

Discovery and Exploration of Computational Models of Epithelial Transport

Dewan Sarwar, Tommy Yu, Peter Hunter, David Nickerson
Auckland Bioengineering Institute (ABI), University of Auckland, New Zealand

Background

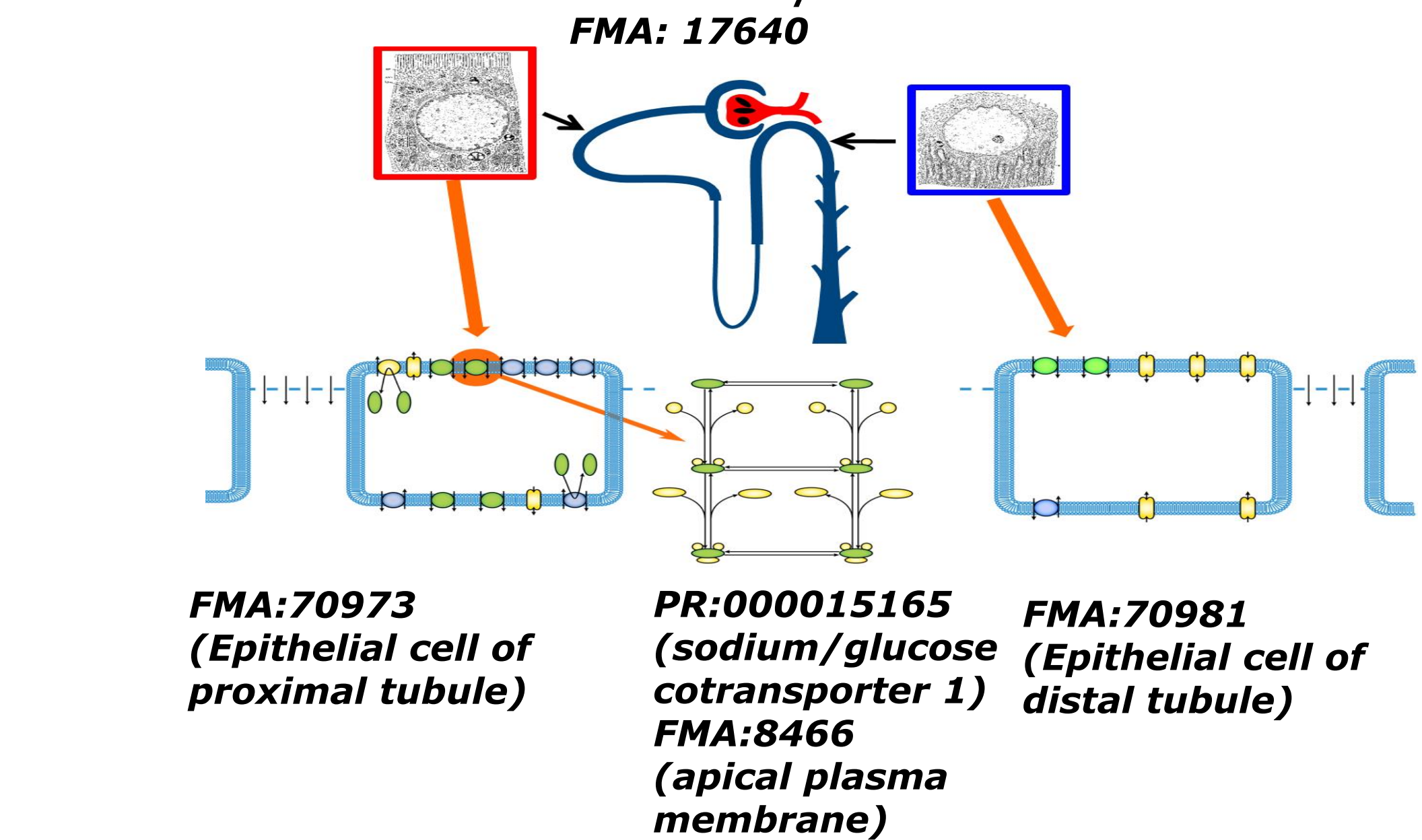
Comprehensive descriptions of mathematical models of biological systems captured in computable formats have the potential to significantly contribute to biomedical and clinical research. We achieve such computable descriptions with semantic annotation, using standard semantic web technologies to describe model entities using terms from common terminologies and ontologies. Such annotations capture the biological phenomena encapsulated by the model and aid in the discovery and comprehension of the model by independent scientists.

