The CellDesigner Layout Proposal

Naoki TANIMURA[1], Maki NAKAYAMA[2], Yuichiro INAGAKI[1], Takayuki SAITO[2], Akira FUNAHASHI[3], Hiroaki KITANO[3, 4]

CellDesigner development team

[1] Fuji Research Institute Corporation
[2] Ad-hoc Network Computing Laboratory, Inc.
[3] Kitano Symbiotic Systems Project, ERATO-SORST, JST
[4] The Systems Biology Institute

Introduction

This proposal contains explanation of some new tags for CellDesigner's [1] editorial contents and description of current implementation of SBML [2] in CellDesigner. The tags will be actually enclosed in annotation and tag's name will be under "celldesigner:" name space, in respect for original SBML. We don't stick this proposal, but these new tags have been generated from actual CellDesigner's needs to store the diagram information in SBML. Please think our scheme and tags only for proposal, but we're pleased if this experience contributes for further SBML development.

Type Information

The main purpose of CellDesigner is to draw process network diagrams using symbolic notation system proposed by Kitano [3]. In the notes there are various types for Species (i.e. Protein, Gene, RNA, and Ion.) and reactions (i.e. Activation, Dimer formation, Dissociation, Catalysis, and Inhibition). Drawing such kind of figures, each Species and reactions must contain its type information, i.e. CaM as Protein, Ca2+ as Ion, some reaction as Activation, some reaction as Dimer formation, and so on.
So that, we have defined "class" tag in Species tag and "reactionType" tag in Reaction tag.

Example

```
<species name="s1" initialAmount="0.0" compartment="uVol">
      <class>PROTEIN</class>
</species>

<reaction name="r1">
      <reactionType>DIMER_FORMATION</reactionType>
      <listOfReactants>
            list of speciesReferences
      </listOfReactants>
      <listOfProducts>
            list of speciesReferences
      </listOfProducts>
```

```
</reaction>
```

Reading type information, CellDesigner draws typed figures, ellipse for simple molecule rectangle for Gene, and so on. The relations of figures and types (e.g. ellipse for simple molecule) are defined by [3].

Actually, these tags will be noted as:

```
<annotation>
      <celldesigner:reactionType="DIMER_FORMATION"/>
</annotation>
```

so that the introduced tags won't break the definition of SBML. This notation rule is assumed in all tags below in this proposal.

Alias

CellDesigner is a process-diagram editor, so that same species may appear more than once on a diagram. This means that, the view-information of appearing species on the diagram must be distinguished from their original information of the species, which is in listOfSpecies tag (Fig.1, Fig.2).

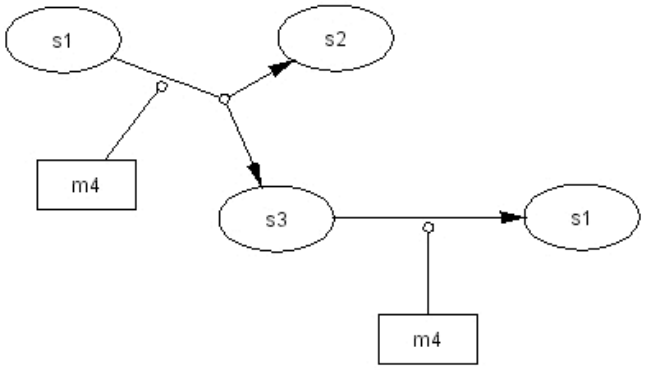

Fig.1: An example of diagram which contains alias species (s1 and m4).

