MecCog

A framework for representing Disease Mechanisms

http://www.meccog.org

Visualization Tutorial

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I. About MecCog

MecCog is a web-based framework for describing biological mechanisms based on emerging concepts in the philosophy of biology. The framework is implemented in a web infrastructure that uses contemporary methods of computational biology to represent mechanism. The initial implementation focuses on capturing mechanisms relating genetic variants to disease phenotypes.

MecCog is hosted at http://www.meccog.org

II. MecCog Homepage

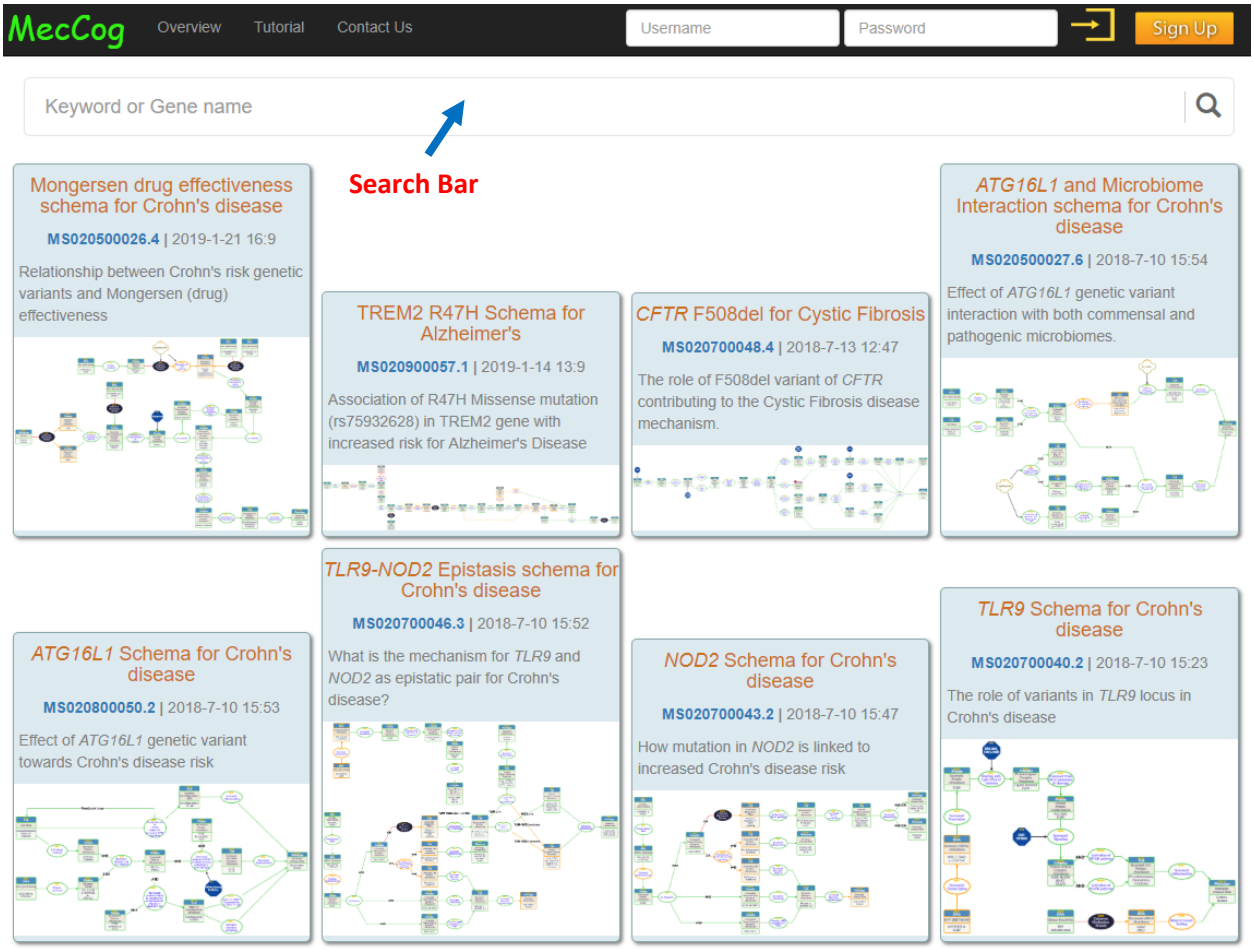
The homepage of MecCog provides a masonry layout of the all the published mechanism schemas. The page has three components:

1. Header Bar: It provides link to MecCog project overview page (*Overview*), tutorial page (*Tutorial*) and contact us form (*Contact Us*).

