BioNetGen-to-MCell Converter

Introduction

The converter creates spatial MCell modles from BioNetGen. The feature requires two input files: 1) a BioNetGen model file (.bngl), which is to be translated into a MCell model, and 2) a geometry file (.mdl) definiing the compartment geometries of the model. To implement the feature, an additional command "writeMDL();" should be added in the actions block of the BioNetGen file. The geometry file should be created using CellBlender, a software that uses Blender interface to create MCell geometries. Both input files must be kept in the same directory. Execution of the BioNetGen file will create two output files: a translated MCell model file (.mdl) and a modified version of the geometry file (.mdl). Both output files will be placed into a newly created directory named 'MDL' inside the current working directory.

BioNetGen input file

The BioNetGen model can be specified either as a noncompartmental mdoel or a compartmental model. Example BioNetGen model files are provided in the 'MCell' directory, which is in the Models2 folder of the BioNetGen home directory.

If it is a non-compartmental model, it will load a default geometry, which is an sphere of volume of 1,000 μ^3. The default geometry file (default.geometry.mdl) needed for execution of a non-compartmental model can be found in the MCell directory.

If a model is defined as a compartmental model but no user-defined custom geometry file is provided, the converter will automatically define concentric spheres for each 3D compartments specified in the BioNetGen model. The sphere sizes will be automatically defined such that the volmes of each 3D compartment (shell space or sphere volumes) becomes equal to corresponding 3D compartments defined in the BioNetGen file. The same default geometry file (default.geometry.mdl) used for a noncompartmental model must be provided, as it will be used as a template file in the automatic creation of geometries.
If a model is a defined as a compartmental model and the user provides a custom geometry file, the custom geometry file will be used instead of default or automated geometries. In the cuestom geometry file, compartment names and sizes should be correctly mapped to those specified in the BioNetGen file.

If the model is non-compartmental, conventional BioNetGen units should be used. However, for a compartmental model user must follow some convention in specifying the parameters in the BioNetGen file so that the translated parameters get correct values and units consistent with a MCell model. The conventions for parameter specification for a compartmental model are as discussed below.

Parameter specification for a compartmental model

In a compartmental BioNetGen model, user should specify parameter values in units as shown in the example model files (see MCell directory.) The conventions used in the example files

should be followed to make sure that the converted parameters get correct values or units in the MCell model.

Concentration of proteins should be defined in number of molecules (copy number). Forward rate constants should be provided in $M^{-1}s^{-1}$, and reverse rate constants should be specified in s^{-1}. Compartment volumes should be specified in μ^3. (The converter will assume any number provided as a compartment volume in μ^3).

It should be noted that 2D compartments in BioNetGen are specified as 3D volumes. The converter will internally divide the volume of a 2D compartment with 0.01 to get an effective area for the surface of that compartment. For example, if the user assigns a 2D compartment comparment volume as 1 μ^3, the converter will assume its thickness as 0.01 μ, and the translated surface area of the compartment in th MCell model will be $1/0.01 = 100$ μ^2.

Compartments

Compartment names and sizes provided in the BNG file should be consistent with the names and sizes provided in the geometry file.

The outermost compartment must be a 2D compartment although standard cBNG allows a 3D compartment as the outermost compartment in a model. This restriction in writeBNG() is enforced because MCell does not permit a 3D space to be defined without a bordering 2D surface. Therefore, a 2D compartment should be defined as the outermost compartment regardless of any species or reaction involves the compartment or not. This 2D compartment can be thought of as a boundary for the entire system in a model.

If a 2D compartment in the BNG file is mapped to a partial region of an object surface in the geometry file, user should treat the partial region as an outside compartment for the adjanced (inside) 3D compartment, and define the relationship accordingly in the compartment bloc of the BNG file.

Geometry file

The geometry file must be created in MDL format in CellBlender mode. All compartments specified in the BNG file should be mapped to different objects in the geometry file. An object in the geometry file is a defined geometry for a cube, sphere, cylinder or other irregular shape.

Below is an example how a compartment bloc in the BNG file should be mapped to objects in a geometry file. A compartment bloc in cBNG may look as follows:

```
begin compartments
  Wall   2    vol_wall
  EC     3    vol_EC    Wall
  PC     2    vol_PC    EC
  CT     3    vol_CT    PC
end compartments
```

where `Wall` is a 2D compartment representing the boundary of the extracellular space; `EC` is a 3D compartment representing the extracellular space; `PC` is a 2D compartment representing a small region of interest on the plasma membrane; and `CT` is a 3D compartment representing

the cytoplasmic volume.