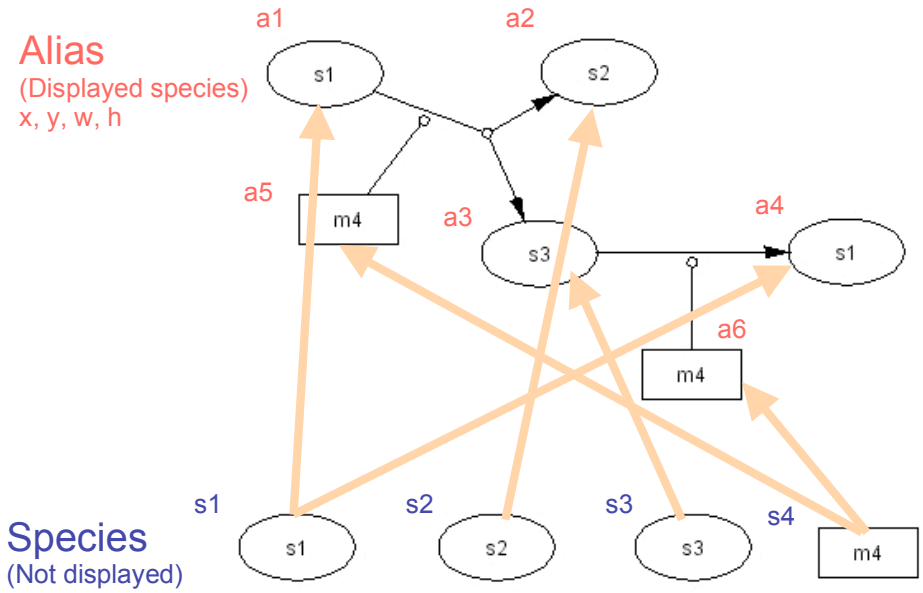

Fig.2: An internal structure of Fig 1

For this purpose, we have prepared alias scheme to express plural view of species on process chart.

Example

```
<listOfSpecies>
      <Species name="s1" initialAmount="0.0" compartment="uVol">
</listOfSpecies>

<listOfSpeciesAliases>
      <speciesAlias id="a1" species="s1">
            <bounds x="x1" y="y1" w="w1" h="h1"/>
      </speciesAlias>
      <speciesAlias id="a2" species="s1">
            <bounds x="x2" y="y2" w="w2" h="h2"/>
      </speciesAlias>
<listOfSpeciesAliases>

<reaction name="r1">
      <listOfReactants>(or <listOfProducts>)
            <speciesReference species="s1">
                  <alias>a1</alias>
            </speciesReference>
      </listOfReactants>
</reaction>


<reaction name="r2">
      <listOfReactants>(or <listOfProducts>)
```

```
            <speciesReference species="s1">
                  <alias>a2</alias>
            </speciesReference>
      </listOfReactants>
</reaction>
```

With these alias information, the same species "s1" may appear on different places (x1, y1) and (x2,y2) on 2-Dimensional process chart, but it refers to identical species -- speciesReference tag refers the same "s1"--, so that this alias tag won't break the result of quantitative simulation.

CellDesigner can draw species by any size, so that an alias needs to store its information of width and height, in addition to its geometry x and y.

Regulation

In SBML Level-1, the general scheme of reaction is represented as follows:

```
<reaction name="r1">
      <listOfReactants>
            list of speciesReferences (x1,..,xn)
      </listOfReactants>
      <listOfProducts>
            list of speciesReferences (y1,..,yn)
      </listOfProducts>
      <kineticLaw formula="f(x1,..,xn, y1,..,yn, z1,..,zn)">
</reaction>
```

This means amounts of reactants(x1,..,xn) and products(y1,..,yn) may be changed, but there are some species(z1,..,zn) which regulate the reaction process but whose amounts will not change in the process; a typical example is catalyst. Here, we call such species (z1,..,zn) as "regulator".

The main purpose of CellDesigner is to draw such regulating-relation-chart concretely on process diagram chart, so that it requires explicit information of existence of regulators. (We can know the information of regulators via kineticLaw, but CellDesigner doesn't require the existence of kineticLaw tag. The specification of SBML doesn't require kineticLaw for each reaction, and the user may want to draw a topological diagram, describing the relations between species without thinking of kineticLaw, so that CellDesigner must not rely upon the kineticLaw formula for such purpose.)