2. Search Bar: The user can enter a gene name or keywords to filter mechanism schemas.

3. The mechanism schema thumbnail displays the schema name, accession number, short description, and hyperlinked image of the schema. Clicking on the accession number directs to the landing page of the schema and clicking on the image directs to the *Schema Visualizer*.

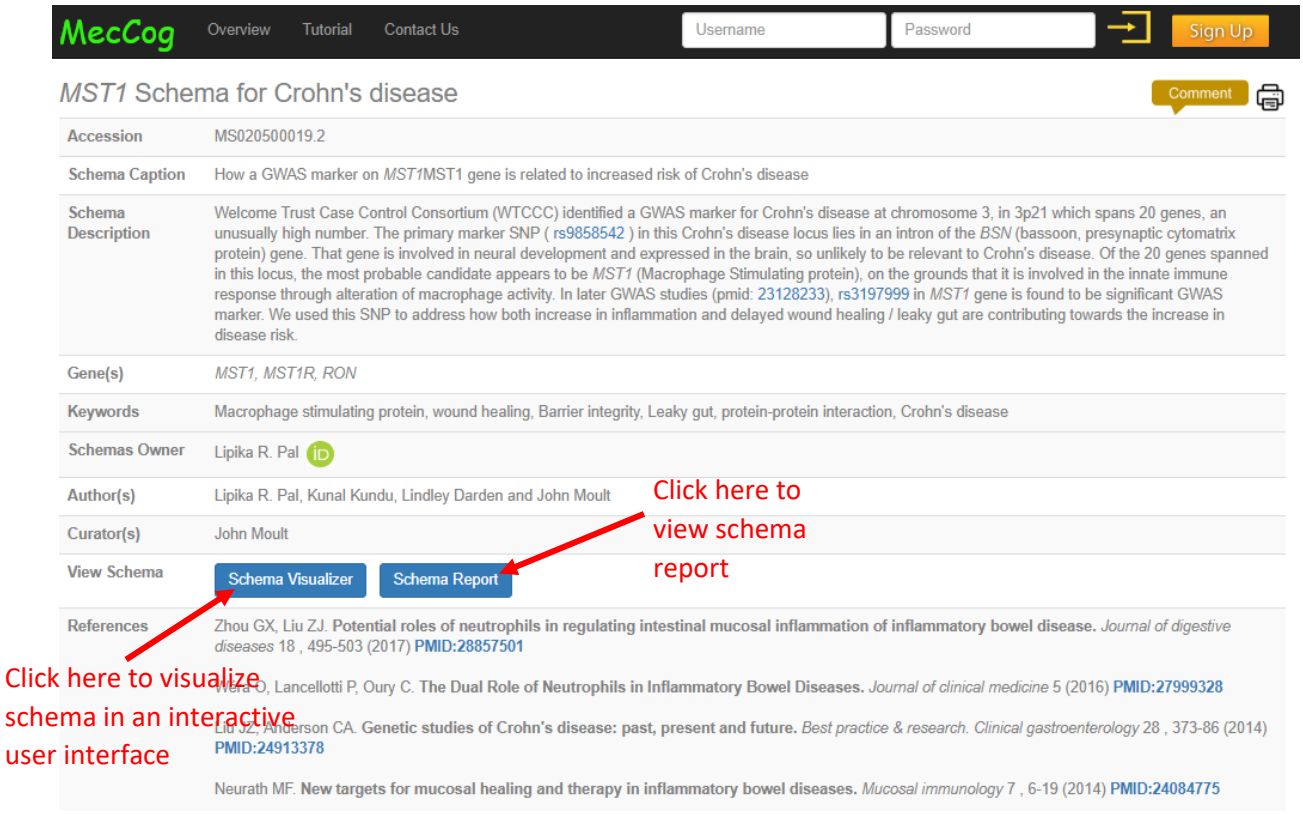
The home page of MecCog appears as shown below:



III. Mechanism schema landing page

Each mechanism schema has a landing page that displays the meta-information of the schema such as the Schema Name, Accession, Description, Gene(s), Keywords, Schema Owner, Authors and References. It also provides links to the "*Schema Visualizer*" an interactive user interface for visualizing schemas and the "*Schema Report*" that lists the annotations of the mechanism components in the schema.

