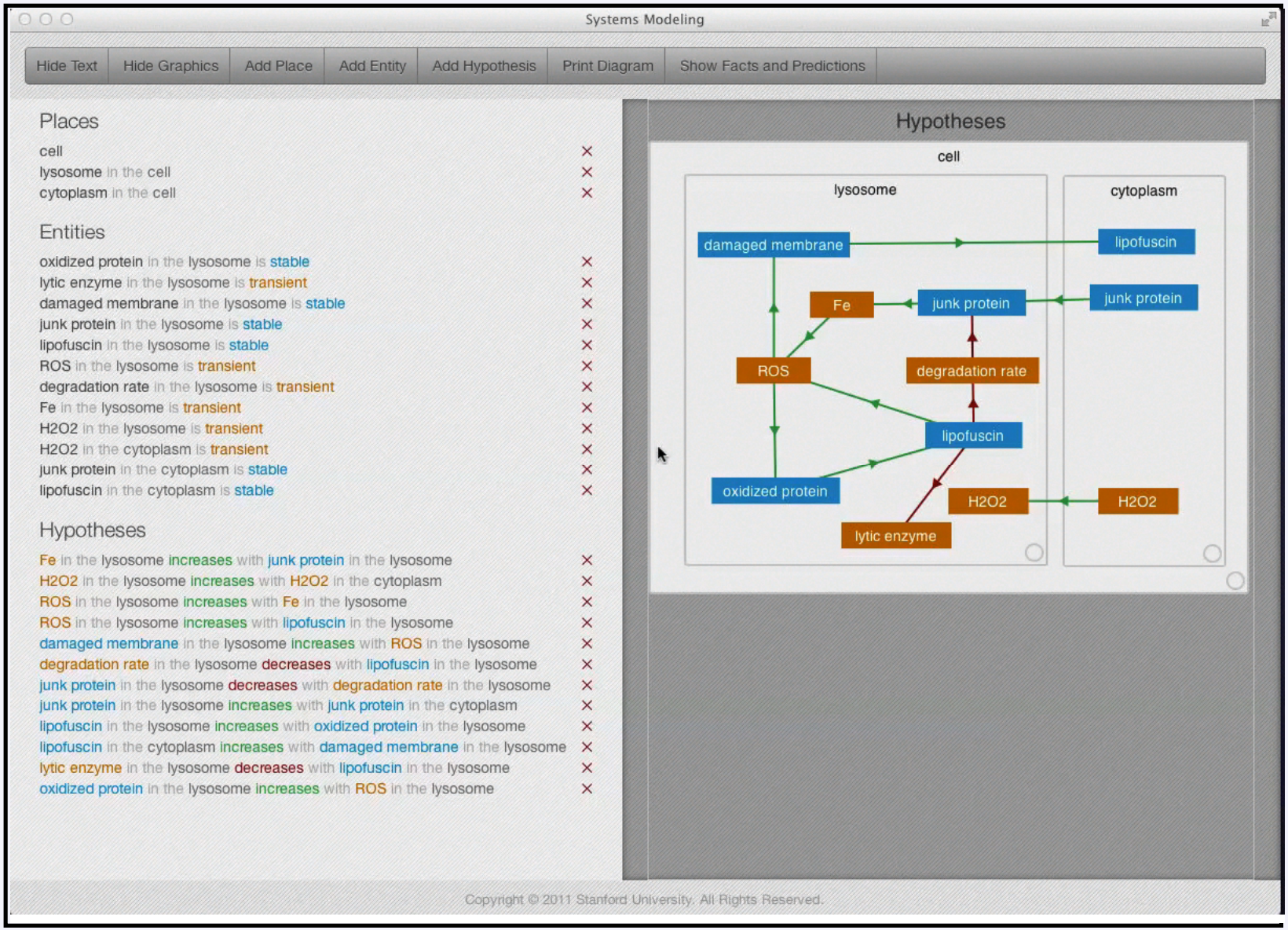
Key Contributions

In summary, we are developing an interactive environment for biological modeling that supports:

- Abstract yet *interpretable* models of aging that state causal relationships among biological quantities;
- *Interactive extension* of models to improve their coverage that requires little training and effort; and
- Reasoning over these models in ways that answer *generate predictions* and *explain* them.

We are still developing the system, but a more advanced version should offer many benefits to the SENS community.

Demonstration of Modeling Environment



End of Presentation