So we have defined modification tag containing the explicit information of modifiers, as shown below. Using this scheme, the user can draw explicit regulative-relationship without kineticLaw formula.

```
<reaction name="r1">
      <listOfReactants>
            list of speciesReferences (x1,.,xn)
      </listOfReactants>
      <listOfProducts>
```

```
            list of speciesReferences (y1,..,yn)
      </listOfProducts>
      <listOfModification>
            list of modifiers
      </listOfModification>
</reaction>
```

In SBML Level-2, listOfModifiers and modifierSpeciesReference tags are used to represent such regulations. We have proposed our regulation scheme for SBML Level-1, because there was only SBML Level-1 definition at that time. Currently, we are implementing SBML Level-2 support for CellDesigner, which means that CellDesigner will be able to parse listOfModifiers and modifierSpeciesReference tags to represent regulations.

Example

Following example represents a reaction from s1 to s2, and s3 promotes the reaction.

```
<reaction>
      <type>ACTIVATION</TYPE>
      <listOfReactants>
            <speciesReference species="s1">
                  <alias>a1</alias>
            </speciesReference>
      </listOfReactants>
      <listOfProducts>
            <speciesReference species="s2">
                  <alias>a3</alias>
            </speciesReference>
      </listOfProducts>
      <listOfModification>
            <modification type="CATALYSIS" modifiers="s3"
aliases="a3"/>
      </listOfModification>
</reaction>
```

This example will close up the CellDesigner's need for drawing symbolical diagram that has explicit semantics of reaction process.

Graphical Information

In the CellDesigner's system of drawing, graphical forms of symbols are pre-defined in its own notational system. Therefore, only the configuration of bounding box is required to draw a species. Once bounding box is defined, its symbol will be automatically drawn inside the bounding box with their shape according to the notation system.

```
<celldesigner:speciesAlias id="a5" species="s1">
      <celldesigner:bounds x="450.0" y="28.0" w="80.0" h="25.0"/>
</celldesigner:speciesAlias>
```

For arrows of Reactions and Regulators, these graphics are automatically drawn so as to connect species, whose positions are determined by bounding boxes; other information is not necessary to draw the arrows.
Also, current version of CellDesigner supports graphical decoration schemes. "Paint" tag is used to specify a color for each species and compartment, as shown in the following example

```
<celldesigner:speciesAlias id="a5" species="s1">
      <celldesigner:bounds x="450.0" y="28.0" w="80.0" h="25.0"/>
      <celldesigner:paint color="AARRGGBB" scheme="SCHEMENAME"/>
</celldesigner:speciesAlias>
```

where "AARRGGBB" is a hexagonal expression of an integer and the A, R, G and B are for alpha, red, green and blue channels respectively. "SCHEMENAME" will be either "Gradation" or "Color" (unique color).
"singleLine" and "doubleLine" tags are used to specify the line width or thickness of membranes and their outer and inner line widths.

```
<celldesigner:singleLine width="DOUBLE"/>
<celldesigner:doubleLine thickness="DOUBLE" outerWidth="DOUBLE"
innerWidth=" DOUBLE"/>
```

where "DOUBLE" is a double value.

Example

Following example represents graphical information stored in celldesigner: namespace including geometry, color and line width for each speciesAlias.

```
<celldesigner:listOfSpeciesAliases>
      <celldesigner:speciesAlias compartmentAlias="ca1" id="a1"
species="s1">
            <celldesigner:bounds h="40.0" w="80.0" x="99.0" y="47.0"/>
            <celldesigner:singleLine width="1.0"/>
            <celldesigner:paint color="ff7f0000" scheme="Gradation"/>
      </celldesigner:speciesAlias>
      <celldesigner:speciesAlias compartmentAlias="ca2" id="a2"
species="s2">
            <celldesigner:bounds h="50.0" w="80.0" x="353.0"
y="189.0"/>
            <celldesigner:singleLine width="1.0"/>
            <celldesigner:paint color="ff007f00" scheme="Gradation"/>
</celldesigner:speciesAlias>
```

The graphical information of CellDesigner is stored in <bounds>, <paint> and <single/doubleLine> tags (and in <modelDipslay> tag at the top of SBML, which displays the size of whole diagram).

