

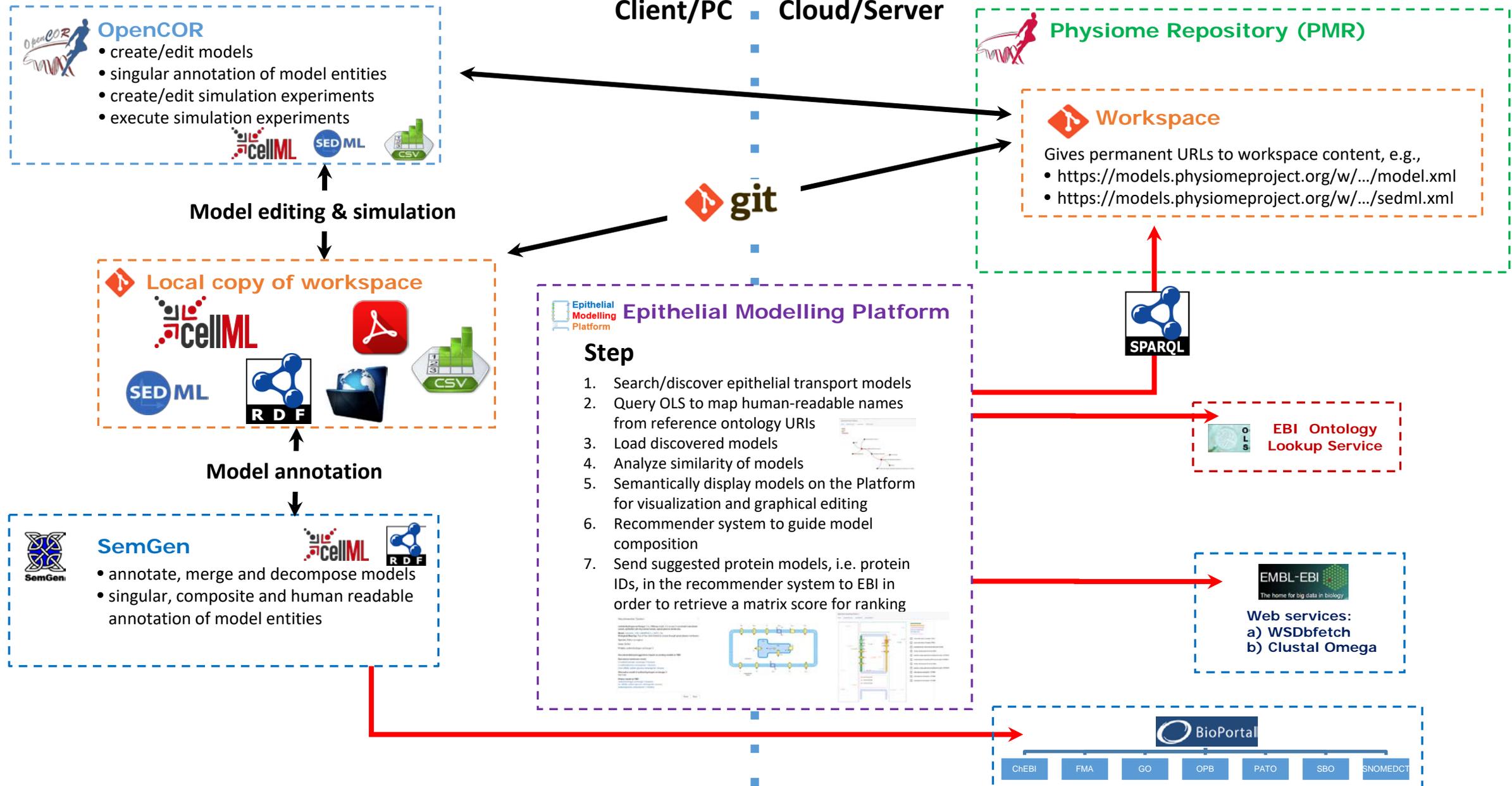
# Semantics-based model discovery (and assembly) for renal transport

