Multi-State Model Builder (MSMB): a flexible editor for complex biochemical models

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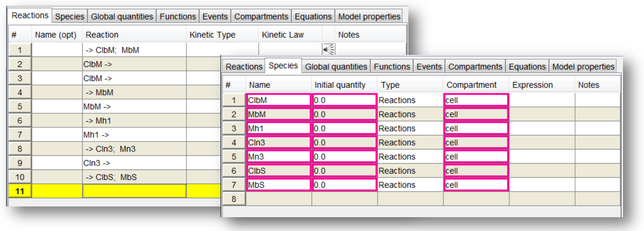
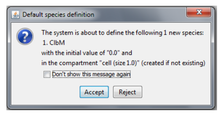
The Multi-State Model Builder

MSMB is a software tool that aims to help users write biological models as chemical reaction systems. A compact spreadsheet interface allows the user to edit different parts of the model (Reactions, Species, Parameters, etc.) in an easy and intuitive way. MSMB offers many innovative features.

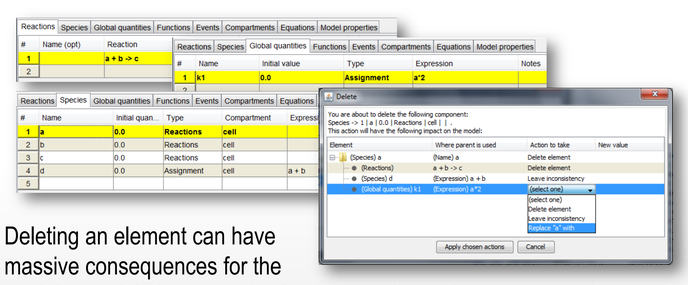
Autocompletion support.



Just type the reactions (e.g. **ClbM ->**) and MSMB fills the Species table with default values.If the option "show pop-up messages" is on, autocompletions must be explicitly accepted by the user. Cells with system-generated default values have a different color until the user acknowledges their correctness. Models can be exported to SBML/COPASI for simulation/analysis.



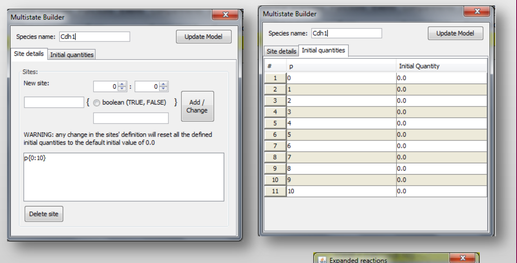
Support with model changes: deletion, renaming, etc.



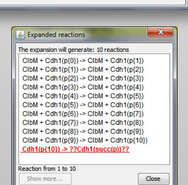
Deleting an element can have massive consequences for the model (e.g. deleting a species leaves dangling reference in reactions, expressions, etc.). MSMB walks the user through the problematic areas and different options are available to the user to address the issues.

Multi-state GUI.

Popup windows help the user unfamiliar with our multistate syntax to define the multistate species of the model.

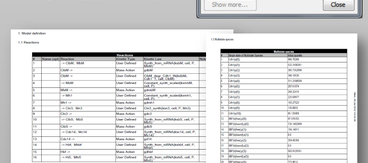


Inconsistencies between the species definition and the range used in a multistate reaction are presented to the user
(e.g. with Cdh1 defined as Cdh1(p{0:10}), the following reaction generates the error on the right : Cdh1(p{0:10}) + ClbM -> Cdh1(succ(p)) + ClbM)



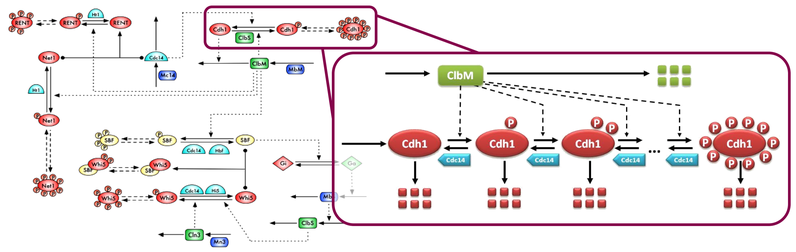
Import/Export SBML and COPASI.

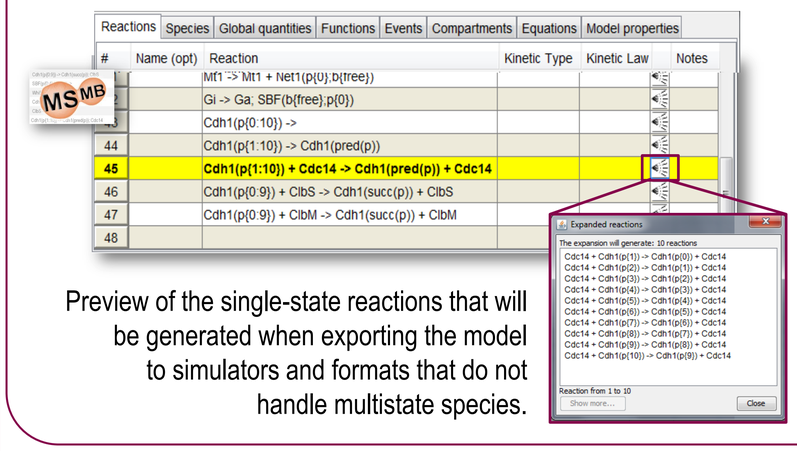
Print tables to PDF.