References

1. Funahashi, A., Tanimura, N., Morohashi, M., and Kitano, H.: "CellDesigner: a process diagram editor for gene-regulatory and biochemical networks", BIOSILICO, 1:159-162, 2003
2. Hucka, M.; Finney, A.; Sauro, H.M.; Bolouri, H.; Doyle, J.C.; Kitano, H. et al.: "The Systems Biology Markup Language (SBML): A Medium for Representation and Exchange of Biochemical Network Models. Bioinformatics." 19, 524-531, 2003.
3. Kitano, H.: "A Graphical Notation for Biological Networks" BIOSILICO, 1:169-176, 2003.

Appendix: Full Example

Here, we will show an SBML representation of a diagram. This diagram is shown in Fig.1. It consists of 4 species with 6 aliases and 3 reactions. The diagram information is stored in annotation tags under "celldesigner:" namespace, so that it won't break the SBML Level-1 specification.

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml xmlns="http://www.sbml.org/sbml/level1" level="1" version="2" xmlns:html="http://www.w3.org/1999/xhtml"
xmlns:celldesigner="http://www.sbml.org/2001/ns/celldesigner">
  <model>
    <annotation>
      <celldesigner:modelVersion>2.2</celldesigner:modelVersion>
      <celldesigner:modelDisplay sizeX="600" sizeY="400"/>
      <celldesigner:listOfCompartmentAliases>
      </celldesigner:listOfCompartmentAliases>
      <celldesigner:listOfSpeciesAliases>
        <celldesigner:speciesAlias id="a1" species="s1">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="52.0" y="96.0" w="70.0" h="40.0"/>
        </celldesigner:speciesAlias>
        <celldesigner:speciesAlias id="a2" species="s2">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="218.0" y="95.0" w="70.0" h="40.0"/>
        </celldesigner:speciesAlias>
        <celldesigner:speciesAlias id="a3" species="s3">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="182.0" y="205.0" w="70.0" h="40.0"/>
        </celldesigner:speciesAlias>
        <celldesigner:speciesAlias id="a4" species="s1">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="368.0" y="204.0" w="70.0" h="40.0"/>
        </celldesigner:speciesAlias>
        <celldesigner:speciesAlias id="a5" species="s4">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="71.0" y="189.0" w="60.0" h="30.0"/>
        </celldesigner:speciesAlias>
        <celldesigner:speciesAlias id="a6" species="s4">
          <celldesigner:activity>inactive</celldesigner:activity>
          <celldesigner:bounds x="279.0" y="283.0" w="60.0" h="30.0"/>
        </celldesigner:speciesAlias>
      </celldesigner:listOfSpeciesAliases>
      <celldesigner:listOfGroups>
      </celldesigner:listOfGroups>
      <celldesigner:listOfProteins>
      </celldesigner:listOfProteins>
    </annotation>
    <listOfCompartments>
      <compartment name="default"/>
```