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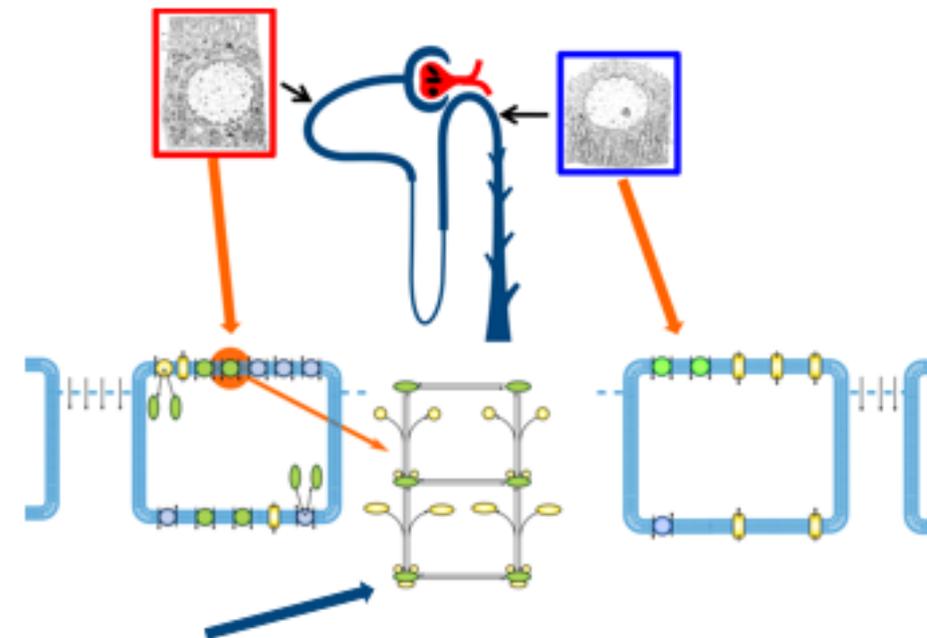
# Motivation

- Given a collection of mechanisms and/or observations, e.g.,
  - electrophysiology measurements
  - imaging data
  - diseases (SNOMED-CT, ICD, Human Disease Ontology...)
  - drug actions
  - clinical observations (openEHR archetypes)
  - etc...
- can we extract a model from the Physiome Model Repository suitable for testing clinical or experimental hypotheses?



# Kidney Model Annotation

- Comprehensive descriptions of the underlying anatomical connectivity across multiple renal scales are being mapped to the biologically-meaningful variables in each of the model.
- UniProt identifiers, FMA terms, variables biological meaning, species used, etc.



## Renal SGLT1 model

**Protein:** Sodium/glucose cotransporter 1 (SGLT1)

**UniProt ID:** P11170

**Gene:** SLC5A1

**Species:** Oryctolagus cuniculus (Rabbit)

**Located in:**

- Proximal convoluted tubule (FMA:17693)
- Apical plasma membrane (FMA:84666)
- Epithelial cell of proximal tubule (FMA:70973)
- Proximal straight tubule (FMA:17716)