Cell Cycle (multisite phosphorylation)

D. Barik, W.T. Baumann, M.R. Paul, B. Novak, and J.J. Tyson. Molecular Systems Biology, 6(1), 2010





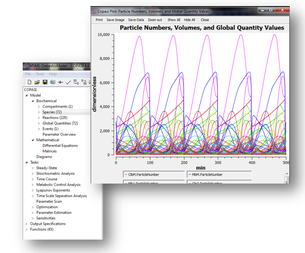
Preview of the single-state reactions that will be generated when exporting the model to simulators and formats that do not handle multistate species.

Species definition: Cdh1(p{0:10})
species name; site name; site states (range)

Reactions:
Cdh1(p{1:10}) + Cdc14 -> Cdh1(pred(p)) + Cdc14
Cdh1(p{0:9}) + ClbM -> Cdh1(succ(p)) + ClbM
Cdh1(p{0:10}) ->

Expressions:
Cdh1T = SUM(Cdh1) (or SUM(Cdh1,p{0:10}))
operators on groups of states

Expanded model, exported to **SBML** and simulated in **COPASI**



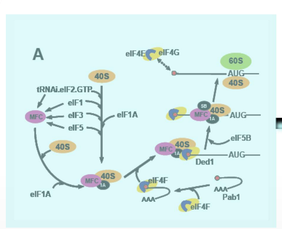
Parametric definition:
Cdh1(p{lower:upper}) lower = 0, upper = 10
Cdh1(p{lower+1:upper}) + Cdc14 -> …
Cdh1(p{lower:upper-1}) + ClbM -> …
To have a different model, the user can easily change lower/upper values, MSMB will generate the new model automatically.

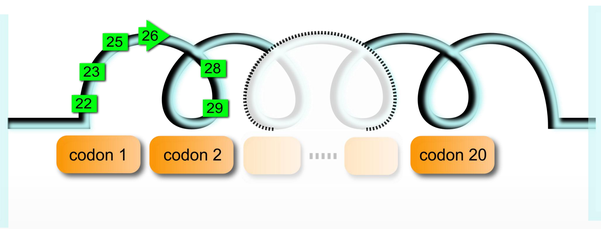
Original model	Model in MSMB
Species: 72	**Species: 23**
Parameters: 72	Parameters: 72
Reactions: 220	**Reactions: 73**
Events: 2	Events: 2

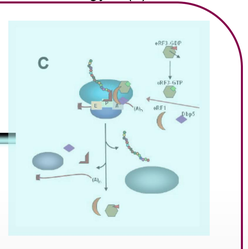
mRNA translation (location on the string)

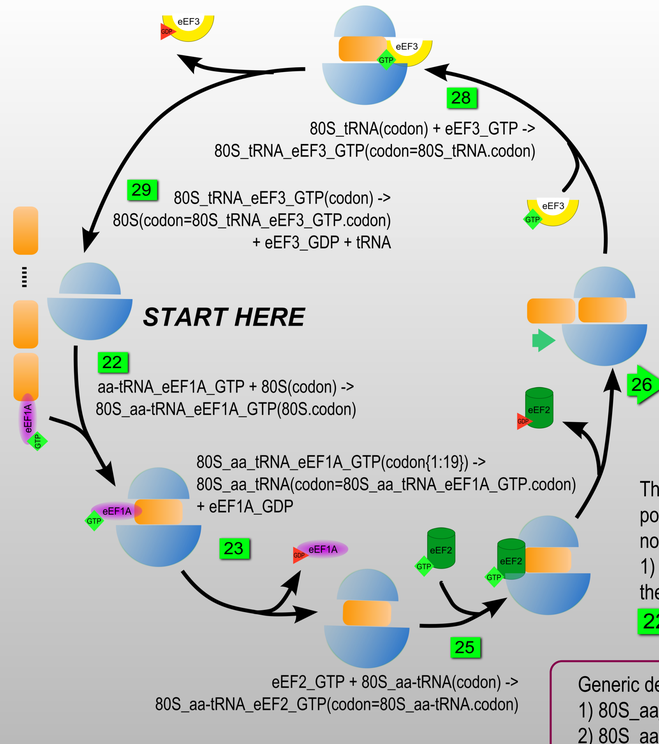
H. Firczuk, S. Kannambath, J. Pahle, A. Claydon, R. Beynon, … and J.E. McCarthy. Molecular Systems Biology, 9(1), 2013

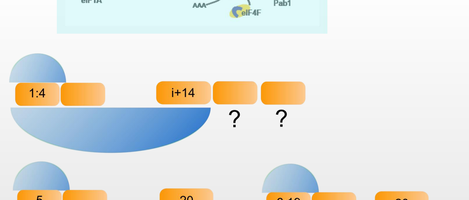
Initiation (A) and Termination (C) are set of simple Mass Action reactions. The **Elongation step** follows a "spiral sequence" of reactions that represent the movement of the ribosome on the different codons of the mRNA string.











