

Epithelial Modelling Platform: A Tool for Investigating Hypotheses through Discovery and Assembly of Computational Models of Epithelial Transport

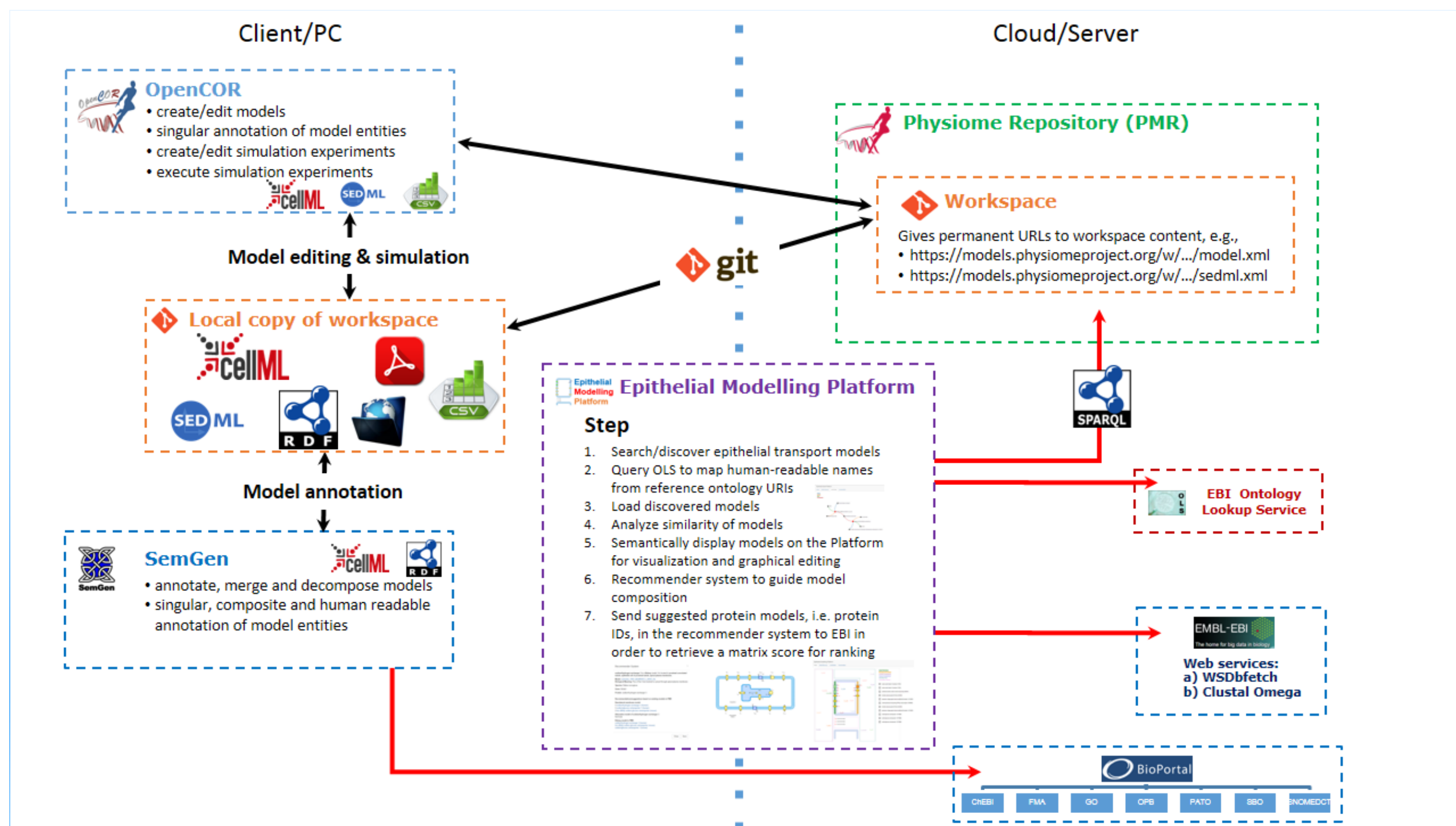
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Background

Scientists often leverage computational models of biological systems to investigate hypotheses which are difficult or prohibitively expensive to achieve experimentally. Such investigations are best achieved by utilizing suitable computational models, reusing existing validated models where possible and creating novel models consistently as needed. This requires tools which enable the discovery and exploration of existing models matched with assistance in constructing and testing new models. Enabling biomedical engineers to use such a tool by allowing them to describe their requirements in a manner familiar to them greatly improves the utility of the tool. This tool is not quite ready for pure biologists or clinicians to use.