A	B	C	
Model workspace	CellML document	model entity	description
<b>Weinstein 1995</b>			
<a href="https://models.physioimeproject.org/w/andre/weinstein_1995">https://models.physioimeproject.org/w/andre/weinstein_1995</a>	Weinstein_1995_NHE3.cellml	model=weinstein_1995	<a href="#">A kinetically defined Na+/H+ Antiporter within a Mathematical</a>
<a href="#">semgen-annotation / weinstein_1995-semgen.cellml</a>		Na+/H+ antiporter (NHE3)	NHE3 exchanger/antiporter; NHE3 is a protein - UniProt ID: P11170
		Compartments	Three compartments: lumen, cytosol, cell membrane
		Background	Located in Proximal convoluted tubule, Apical plasma membr.
			Appears to be a key mediator of perfusion-absorption balance
			Recognized as a family of transport proteins, with the proxims
			Gene has been cloned and sequenced (Tse et al, 1991) and tl
	Variable URIs relative to above workspace URL		
	Weinstein_1995_NHE3.cellml#035	component=NHE3 / variable=J_NHE3_Na	Flux of Na+ transmembrane solute through Na+/H+ antiporter
	Weinstein_1995_NHE3.cellml#036	component=NHE3 / variable=J_NHE3_H	Flux of H+ transmembrane solute through Na+/H+ antiporter f
	Weinstein_1995_NHE3.cellml#037	component=NHE3 / variable=J_NHE3_NH4	Flux of NH4+ transmembrane solute through Na+/NH4+ antip
	??? not in the CellML model ???	component=NHE3 / variable=J_NHE3_Na_Max	Maximum Flux of Na+ transmembrane solute through Na+/H+
	Weinstein_1995_NHE3.cellml#022	component=NHE3 / variable=XTxP_NHE3_Na	Permeation velocity of Na+ from extracellular (lumen) to intrac
	Weinstein_1995_NHE3.cellml#023	component=NHE3 / variable=XTxP_NHE3_H	Permeation velocity of H+ from intracellular (cytosol) to extrac
	Weinstein_1995_NHE3.cellml#024	component=NHE3 / variable=XTxP_NHE3_NH4	Permeation velocity of NH4+ from intracellular (cytosol) to ext
	Weinstein_1995_NHE3.cellml#028	component=NHE3 / variable=alpha_ext_Na	Normalized concentration ratio of Na+ in the extracellular (lume
	Weinstein_1995_NHE3.cellml#031	component=NHE3 / variable=alpha_int_Na	Normalized concentration ratio of Na+ in the intracellular (cyt
	Weinstein_1995_NHE3.cellml#029	component=NHE3 / variable=beta_ext_H	Normalized concentration ratio of H+ in the extracellular (lumen
	Weinstein_1995_NHE3.cellml#032	component=NHE3 / variable=beta_int_H	Normalized concentration ratio of H+ in the intracellular (cytos
	Weinstein_1995_NHE3.cellml#030	component=NHE3 / variable=gamma_ext_NH4	Normalized concentration ratio of NH4+ in the extracellular (lun
	Weinstein_1995_NHE3.cellml#033	component=NHE3 / variable=gamma_int_NH4	Normalized concentration ratio of NH4+ in the intracellular (cy
	Weinstein_1995_NHE3.cellml#034	component=NHE3 / variable=sum_NHE3	Permeation velocity in the NHE3 protein model
	Weinstein_1995_NHE3.cellml#001	component=concentrations / variable=C_ext_Na	Concentration of Na+ in the extracellular (lumen) compartmen
	Weinstein_1995_NHE3.cellml#002	component=concentrations / variable=C_ext_H	Concentration of H+ in the extracellular (lumen) compartment
	Weinstein_1995_NHE3.cellml#003	component=concentrations / variable=C_ext_NH4	Concentration of NH4+ in the extracellular (lumen) compartme
	Weinstein_1995_NHE3.cellml#004	component=concentrations / variable=C_int_Na	Concentration of Na+ in the intracellular (cytosol) compartme
	Weinstein_1995_NHE3.cellml#005	component=concentrations / variable=C_int_H	Concentration of H+ in the intracellular (cytosol) compartment
	Weinstein_1995_NHE3.cellml#006	component=concentrations / variable=C_int_NH4	Concentration of NH4+ in the intracellular (cytosol) compartm
	Weinstein_1995_NHE3.cellml#007	component=concentrations / variable=time	Time (??? Time dimension ???)
	Weinstein_1995_NHE3.cellml#008	component=NHE3_Parameters / variable=XTxP0_NHE3_Na	Permeation velocity constant of Na+ from extracellular (lumen
	Weinstein_1995_NHE3.cellml#009	component=NHE3_Parameters / variable=XTxP0_NHE3_H	Permeation velocity constant of H+ from intracellular (cytosol)
	Weinstein_1995_NHE3.cellml#010	component=NHE3_Parameters / variable=XTxP0_NHE3_NH4	Permeation velocity constant of NH4+ from intracellular (cytosol) to extracellular (lumen) compartment through the cell membrane
	Weinstein_1995_NHE3.cellml#011	component=NHE3_Parameters / variable=K_NHE3_Na	Equilibrium binding constant of Na+ in the NHE3 protein model
	Weinstein_1995_NHE3.cellml#012	component=NHE3_Parameters / variable=K_NHE3_H	Equilibrium binding constant of H+ in the NHE3 protein model
	Weinstein_1995_NHE3.cellml#013	component=NHE3_Parameters / variable=K_NHE3_NH4	Equilibrium binding constant of NH4+ in the NHE3 protein model