To annotate the typical range of biological phenomena seen in physiological models requires a diverse collection of reference ontologies and a repository to enable discovery and dissemination of such knowledge resources. To address this, computational tools and standards have evolved over the years such as CellML [1] to encode mathematical models of biological systems; SemGen [2] to annotate models; and the Physiome Model Repository (PMR) [3] to store these models and annotations to ensure the encoded knowledge is persistent, identifiable, discoverable, and sharable.

The discovery and reuse of data and models is a key component in achieving the goals of the IUPS Physiome Project [4] and the Virtual Physiological Human [5].

Kidney Model Annotation

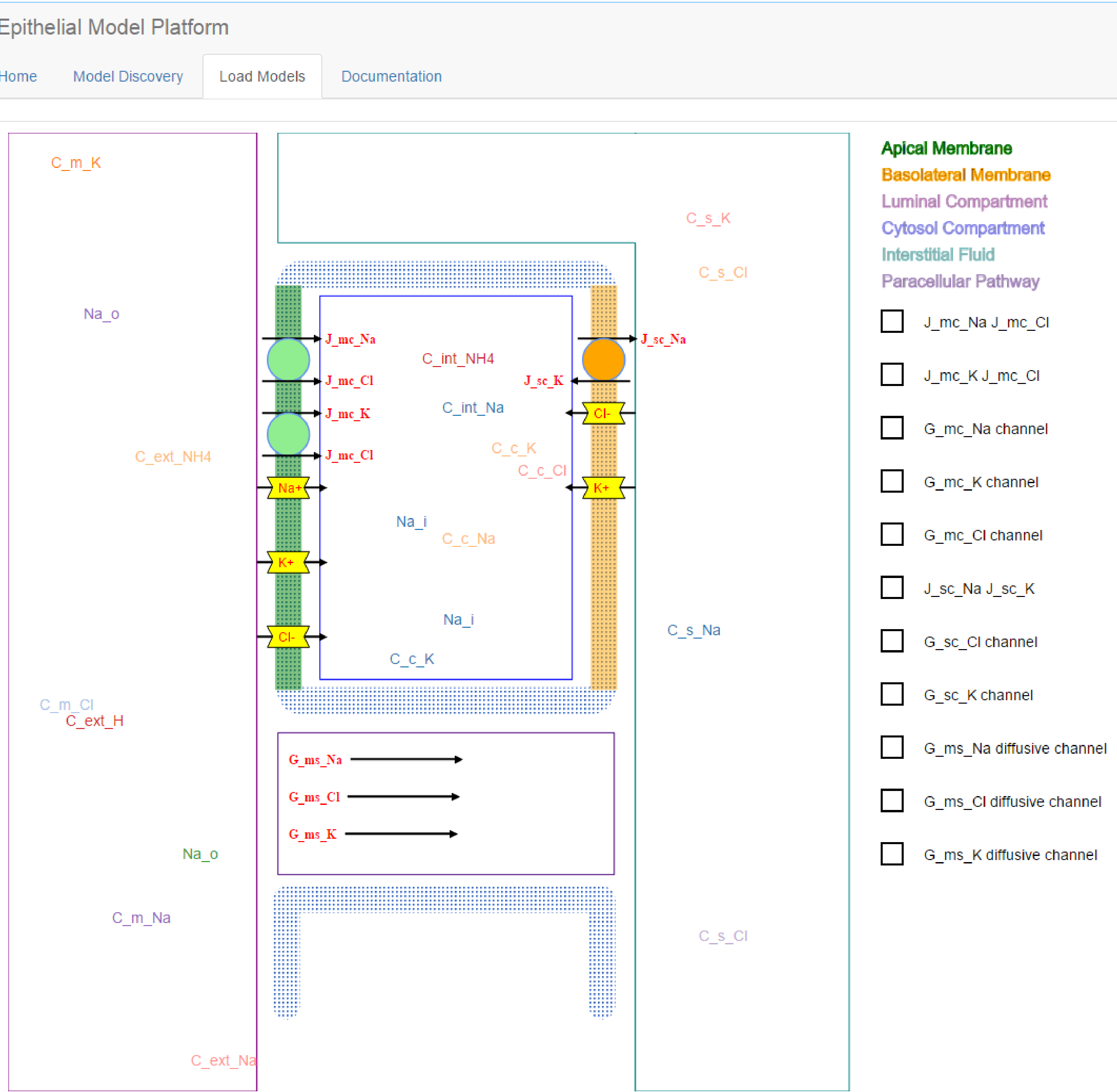
Presented below demonstrates some of the information with which we have extended existing descriptions of models relevant to the kidney.