A typical landing page of a mechanism schema looks as shown below:



IV. Schema Visualizer

The visualizer allows users to interact with the schema. The visualizer interface has four panels:

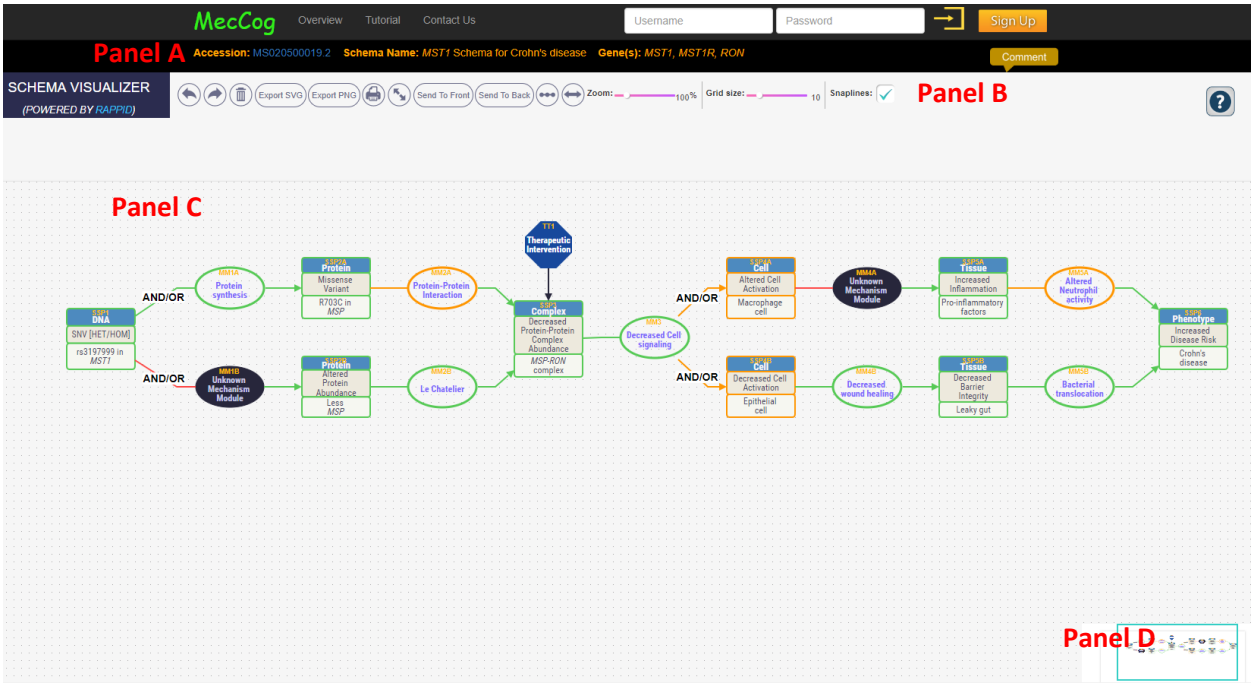
Panel A: Mechanism Schema Info Panel that shows the meta-information for a mechanism schema such as accession number, schema name, and gene name(s).

Panel B: Toolbar Panel for editing mechanism schema.

Panel C: Visualization Board is the panel where mechanism schemas are displayed.

Panel D: A Bird's Eye View Panel that facilitates navigation of big complex schemas.