```
    </listOfCompartments>
    <listOfSpecies>
      <species name="s1" compartment="default" initialAmount="0.0">
        <annotation>
          <celldesigner:positionToCompartment>inside</celldesigner:positionToCompartment>
          <celldesigner:speciesIdentity>
            <celldesigner:class>SIMPLE_MOLECULE</celldesigner:class>
            <celldesigner:name>s1</celldesigner:name>
          </celldesigner:speciesIdentity>
        </annotation>
      </species>
      <species name="s2" compartment="default" initialAmount="0.0">
        <annotation>
          <celldesigner:positionToCompartment>inside</celldesigner:positionToCompartment>
          <celldesigner:speciesIdentity>
            <celldesigner:class>SIMPLE_MOLECULE</celldesigner:class>
            <celldesigner:name>s2</celldesigner:name>
          </celldesigner:speciesIdentity>
        </annotation>
      </species>
      <species name="s3" compartment="default" initialAmount="0.0">
        <annotation>
          <celldesigner:positionToCompartment>inside</celldesigner:positionToCompartment>
          <celldesigner:speciesIdentity>
            <celldesigner:class>SIMPLE_MOLECULE</celldesigner:class>
            <celldesigner:name>s3</celldesigner:name>
          </celldesigner:speciesIdentity>
        </annotation>
      </species>
      <species name="s4" compartment="default" initialAmount="0.0">
        <annotation>
          <celldesigner:positionToCompartment>inside</celldesigner:positionToCompartment>
          <celldesigner:speciesIdentity>
            <celldesigner:class>GENE</celldesigner:class>
            <celldesigner:name>m4</celldesigner:name>
          </celldesigner:speciesIdentity>
          <celldesigner:listOfCatalyzedReactions>
            <celldesigner:catalyzed reaction="r1"/>
            <celldesigner:catalyzed reaction="r2"/>
          </celldesigner:listOfCatalyzedReactions>
        </annotation>
      </species>
    </listOfSpecies>
    <listOfReactions>
      <reaction name="r1" reversible="false">
        <annotation>
          <celldesigner:reactionType>DISSOCIATION</celldesigner:reactionType>
          <celldesigner:baseReactants>s1</celldesigner:baseReactants>
          <celldesigner:baseProducts>s2,s3</celldesigner:baseProducts>
          <celldesigner:editPoints>0.3333333333333335,0.0 0.6666666666666667,1.1102230246251565E-16
0.3333333333333337,-4.440892098500626E-16 0.6666666666666667,0.0
0.3333333333333304,4.440892098500626E-16 0.6666666666666665,2.220446049250313E-16
0.3333333333333326,0.3333333333333326</celldesigner:editPoints>
          <celldesigner:listOfModification>
            <celldesigner:modification type="CATALYSIS" modifiers="s4" aliases="a5" targetLineIndex="0,1"
editPoints="0.3333333333333326,0.0 0.6666666666666665,0.0"/>
          </celldesigner:listOfModification>
        </annotation>
        <listOfReactants>
          <speciesReference species="s1">
            <annotation>
              <celldesigner:alias>a1</celldesigner:alias>
            </annotation>
          </speciesReference>
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="s2">
```

```
                <annotation>
                  <celldesigner:alias>a2</celldesigner:alias>
                </annotation>
              </speciesReference>
              <speciesReference species="s3">
                <annotation>
                  <celldesigner:alias>a3</celldesigner:alias>
                </annotation>
              </speciesReference>
            </listOfProducts>
          </reaction>
          <reaction name="r2" reversible="false">
            <annotation>
              <celldesigner:reactionType>STATE_TRANSITION</celldesigner:reactionType>
              <celldesigner:baseReactants>s3</celldesigner:baseReactants>
              <celldesigner:baseProducts>s1</celldesigner:baseProducts>
              <celldesigner:editPoints>0.33333333333333304,6.8833827526759706E-15
0.6666666666666663,1.4210854715202004E-14</celldesigner:editPoints>
              <celldesigner:listOfModification>
                <celldesigner:modification type="CATALYSIS" modifiers="s4" aliases="a6" targetLineIndex="-1,1"
editPoints="0.33333333333333304,-8.881784197001252E-16 0.6666666666666665,8.881784197001252E-16"/>
              </celldesigner:listOfModification>
            </annotation>
            <listOfReactants>
              <speciesReference species="s3">
                <annotation>
                  <celldesigner:alias>a3</celldesigner:alias>
                </annotation>
              </speciesReference>
            </listOfReactants>
            <listOfProducts>
              <speciesReference species="s1">
                <annotation>
                  <celldesigner:alias>a4</celldesigner:alias>
                </annotation>
              </speciesReference>
            </listOfProducts>
          </reaction>
        </listOfReactions>
      </model>
    </sbml>
```