We have developed a web-based tool, the Epithelial Modelling Platform, for discovery of relevant models and assemble them into a novel model customized for investigating their hypotheses. While our tool specifically focuses on epithelial transport, by utilizing relevant community standards and publicly accessible knowledge repositories, it is extensible to other areas of application. The platform abstracts underlying mathematics of the computational models and provides a visual environment which mimics biophysical phenomena of an epithelial cell.

Presented below is an overview of our knowledge management platform being developed and utilized in this work.

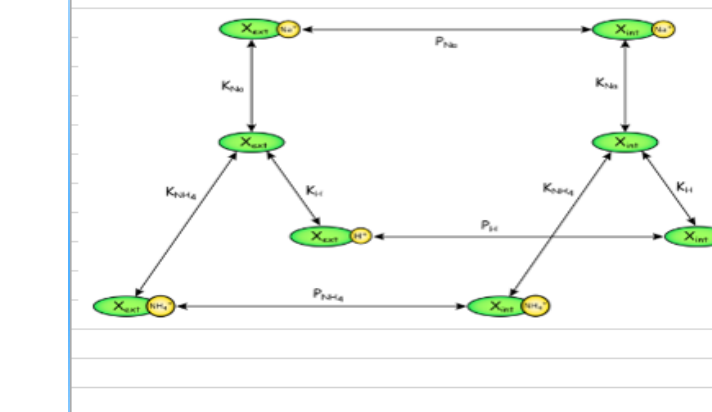


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Model Annotation

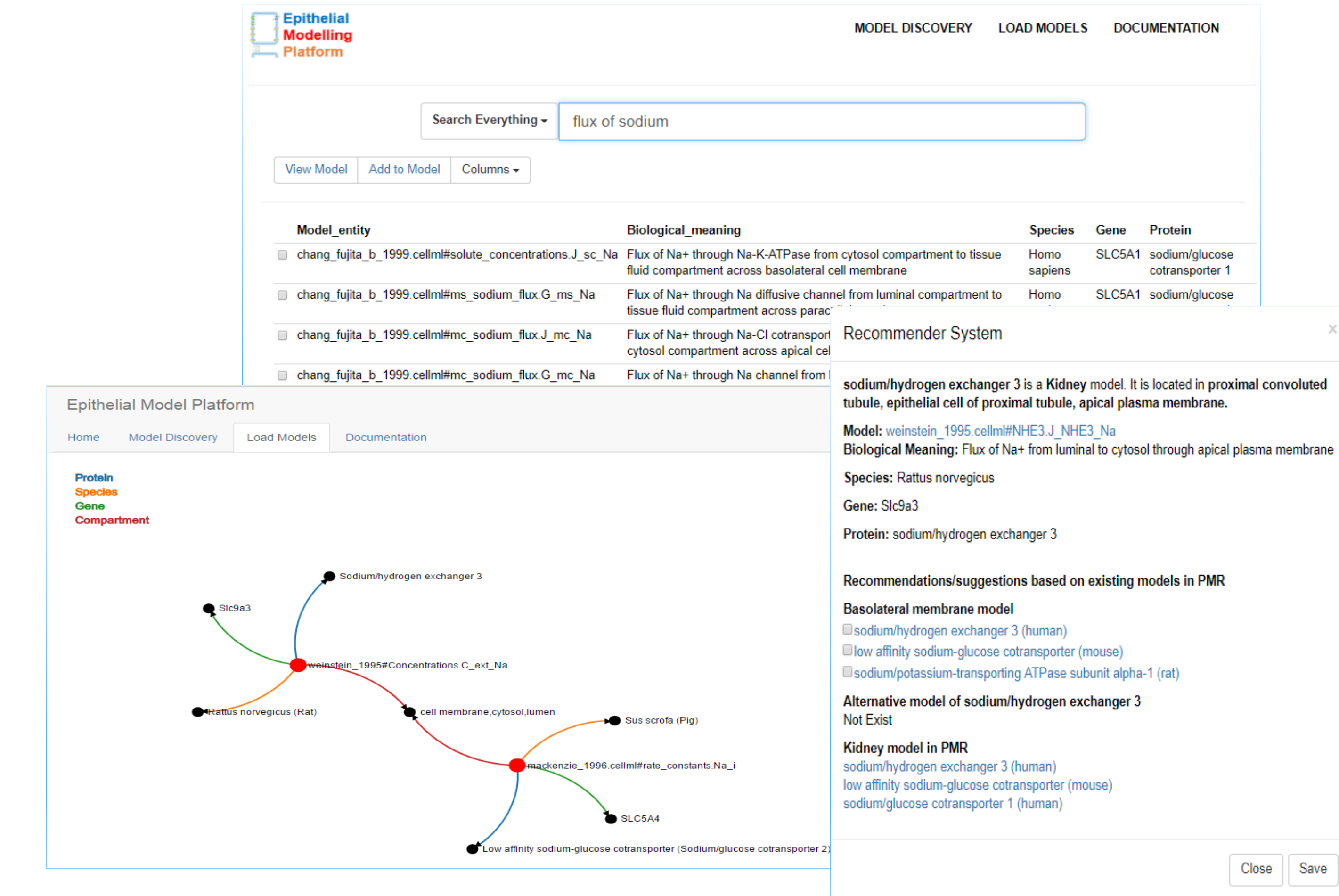
The figure below presents some of the information with which we have enriched a cohort of kidney models meta-data in the form of semantic annotations available in the Physiome Model Repository (PMR). In particular, we extracted each of the mathematical variables from the models and associated them with a biologically meaningful knowledge.