Model workspace	CellML document	model entity	description
Weinstein 1995 http://models.physionet.org/record/weinstein_1995	Weinstein_1995_NHE3.cml	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		compartments	Three compartments: lumen, cytosol, cell membrane
		Background	Located in Proximal convoluted tubule, Apical plasma membrane, and Epithelial cell of proximal tubule
		Variable URIs relative to above workspace URL	Appears to be a key mediator of perfusion-absorption balance, i.e., the flow-dependent component of glomerulotubular balance
		component-NHE3 / variable-J_NHE3_Na	Recognized as a family of transport proteins, with the proximal tubule lumen membrane exchange identified as NHE3
		component-NHE3 / variable-J_NHE3_H	Gene has been cloned and sequenced (Tse et al. 1991) and the product identified immunocytochemically in the brush border membrane
		component-NHE3 / variable-J_NHE3_NH4	Flux of Na+ transmembrane solute through Na/H+ antiporter from extracellular (lumen) to intracellular (cytosol) compartment
		component-NHE3 / variable-J_NHE3_Na	Flux of NH4+ transmembrane solute through Na/H+ antiporter from intracellular (cytosol) to extracellular (lumen) compartment
		component-NHE3 / variable-J_NHE3_NH4	Maximum flux of Na+ transmembrane solute through Na/H+ antiporter from extracellular (lumen) to intracellular (cytosol) compartment
		component-NHE3 / variable-J_NHE3_Na	Permeation velocity of Na+ from extracellular (lumen) to intracellular (cytosol) compartment through the cell membrane
		component-NHE3 / variable-J_NHE3_H	Permeation velocity of H+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
		component-NHE3 / variable-J_NHE3_NH4	Permeation velocity of NH4+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
		component-NHE3 / variable-alpha_ext_Na	Normalized concentration ratio of Na+ in the extracellular (lumen) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-alpha_ext_H	Normalized concentration ratio of H+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-alpha_ext_NH4	Normalized concentration ratio of NH4+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-beta_ext_H	Normalized concentration ratio of H+ in the extracellular (lumen) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-beta_ext_Na	Normalized concentration ratio of Na+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-beta_ext_NH4	Normalized concentration ratio of NH4+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-gamma_ext_NH4	Normalized concentration ratio of NH4+ in the intracellular (cytosol) compartment (property of a constitutive relation, dimensionless)
		component-NHE3 / variable-rum_NHE3	Permeation velocity in the NHE3 protein model
		component-concentrations / variable-C_ext_Na	Concentration of Na+ in the extracellular (lumen) compartment
		component-concentrations / variable-C_ext_H	Concentration of H+ in the extracellular (lumen) compartment
		component-concentrations / variable-C_ext_NH4	Concentration of NH4+ in the extracellular (lumen) compartment
		component-concentrations / variable-C_int_Na	Concentration of Na+ in the intracellular (cytosol) compartment
		component-concentrations / variable-C_int_H	Concentration of H+ in the intracellular (cytosol) compartment
		component-concentrations / variable-C_int_NH4	Concentration of NH4+ in the intracellular (cytosol) compartment
		component-concentrations / variable-C_ext_Na	Concentration of Na+ in the extracellular (lumen) compartment
		component-concentrations / variable-C_ext_H	Concentration of H+ in the extracellular (lumen) compartment
		component-concentrations / variable-C_ext_NH4	Concentration of NH4+ in the extracellular (lumen) compartment
		component-concentrations / variable-time	Time (777 Time dimension 777)
		component-NHE3_Parameters / variable-XTXP_NHE3_Na	Permeation velocity constant of Na+ from extracellular (lumen) to intracellular (cytosol) compartment through the cell membrane
		component-NHE3_Parameters / variable-XTXP_NHE3_H	Permeation velocity constant of H+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
		component-NHE3_Parameters / variable-XTXP_NHE3_NH4	Permeation velocity constant of NH4+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
		component-NHE3_Parameters / variable-K_NHE3_Na	Equilibrium binding constant of Na+ in the NHE3 protein model
		component-NHE3_Parameters / variable-K_NHE3_H	Equilibrium binding constant of H+ in the NHE3 protein model
		component-NHE3_Parameters / variable-K_NHE3_NH4	Equilibrium binding constant of NH4+ in the NHE3 protein model