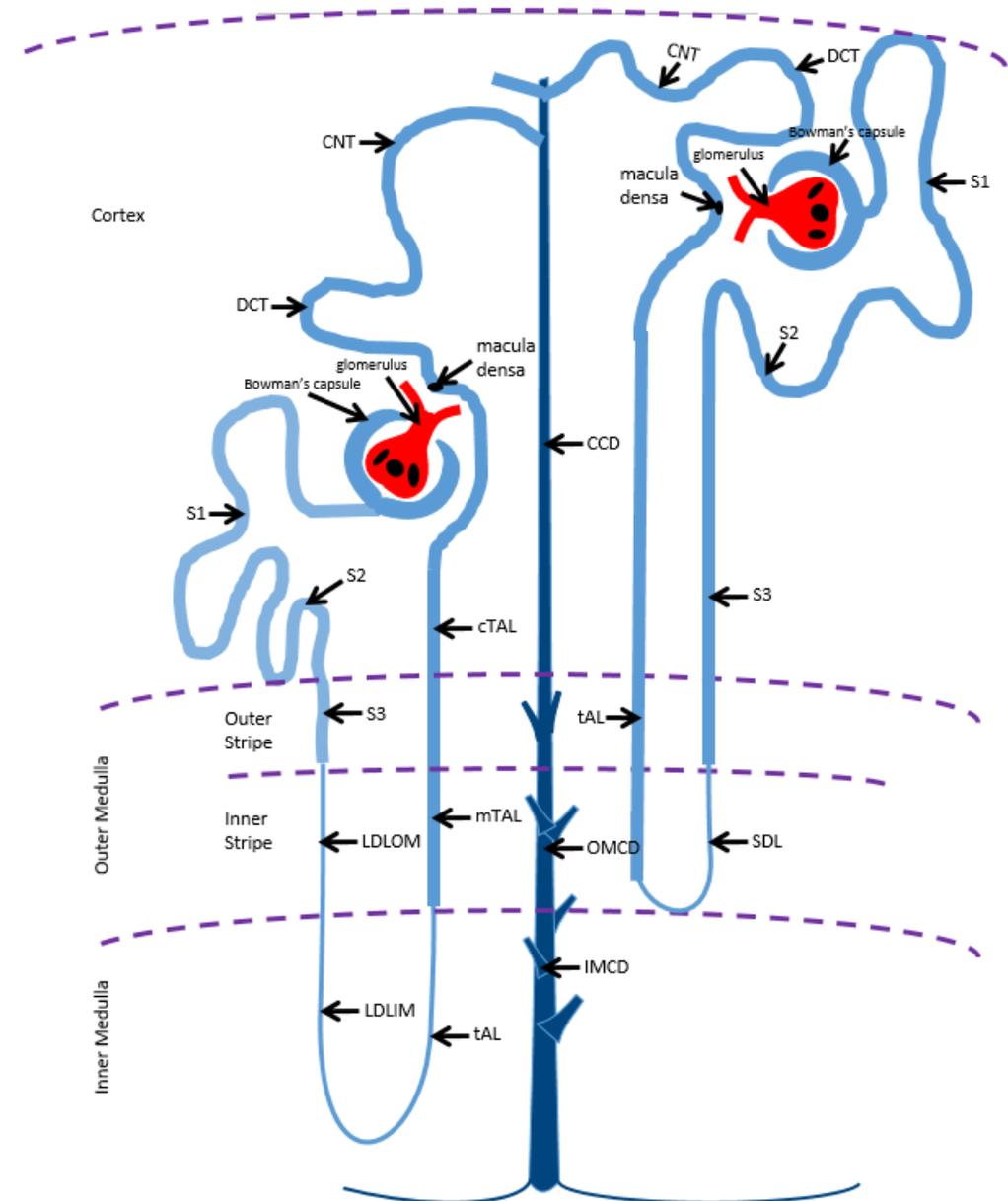
# Example source of knowledge



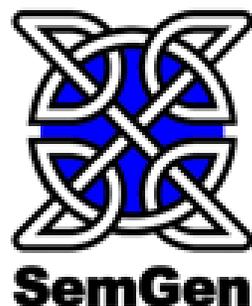
## Epithelial Systems Biology Laboratory (ESBL)