Model workspace	CellML document	model entity	description
Weinstein 1995	Weinstein_1995_NHE3.cellml	model:weinstein_1995_Na+H+ antiporter (NHE3)	A kinetically defined Na+H+ antiporter within a Mathematical Model of the Rat Proximal Tubule
semgen-annotation: /weinstein_1995-semgen.cellml			
	Variable URIs relative to above workspace URL	component:NHE3 / variable:J_NHE3_Na	Flux of Na+ transmembrane solute through Na+H+ antiporter from extracellular (lumen) to intracellular (cytosol) compartment
	Weinstein_1995_NHE3.cellml#035	component:NHE3 / variable:J_NHE3_H	Flux of H+ transmembrane solute through Na+H+ antiporter from intracellular (cytosol) to extracellular (lumen) compartment
	Weinstein_1995_NHE3.cellml#036	component:NHE3 / variable:J_NHE3_NH4	Flux of NH4+ transmembrane solute through Na+H+ antiporter from intracellular (cytosol) to extracellular (lumen) compartment
	Weinstein_1995_NHE3.cellml#037	component:NHE3 / variable:J_NHE3_Na_Max	Maximum flux of Na+ transmembrane solute through Na+H+ antiporter from extracellular (lumen) to intracellular (cytosol) compartment
	777 not in the CellML model 777	component:NHE3 / variable:J_NHE3_Na	Permeation velocity of H+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
	Weinstein_1995_NHE3.cellml#022	component:NHE3 / variable:J_NHE3_H	Permeation velocity of H+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
	Weinstein_1995_NHE3.cellml#023	component:NHE3 / variable:J_NHE3_H	Permeation velocity of H+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
	Weinstein_1995_NHE3.cellml#024	component:NHE3 / variable:alpha_ext_Na	Normalized concentration ratio of Na+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#028	component:NHE3 / variable:alpha_ext_Na	Normalized concentration ratio of Na+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#031	component:NHE3 / variable:alpha_ext_Na	Normalized concentration ratio of H+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#029	component:NHE3 / variable:beta_ext_H	Normalized concentration ratio of H+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#032	component:NHE3 / variable:beta_ext_H	Normalized concentration ratio of H+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#030	component:NHE3 / variable:gamma_ext_NH4	Normalized concentration ratio of NH4+ in the extracellular (lumen) compartment (property of a constitutive relation, dimensionless)
	Weinstein_1995_NHE3.cellml#033	component:NHE3 / variable:gamma_ext_NH4	Normalized concentration ratio of NH4+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)

Model Discovery

Utilizing these biological annotations, we are able to frame queries to PMR using biologically relevant terms. Our prototype web interface presents the search results obtained from querying the PMR services with the biological context; including models of similar biology and a recommender system.