Epithelial Modelling Platform

Presented below is the web-based epithelial modelling platform to discover, explore and assemble models where users would be able to create and validate new epithelial models. This platform allows users to drag and drop models between apical and basolateral membranes. Solutes, e.g. sodium, potassium, encoded in CellML will be floating in specific compartments. Novice modellers could use this platform as a learning tool.



References

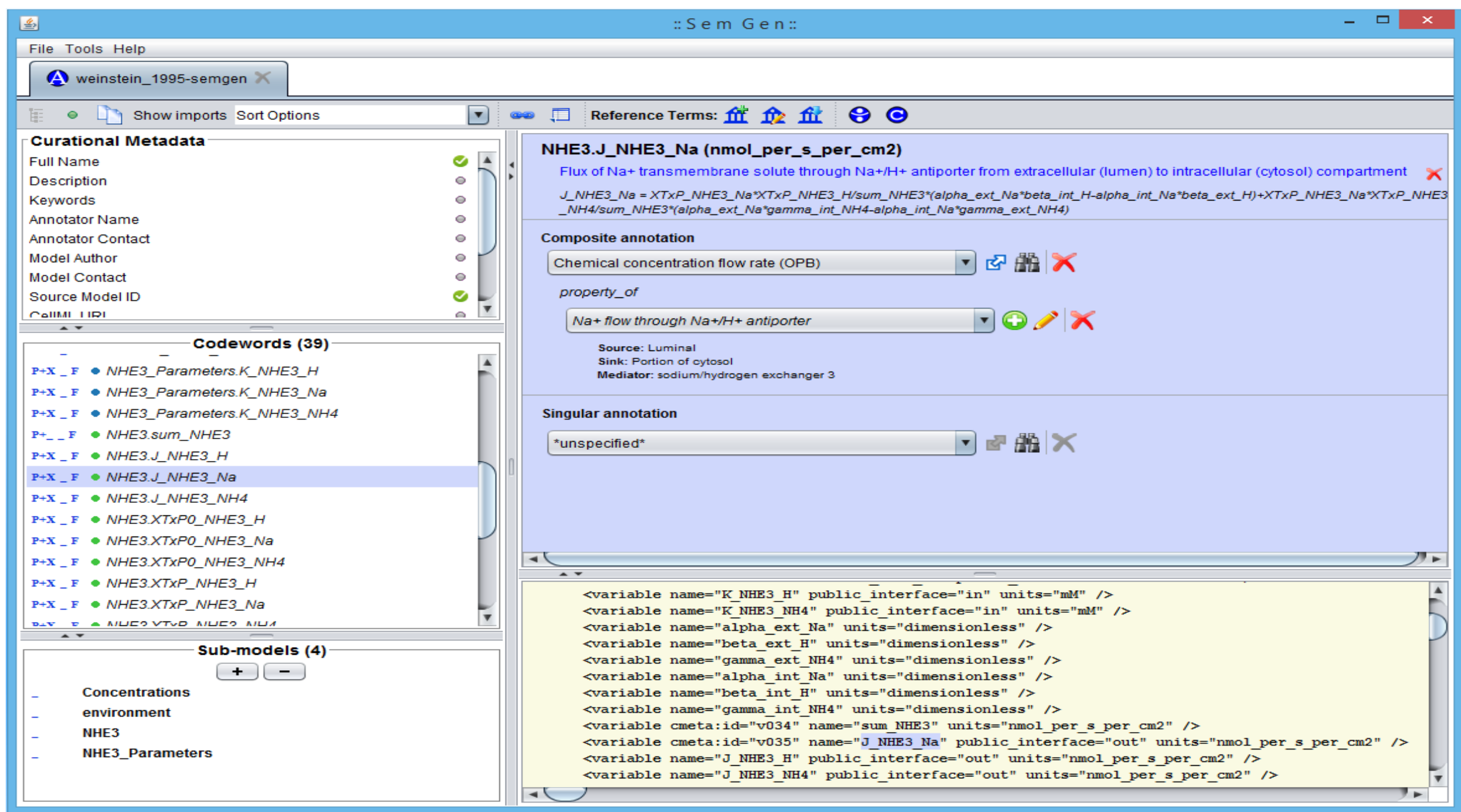
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This poster at