### RNA-seq Identification of Transcripts Expressed along the Renal Tubule

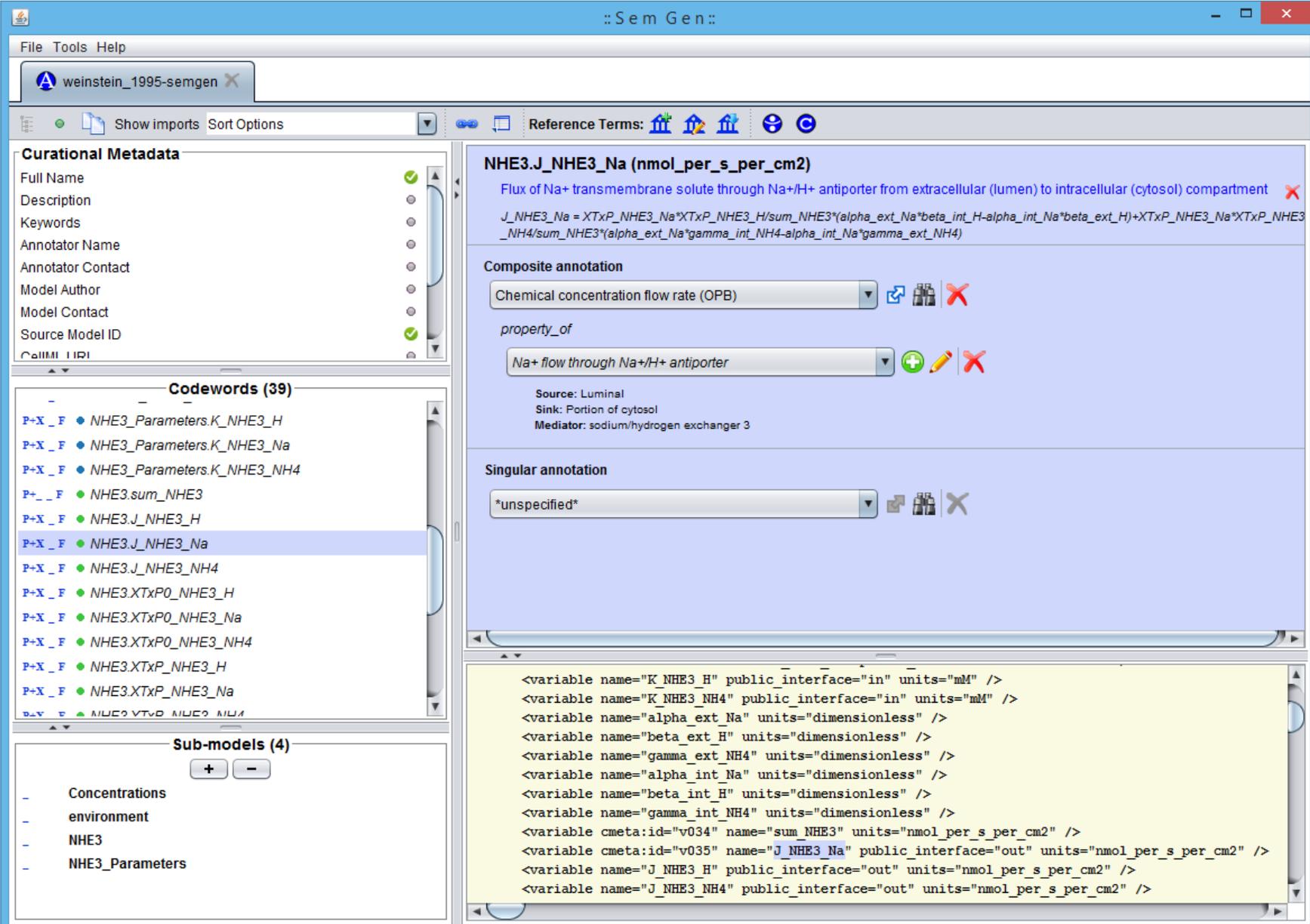
- **NHE3**: S1, S2, SDL, LDLOM, tAL, mTAL, cTAL, DCT
- **SGLT1**: cTAL
- **TSC**: S1, S2, cTAL, DCT
- **SGLT2**: Not exist



# SemGen Annotator Interface



Illustrative example of SemGen annotator interface of the Weinstein model where codewords identifies CellML variables and annotates flux of sodium from luminal compartment to cytosol compartment through sodium/hydrogen exchanger 3.



The screenshot shows the SemGen software interface with the following components:

- File Tools Help** menu bar.
- Tab: `weinstein_1995-semgen`
- Buttons: `Show imports`, `Sort Options`, `Reference Terms` (with icons for adding, deleting, and refreshing).
- Curational Metadata** panel (left):
  - Full Name: ✓
  - Description: ○
  - Keywords: ○
  - Annotator Name: ○
  - Annotator Contact: ○
  - Model Author: ○
  - Model Contact: ○
  - Source Model ID: ✓
  - CellML URI: ○
- Codewords (39)** panel (middle):
  - List of codewords including `NHE3.Parameters.K_NHE3_H`, `NHE3.Parameters.K_NHE3_Na`, `NHE3.Parameters.K_NHE3_NH4`, `NHE3.sum_NHE3`, `NHE3.J_NHE3_H`, `NHE3.J_NHE3_Na`, `NHE3.J_NHE3_NH4`, `NHE3.XTxP0_NHE3_H`, `NHE3.XTxP0_NHE3_Na`, `NHE3.XTxP0_NHE3_NH4`, `NHE3.XTxP_NHE3_H`, `NHE3.XTxP_NHE3_Na`, and `NHE3.XTxP_NHE3_NH4`.
- Sub-models (4)** panel (bottom left):
  - Concentrations
  - environment
  - NHE3
  - NHE3\_Parameters
- Main Annotation Area** (right):
  - NHE3.J\_NHE3\_Na (nmol\_per\_s\_per\_cm2)**: Flux of Na<sup>+</sup> transmembrane solute through Na<sup>+</sup>/H<sup>+</sup> antiporter from extracellular (lumen) to intracellular (cytosol) compartment. Includes a mathematical formula.
  - Composite annotation**:
    - Dropdown: `Chemical concentration flow rate (OPB)`
    - property\_of* dropdown: `Na+ flow through Na+/H+ antiporter`
    - Source: Luminal; Sink: Portion of cytosol; Mediator: sodium/hydrogen exchanger 3.
  - Singular annotation**:
    - Dropdown: `*unspecified*`
- Code Editor** (bottom right):

```
<variable name="K_NHE3_H" public_interface="in" units="mM" />
<variable name="K_NHE3_NH4" public_interface="in" units="mM" />
<variable name="alpha_ext_Na" units="dimensionless" />
<variable name="beta_ext_H" units="dimensionless" />
<variable name="gamma_ext_NH4" units="dimensionless" />
<variable name="alpha_int_Na" units="dimensionless" />
<variable name="beta_int_H" units="dimensionless" />
<variable name="gamma_int_NH4" units="dimensionless" />
<variable cmeta:id="v034" name="sum_NHE3" units="nmol_per_s_per_cm2" />
<variable cmeta:id="v035" name="J_NHE3_Na" public_interface="out" units="nmol_per_s_per_cm2" />
<variable name="J_NHE3_H" public_interface="out" units="nmol_per_s_per_cm2" />
<variable name="J_NHE3_NH4" public_interface="out" units="nmol_per_s_per_cm2" />
```