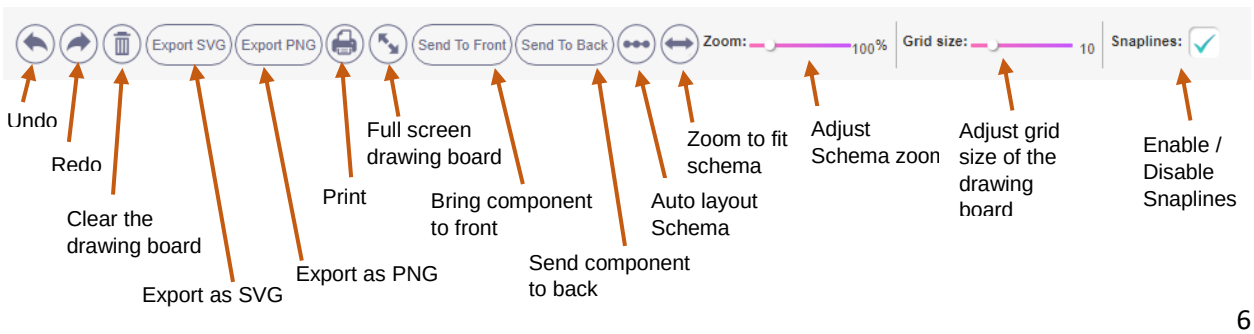
Help icon displays the Legend Key for a mechanism schema. If the help icon is not visible, try to adjust the resolution of the browser. The help icon always appears on the top right corner of the screen as shown the image below.



Toolbar Panel

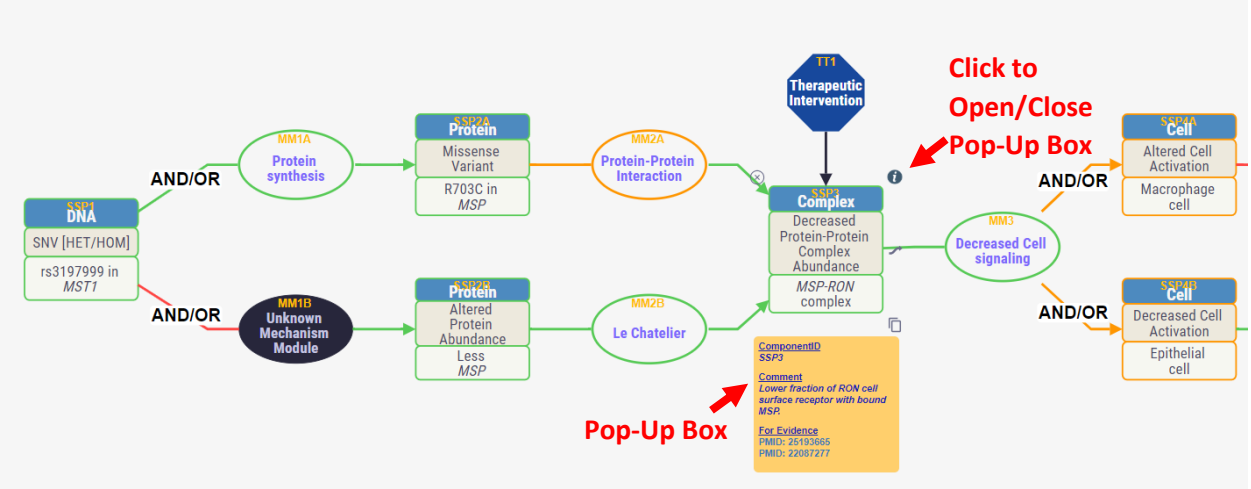
The toolbar of *Schema Builder* provides a number of utility tools to enhance the user's interactive experience with the mechanism schema.

Below images show all the options present in the tool bar –



Interactive actions in Visualization board (Panel C)

Every mechanism component is accompanied by a pop-up box that contains evidence information. The pop-up box can be opened by first clicking on the component that display an info icon ( ) and then clicking on the info icon as shown below:

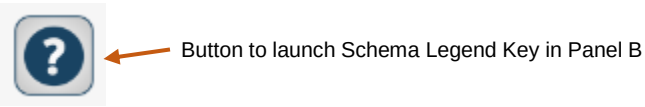


All the PubMed IDs on the pop-up box are hyperlinked to the PubMed database. The *For Evidence* lists the PMIDs that supports the fact in the schema and the *Against Evidence* lists the contradicting PMIDs. The *Comment* section in the box summarizes the evidence information based on the linked PMIDs.