Three different cases:
1) 80S_aa_tRNA_eEF2_GTP(codon{1:4}) ->
80S_tRNA(codon=**succ**(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP
2) 80S_aa_tRNA_eEF2_GTP(codon{5}) ->
80S_tRNA(codon=**succ**(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP
3) 80S_aa_tRNA_eEF2_GTP(codon{6:19}) ->
80S_tRNA(codon=**succ**(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP

The kinetic depends on the fact that any of the 15 following positions may be occupied. For reactions from position 6 to 19, no following codon can be occupied, so 3) is a simple Mass Action reaction.
1) and 2) have a kinetic function that depends on the occupancy of the next 15 positions.
22 23 25 28 29 have simple Mass Action kinetic.

Original model	Model in MSMB
Species: 166	**Species: 56**
Parameters: 12	Parameters: 12
Reactions: 200	**Reactions: 58**

1 reaction in MSMB = 19 reactions in COPASI

5	reaction23_1	80S_aa-tRNA_eEF1A_GTP_1 -> 80S_aa-tRNA_1 + eEF1A_GDP
39	reaction23_10	80S_aa-tRNA_eEF1A_GTP_10 -> 80S_aa-tRNA_10 + eEF1A_GDP
43	reaction23_11	80S_aa-tRNA_eEF1A_GTP_11 -> 80S_aa-tRNA_11 + eEF1A_GDP
47	reaction23_12	80S_aa-tRNA_eEF1A_GTP_12 -> 80S_aa-tRNA_12 + eEF1A_GDP
51	reaction23_13	80S_aa-tRNA_eEF1A_GTP_13 -> 80S_aa-tRNA_13 + eEF1A_GDP
55	reaction23_14	80S_aa-tRNA_eEF1A_GTP_14 -> 80S_aa-tRNA_14 + eEF1A_GDP
59	reaction23_15	80S_aa-tRNA_eEF1A_GTP_15 -> 80S_aa-tRNA_15 + eEF1A_GDP
63	reaction23_16	80S_aa-tRNA_eEF1A_GTP_16 -> 80S_aa-tRNA_16 + eEF1A_GDP
67	reaction23_17	80S_aa-tRNA_eEF1A_GTP_17 -> 80S_aa-tRNA_17 + eEF1A_GDP
71	reaction23_18	80S_aa-tRNA_eEF1A_GTP_18 -> 80S_aa-tRNA_18 + eEF1A_GDP
75	reaction23_19	80S_aa-tRNA_eEF1A_GTP_19 -> 80S_aa-tRNA_19 + eEF1A_GDP
7	reaction23_2	80S_aa-tRNA_eEF1A_GTP_2 -> 80S_aa-tRNA_2 + eEF1A_GDP
11	reaction23_3	80S_aa-tRNA_eEF1A_GTP_3 -> 80S_aa-tRNA_3 + eEF1A_GDP
15	reaction23_4	80S_aa-tRNA_eEF1A_GTP_4 -> 80S_aa-tRNA_4 + eEF1A_GDP
19	reaction23_5	80S_aa-tRNA_eEF1A_GTP_5 -> 80S_aa-tRNA_5 + eEF1A_GDP
23	reaction23_6	80S_aa-tRNA_eEF1A_GTP_6 -> 80S_aa-tRNA_6 + eEF1A_GDP
27	reaction23_7	80S_aa-tRNA_eEF1A_GTP_7 -> 80S_aa-tRNA_7 + eEF1A_GDP
31	reaction23_8	80S_aa-tRNA_eEF1A_GTP_8 -> 80S_aa-tRNA_8 + eEF1A_GDP
35	reaction23_9	80S_aa-tRNA_eEF1A_GTP_9 -> 80S_aa-tRNA_9 + eEF1A_GDP

Generic definition of reaction 26 with variables lengthmRNA, occupancy, criticalCodon=lengthmRNA-occupancy
1) 80S_aa_tRNA_eEF2_GTP(codon{1:criticalCodon-1}) -> 80S_tRNA(codon=succ(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP
2) 80S_aa_tRNA_eEF2_GTP(codon{criticalCodon}) -> 80S_tRNA(codon=succ(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP
3) 80S_aa_tRNA_eEF2_GTP(codon{criticalCodon+1:lengthmRNA-1}) -> 80S_tRNA(codon=succ(80S_aa_tRNA_eEF2_GTP.codon)) + eEF2_GDP

Adapting the model to a 300 codons long mRNA string will require only changing few numerical variables and MSMB will expand it to 2440 reactions and 1840 species.

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For more information about MSMB and its other interesting features to support the user in the challenging task of editing a biochemical model, visit http://www.copasi.org/SoftwareProjects

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