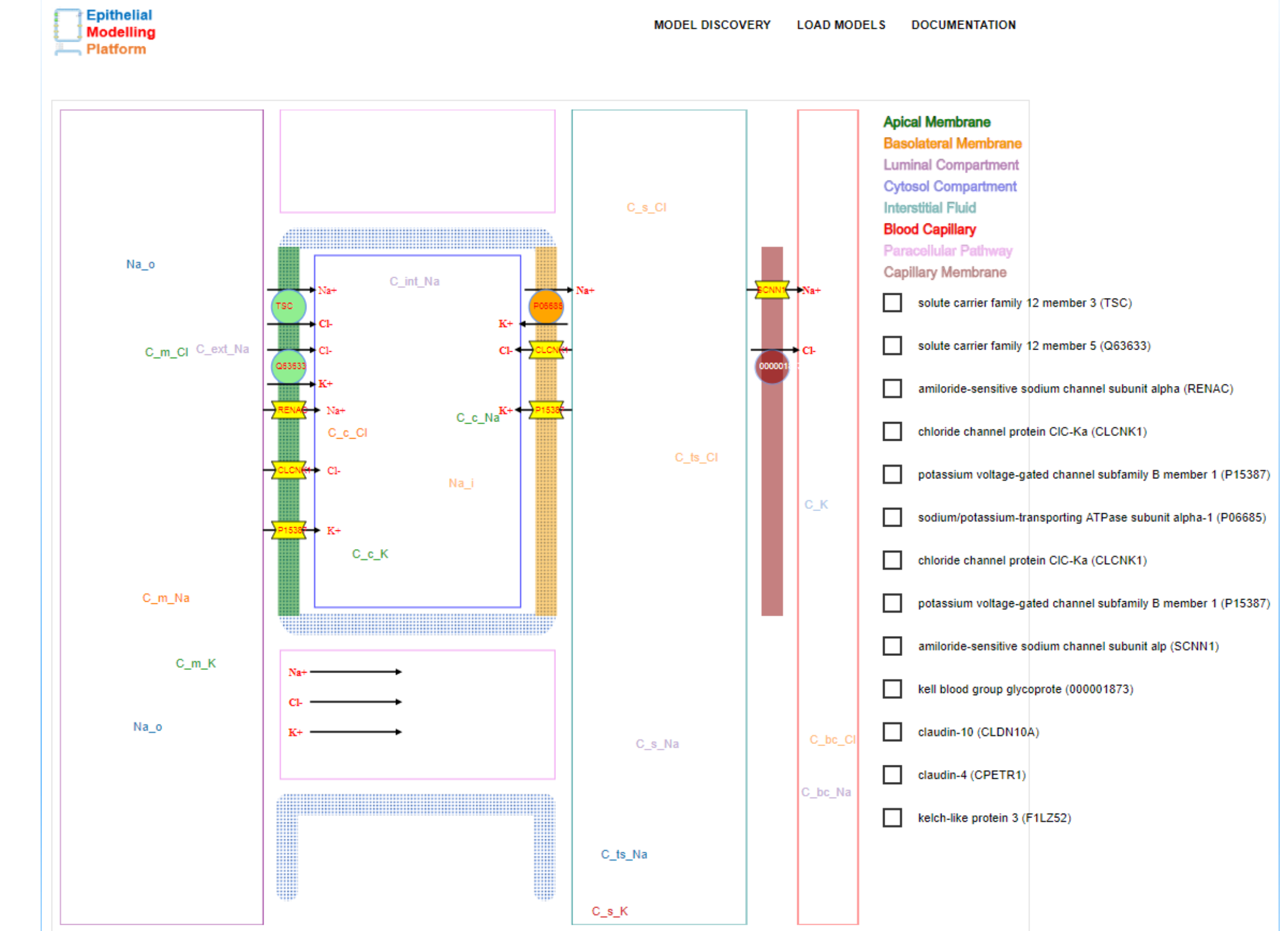
<https://github.com/dewancse/model-discovery-tool>



Modeling Platform

Presented on the top-right column is the web-based epithelial modelling platform to discover, explore and assemble models where users would be able to create and verify new epithelial models. This platform allows users to drag and drop models between apical and basolateral membranes. Solutes, e.g. sodium, potassium, will be floating in specific compartments. Modelers and clinicians can use this platform to build models to help investigate specific research questions and hypotheses.