# Epithelial Modelling Platform



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Search Everything ▾

Model_entity	Biological_meaning	Species	Gene	Protein
<input type="checkbox"/> chang_fujita_b_1999.cellml#solute_concentrations.J_sc_Na	Flux of Na <sup>+</sup> through Na-K-ATPase from cytosol compartment to tissue fluid compartment across basolateral cell membrane	Homo sapiens	SLC5A1	sodium/glucose cotransporter 1
<input type="checkbox"/> chang_fujita_b_1999.cellml#ms_sodium_flux.G_ms_Na	Flux of Na <sup>+</sup> through Na diffusive channel from luminal compartment to tissue fluid compartment across paracellular pathway	Homo sapiens	SLC5A1	sodium/glucose cotransporter 1
<input type="checkbox"/> chang_fujita_b_1999.cellml#mc_sodium_flux.J_mc_Na	Flux of Na <sup>+</sup> through Na-Cl cotransporter from luminal compartment to cytosol compartment across apical cell membrane	Homo sapiens	SLC5A1	sodium/glucose cotransporter 1
<input type="checkbox"/> chang_fujita_b_1999.cellml#mc_sodium_flux.G_mc_Na	Flux of Na <sup>+</sup> through Na channel from luminal compartment to cytosol compartment across apical cell membrane	Homo sapiens	SLC5A1	sodium/glucose cotransporter 1
<input type="checkbox"/> mackenzie_1996.cellml#NBC_current.J_Na	Flux of Na <sup>+</sup> from luminal to cytosol and cytosol to luminal compartment through apical plasma membrane	Mus musculus	Slc5a4a	low affinity sodium-glucose cotransporter
<input type="checkbox"/> weinstein_1995.cellml#NHE3.J_NHE3_Na	Flux of Na <sup>+</sup> from luminal to cytosol through apical plasma membrane	Rattus norvegicus	Slc9a3	sodium/hydrogen exchanger 3

# Epithelial Modelling Platform



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View Delete visualization Epithelial Platform Columns ▾

<input type="checkbox"/> Model_entity	Protein	Species	Gene	Compartment	Located_in
<input type="checkbox"/> chang_fujita_b_1999.cellml#solute_concentrations.J_mc_Na	sodium/glucose cotransporter 1	Homo sapiens	SLC5A1	Apical plasma membrane, Basolateral plasma membrane, Portion of cytosol, Portion of tissue fluid, Luminal	Distal convoluted tubule
<input type="checkbox"/> weinstein_1995.cellml#NHE3.J_NHE3_Na	sodium/hydrogen exchanger 3	Rattus norvegicus	Slc9a3	Luminal, Apical plasma membrane, Portion of cytosol	Epithelial cell of proximal tubule, Apical plasma membrane, Proximal convoluted tubule
<input type="checkbox"/> mackenzie_1996-mouse-baso.cellml#NBC_current.J_Na	low affinity sodium-glucose cotransporter	Mus musculus	Slc5a4a	Apical plasma membrane, Portion of cytosol, Luminal	Epithelial cell of proximal tubule, Basolateral plasma membrane, Proximal convoluted tubule, Proximal straight tubule