To define a spherical geometry for the 2D compartment `Wall`, an spherical object should be defined in the geometry file with a surface area `vol_wall/0.01`. The surface of the object should be named 'Wall', which will map it to the compartment `Wall` in the BNG bloc. The entire object should be named 'EC' referring to the 3D compartment `EC`, for which `Wall` is an outside compartment. The object definition in the geometry file should look as follows:

```
 EC POLYGON_LIST
{
   VERTEX_LIST
  {
    ...
    ...
  }
  ELEMENT_CONNECTIONS
  {
    ...
    ...
  }
   DEFINE_SURFACE_REGIONS
  {
    Wall
    {
      ELEMENT_LIST = [...]
    }
  }
}
```

Similar as above, a second object should be defined to specify the next 2D compartment `PC`. Compartment `PC` represents a partial region on a membrane and does not provide information about the size of the object. User should define this object based on the volume of the 3D compartment `CT`, `vol_CT`.

```
 CT POLYGON_LIST
{
   VERTEX_LIST
  {
    ...
    ...
  }
  ELEMENT_CONNECTIONS
  {
    ...
    ...
  }
   DEFINE_SURFACE_REGIONS
  {
    PC
    {
      ELEMENT_LIST = [...]
```

```
    }
  }
}
```

The parser will map the 3D compartment `EC` to the shell space between objects `EC` and `CT` by defining this space as `EC[obj_wall]-CT[obj_wall]`, where `obj_wall` is a parser-provided common name for object surfaces. User should provide consistent size for this compartment in the BNG compartment bloc, i.e., `vol_EC` must be equal to the volume of the shell space. To define the surfaces of the objects, the parser will re-write the geometry file as follows:

```
 EC POLYGON_LIST
{
   VERTEX_LIST
  {
    ...
    ...
  }
  ELEMENT_CONNECTIONS
  {
    ...
    ...
  }
   DEFINE_SURFACE_REGIONS
  {
    obj_wall
    {
      ELEMENT_LIST = [...]
    }
  }
  {
    Wall
    {
      ELEMENT_LIST = [...]
    }
  }
}

 CT POLYGON_LIST
{
   VERTEX_LIST
  {
    ...
    ...
  }
  ELEMENT_CONNECTIONS
  {
    ...
    ...
  }
   DEFINE_SURFACE_REGIONS
  {
```

```
    obj_wall
    {
      ELEMENT_LIST = [...]
    }
  }
  {
    PC
    {
      ELEMENT_LIST = [...]
    }
  }
}
```

Diffusion

In writeMDL(), a default rate of diffusion is assigned for each compartment, which is mapped to all species located in that compartment. The default values can be changed by manually editing the BioNetGen-exported MDL file. A more advanced feature is under consideration, where distinct diffusion rates may be assigned based on the size and location of species. Diffusion rates can be related to species properties, e.g., shape and size, and to medium properties, e.g., viscosity. The size of a species can be approximated based on the number of molecules it contains. Viscosities can be assigned to a compartment based on the diffusion medium it represents.

To obtain diffusion constant in a 2D membrane compartment, Saffman and Delbruck equation can be used:

$$D = \frac{k_B T ln[(\mu_m h/\mu_h R) - \gamma]}{4\pi\mu_m h} \tag{1}$$

Here, h is the thickness of a 2D membrane, and R is the radius of a cylindrical object diffusing in the membrane. k_B is Boltzmann constant and T is temerature. γ is Euler's constant ($\gamma \approx 0.5722$). μ_m is the viscosity of the membrane and μ_h is the viscosity of fluids in adjacent 3D compartments. An approximate value of R for a given species can be derived from the number of molecules it contains. All membrane species and molecules can be assumed to be cylinders of equal height tethered in the membrane. All molecules can be assumed to have identical volume V, and volume of a species can be approximated to nV, where n is the number of membrane molecules in the species. Then R becomes simply the radius of a cylinder of volume nV , i.e., $R = \sqrt{n}r$, where r the radius of a single molecule.

For diffusion of species in a 3D compartment, Einstein-Stokes equation can be used:

$$D = \frac{k_B T}{6\pi\mu R} \tag{2}$$

where R is the radius of an spherical object. Molecules in a 3D compartment can be assumed to have the same volume as the molecules in a 2D compartment. Based on this assumption, R of a species becomes $R = n^{1/3}r$, where r is the radius of individual spherical molecules.

Default geometries

If a custom geometry is not provided, a default geometry will be integrated with the model. If the model is specified in cBNG format, the parser will create concentric spheres corresponding

to each 3D compartments specified in the BNG compartment bloc. 2D compartments will be mapped to the surfaces of these spheres, and 3D compartments will be mapped to the inside volumes or shell spaces, as appropriate. The shell volumes or sphere sizes will be automatically adjusted based on the size and number of nested compartments specified in the BNG compartment bloc. The automatic size adjustment will be done by scaling up or down a pre-defined sphere in the default geometry file. If the BNG model is a non-compartmental model, a default sphere of 1,000 cubic micron will be loaded and all species in the model will be treated as volume species.