<https://github.com/dewancse/epithelial-modelling-platform>

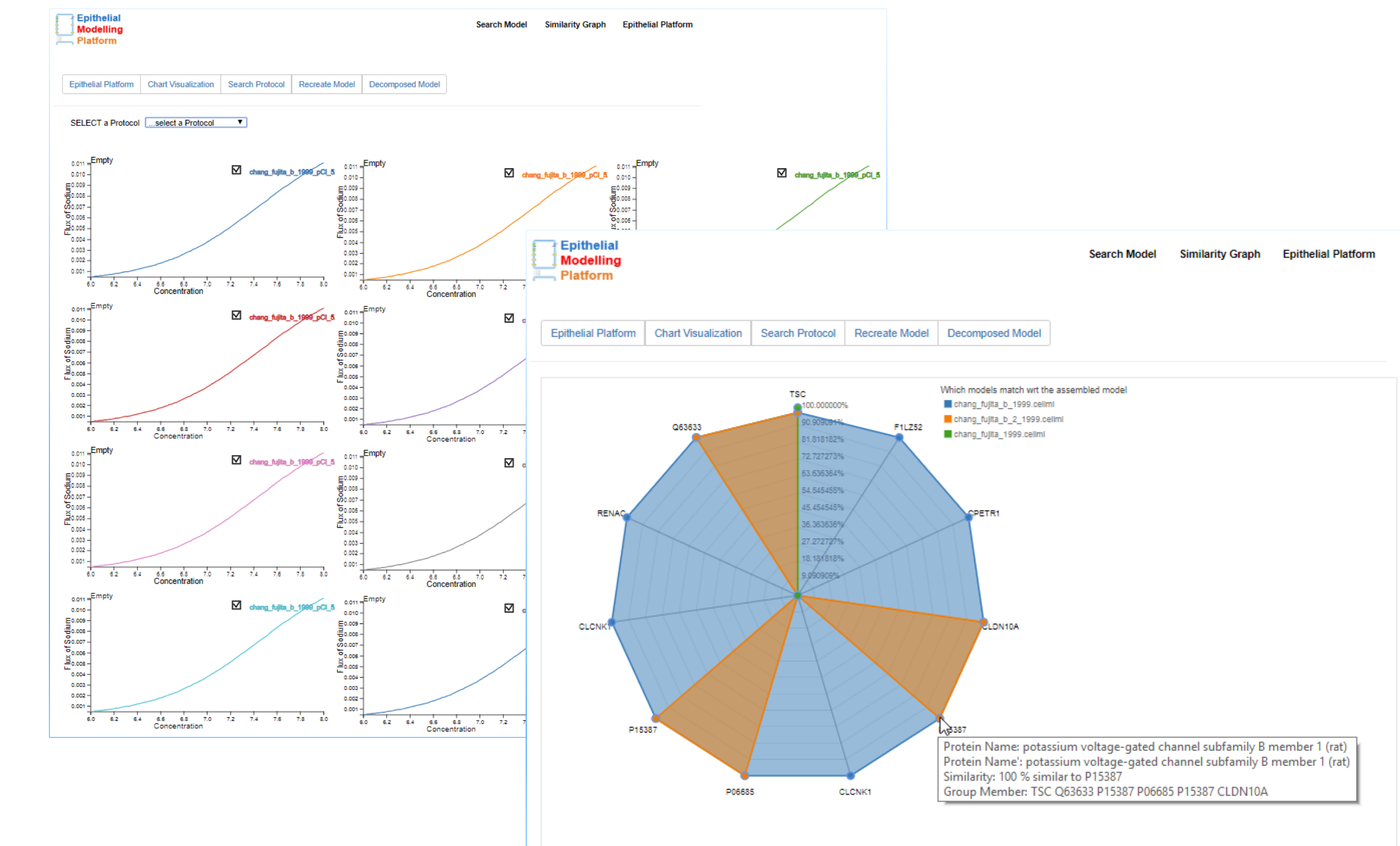


Model Composition

Once a user is satisfied with the model built and graphically edited using our platform, they will then be able to generate a novel model meeting their requirements. Utilizing the modularity and reuse capabilities of CellML, we are able to create a new CellML model by directly reusing and customizing the existing models discovered by the user.

Model Verification

For testing purpose, we have begun implementing a verification system which allows users to discover simulation experiments which match the features of the novel models users create. By executing these simulation experiments with the novel models and comparing to previous model predictions and/or experimental or clinical observations we are able to provide the user with some measure of verification that their model matches, or doesn't match, existing knowledge captured in the various repositories utilized.



Acknowledgements