# Epithelial Modelling Platform

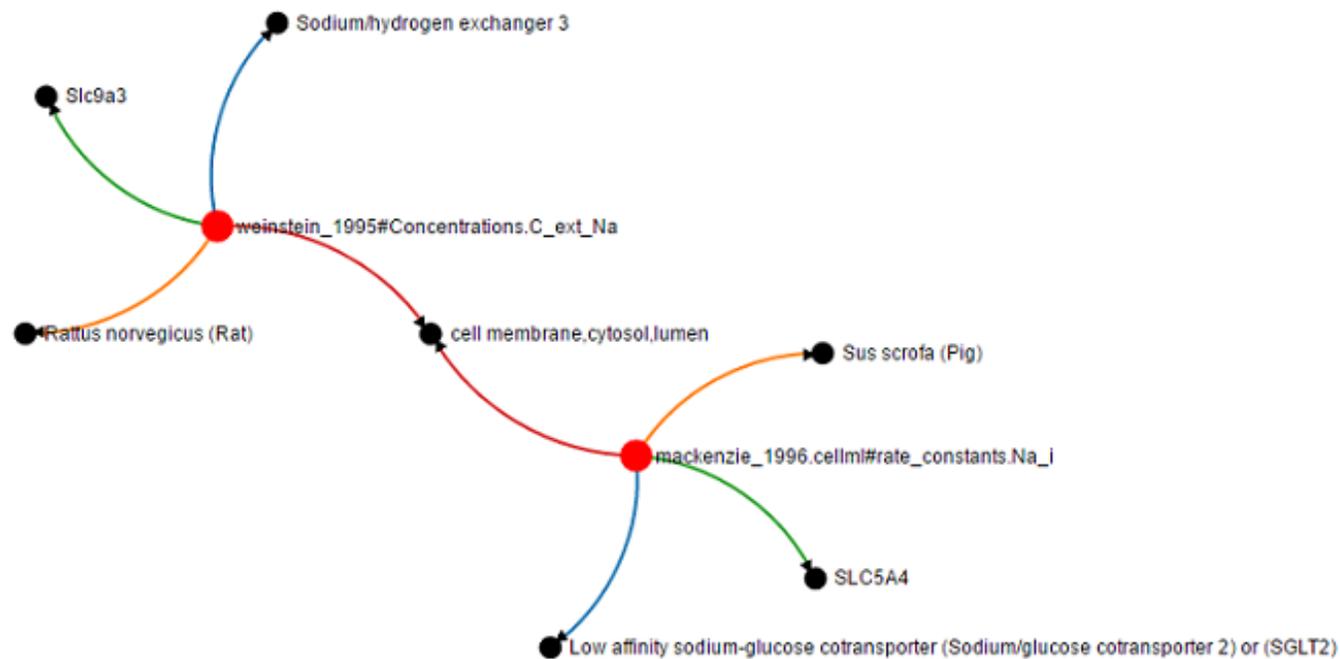


MODEL DISCOVERY

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DOCUMENTATION

Protein  
Species  
Gene  
Compartment



# Epithelial Modelling Platform

### 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#NHE3.J\\_NHE3\\_Na](#)  
**Biological Meaning:** Flux of Na<sup>+</sup> from luminal to cytosol through apical plasma membrane

**Species:** Rattus norvegicus  
**Gene:** Slc9a3  
**Protein:** sodium/hydrogen exchanger 3

**Recommendations/suggestions based on existing models in PMR**

**Basolateral membrane model**

- sodium/hydrogen exchanger 3 (human)
- low affinity sodium-glucose cotransporter (mouse)
- sodium/potassium-transporting ATPase subunit alpha-1 (rat)