Confidence Colors

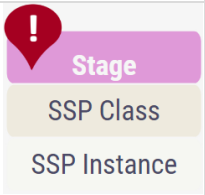
The evidence based confidence scores entered in the annotation form for the mechanism components are converted to confidence color automatically by the MecCog system. A score of 1 converts to red color, score of 5 converts to green color and any score in between converts to orange color.

Schema Key



Here is detailed description of the graphical notations in MecCog:

Component Name	Component Notation	Description
Sub-State Perturbation (SSP)	Stage SSP Class SSP Instance	Notation of a sub-state perturbation (SSP) component represents three types of information – 1. Stage it belongs to. 2. SSP class name and 3. SSP instance name. The framework provides eight stages – DNA, RNA, Protein, Complex, Cell, Tissue, Organ and Phenotype. For each stage, SSP class names have been

		manually curated Based on the type of SSP class, an instance can be annotated.
Biomarker		Notation of a Biomarker component represents three types of information – 1. Stage it belongs to. 2. Biomarker class name and 3. Biomarker instance name. The framework provides eight stages – DNA, RNA, Protein, Complex, Cell, Tissue, Organ and Phenotype.
Mechanism Module (MM)		The graphical notation of a mechanism module (MM) component represents two types of information – 1. Mechanism module class name, 2. An optional Mechanism Module Instance name. 24 mechanism module class names have been manually curated that either operate within a stage or produce a stage transition. This list will be updated as the project progresses.
Unknown Mechanism Module		For a case, where a mechanism is known to link two substate perturbations but its class is unknown, a black oval represents it.
Therapeutic Intervention		For a putative or known therapeutic intervention site, a blue octagon represents it.
Environmental Factor		For an environmental factor that affects disease risk, a mokko shape represents it.

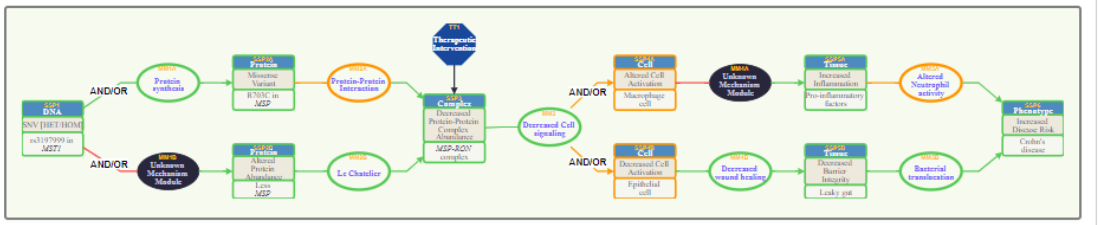
The edges in the schema are labeled with AND, OR, or AND/OR at the start of branches based on evidence supporting the logical operations.

V. Schema Report

All the annotations in the mechanism components of a schema can be converted to a text report. We call this as the schema report. In addition to the annotations, the report also contains the meta-information of the schema.

The figure below shows a typical view of a report:

Report can be saved as PDF by clicking on the print icon



Schema Name	*MST1* Schema for Crohn's disease
Accession	MS020500019.2
Gene(s)	*MST1, MST1R, RON*
Schema Caption	How a GWAS marker on *MST1*MST1 gene is related to increased risk of Crohn's disease
Schema Description	Welcome Trust Case Control Consortium (WTCCC) identified a GWAS marker for Crohn's disease at chromosome 3, in 3p21 which spans 20 genes, an unusually high number. The primary marker SNP (rs9858542) in this Crohn's disease locus lies in an intron of the *BSN* (bassoon, presynaptic cytomatrix protein) gene. That gene is involved in neural development and expressed in the brain, so unlikely to be relevant to Crohn's disease. Of the 20 genes spanned in this locus, the most probable candidate appears to be *MST1* (Macrophage Stimulating protein), on the grounds that it is involved in the innate immune response through alteration of macrophage activity. In later GWAS studies (pmid: 23128233), rs3197999 in *MST1* gene is found to be significant GWAS marker. We used this SNP to address how both increase in inflammation and delayed wound healing / leaky gut are contributing towards the increase in disease risk.
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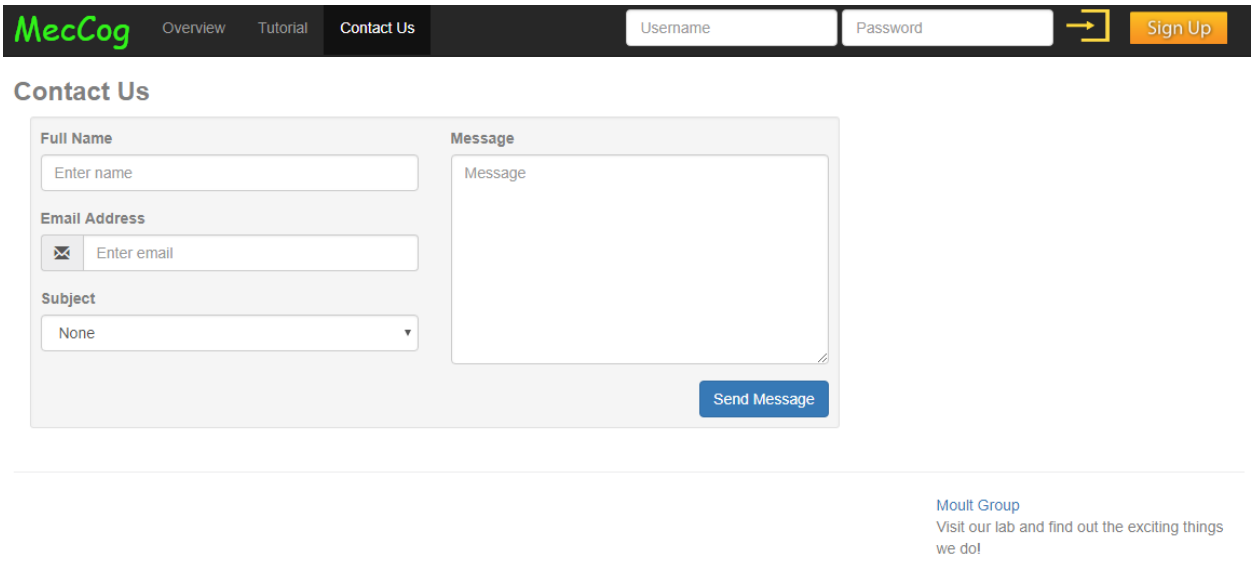
Curator(s)	John Moult
Last Modified	Fri Aug 10 2018 15:13:18 GMT-0400 (EDT)

Sub-state Perturbation (SSP) Annotations

Component ID: SSP1
Stage: DNA
SSP Class: Other
Other SSP Class: SNV [HET/HOM]
Modifier: NA
Ontology:
SSP Instance: rs3197999 in MST1
Confidence Score: 5
Comment: Of the 20 genes spanned in this locus, the most probable candidate appears to be MST1 (macrophage stimulating protein), on the grounds that it is involved in the innate immune response through stimulation of macrophage activity. In later GWAS, rs3197999 became established GWAS marker for Crohn's disease (Jostins et al 140 loci Crohn's disease paper). As these are GWAS marker information, where relationship with increasing disease risk is based on allele frequency, so SNV can be in either heterozygous (HET) or homozygous (HOM) mode. After this SSP, there are conflicting data and theories at the protein level mechanism. Hence there is branching in the next mechanism components from this SSP. We are not sure which branch is correct - so AND/OR labeling in the branches.
For Evidence: PMID:23128233
Against Evidence:

Component ID: SSP2A
Stage: Protein
SSP Class: Other
Other SSP Class: Missense Variant
Modifier: NA
Ontology:
SSP Instance: R703C in MSP
Confidence Score: 5

VI. Contact Us

Users can contact MecCog Project PI and developers for suggestions, problems, and collaborations using a web form as shown below.