Semantic Annotation and Discovery

Screenshot of the SemGen annotator interface of the Weinstein model for flux of sodium from lumen to cytosol through sodium hydrogen exchanger 3 is shown below.



Our prototype web interface presents the search results obtained from querying the PMR services, overlapping models, and a recommender system.

Epithelial Model Platform

Home Model Discovery Load Models Documentation

flux of sodium

View Add to Model

Model entity	Biological meaning	Species	Gene	Protein
mackenzie_1996#NBC_current_J_Na	Flux of Na+ from luminal to cytosol and cytosol to luminal compartment through SGLT2 cotransporter	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
mackenzie_1996#phenomenological_constants_Na_o	Concentration of Na+ in the luminal compartment	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
mackenzie_1996#ion_concentrations_Na_o	Concentration of Na+ in the luminal compartment	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
mackenzie_1996#rate_constants_Na_o	Concentration of Na+ in the luminal compartment	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
mackenzie_1996#ion_concentrations_Na_i	Concentration of Na+ in the intracellular (cytosol) compartment	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
mackenzie_1996#rate_constants_Na_i	Concentration of Na+ in the intracellular (cytosol) compartment	Sus scrofa (Pig)	SLC5A4	Low affinity sodium-glucose cotransporter (Sodium/glucose cotransporter 2) or (SGLT2)
weinstein_1995#NHE3_J_NHE3_Na	Flux of Na+ from luminal antiporter			
weinstein_1995#Concentrations_C_ext_Na	Concentration of Na+ in the extracellular (lumen) compartment			
weinstein_1995#NHE3_C_ext_Na	Concentration of Na+ in the extracellular (lumen) compartment			
weinstein_1995#Concentrations_C_int_Na	Concentration of Na+ in the intracellular (cytosol) compartment			

Recommender System

Sodium/hydrogen exchanger 3 is a Kidney model. It is located in proximal convoluted tubule, epithelial cell of proximal tubule, apical plasma membrane.

Model: weinstein_1995.cellml

Biological Meaning: Flux of Na+ from luminal to cytosol through Na+/H+ antiporter and apical plasma membrane

Species: rattus norvegicus

Gene: SLC9a3

Protein: Sodium/hydrogen exchanger 3

Recommendations/suggestions based on existing models in PMR

Basolateral membrane model

- Low affinity sodium-glucose cotransporter (SGLT2)
- Warren model
- Sodium/hydrogen exchanger 3

Alternative model of Sodium/hydrogen exchanger 3

- sodium/hydrogen exchanger 3 (human)
- sodium/hydrogen exchanger 3 (mouse)
- sodium/hydrogen exchanger 3 (rabbit)

Kidney model in PMR

- Moss network model
- Thomas vasa recta model
- Low affinity sodium-glucose cotransporter (SGLT2)
- Sodium/glucose cotransporter 1 (SGLT1)
- Low affinity sodium-glucose cotransporter (SGLT2)
- Thiazide-sensitive Na-Cl cotransporter (TSC)
- Warren model
- Chang Fujita numerical model

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