**Alternative model of sodium/hydrogen exchanger 3**  
Not Exist

**Kidney model in PMR**

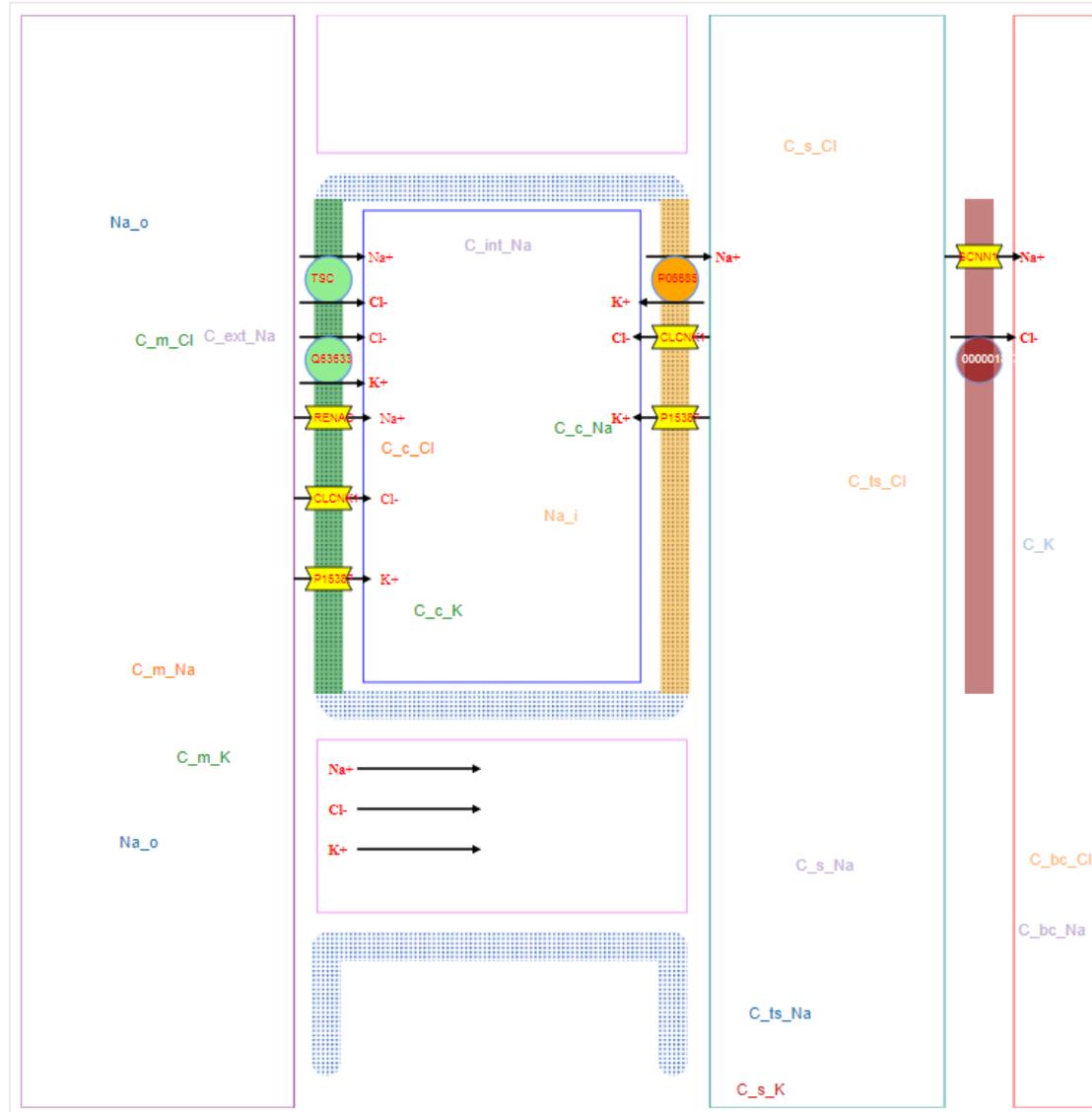
- [sodium/hydrogen exchanger 3 \(human\)](#)
- [low affinity sodium-glucose cotransporter \(mouse\)](#)
- [sodium/glucose cotransporter 1 \(human\)](#)

```
Identity Matrix: #
#
# Percent Identity Matrix - created by Clustal2.1
#
#
1: sp|Q9ET37|S5A4A_MOUSE 100.00 22.86 17.86 21.86
2: sp|P48764|SL9A3_HUMAN 22.86 100.00 19.15 89.49
3: sp|P06685|AT1A1_RAT 17.86 19.15 100.00 18.20
4: sp|P26433|SL9A3_RAT 21.86 89.49 18.20 100.00
```

# Epithelial Modelling Platform



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**Apical Membrane**  
**Basolateral Membrane**  
Luminal Compartment  
Cytosol Compartment  
Interstitial Fluid  
**Blood Capillary**  
Paracellular Pathway  
Capillary Membrane

- solute carrier family 12 member 3 (TSC)
- solute carrier family 12 member 5 (Q63633)
- amiloride-sensitive sodium channel subunit alpha (RENAC)
- chloride channel protein ClC-Ka (CLCNK1)
- potassium voltage-gated channel subfamily B member 1 (P1537)
- sodium/potassium-transporting ATPase subunit alpha-1 (P06685)
- chloride channel protein ClC-Ka (CLCNK1)
- potassium voltage-gated channel subfamily B member 1 (P1537)
- amiloride-sensitive sodium channel subunit alp (SCNN1)
- kell blood group glycoprote (000001873)
- claudin-10 (CLDN10A)
- claudin-4 (CPETR1)
- kelch-like protein 3 (F1LZ52)

## Current status

- Model discovery demonstration: <https://github.com/dewancse/model-discovery-tool>
- Epithelial modelling platform: <https://github.com/dewancse/epithelial-modelling-platform>
- Implementing model composition service
- Extending model similarity to simulation experiment similarity to automate model “verification”
- Future work: language processing to translate user requirements into semantic queries.

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