BioNetGen-to-MCell Converter

Introduction

The BioNetGen-to-MCell converter creates spatial MCell models from BioNetGen. The converter requires two input file: 1) a BioNetGen model file (.bngl), and 2) a geometry file (.mdl) definiing the geometries of model compartments. 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 the Blender interface to create MCell geometries. The two input files should be placed in the same folder. Execution of the BioNetGen file will then create two output files: a translated MCell file (.mdl) and a modified version of the geometry file (.mdl). The output files will be stored in a newly created folder named 'MDL' in the working directory.

BioNetGen input file

The BioNetGen model can be specified either as a non-compartmental mdoel or a compartmental model. Some example model files are included in a folder named 'MCell' in the Models2 folder of BioNetGen home directory.

If a non-compartmental BioNetGen model is used, it will load a default geometry. All molecules and species of a non-compartmental model will be treated as volume species inside a sphere of 1000 μm^3. A template geometry file named default.geometry.mdl, as included in the example folder, must be provided as an input file for a non-compartmental model.

If compartmental model is used but no user-defined custom geometry file is provided, the converter will automatically define concentric sphere for each 3D compartment specified in the model. The size of each sphere will be defined automatically matching the size specified in the BioNetGen file. The same template geometry file used for a non-compartmental model, default.geometry.mdl, should be provided as an input file.

If a compartmental model is used and the user provides a custom geometry file, then the custom geometry file will be loaded. In the custom geometry file, user should provide compartment names and sizes matching those specified in the model file.

For a non-compartmental model, parameters should be specified in conventional BioNetGen units. For compartmental models, however, parameters shoud be specified following the conventiins discussed below.

Parameter specification for a compartmental model

For a compartmental BioNetGen model, parameters should be in units as shown in the example files in the MCell directory. These conventions are used to make sure that the parameters get correct values or units for the converted model.

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

It should be noted that 2D compartments in BioNetGen models are defined essentially as 3D space of small thickness and therefore assigned volume units. The converter will internally assume the thickness of any 2D compartment of a BioNetGen model as 0.01 μm, and calculate its surface area for the MCell model accordingly. For example, if a 2D compartment in BioNetGen is assigned a volume of 1 μm^3, the converter will divide it with 0.01 μm, and corresponding surface area of the compartment in the converted model will be 100 μm^2.

Compartments

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

The outermost compartment must be a 2D compartment although standard compartmental BioNetGen allows a 3D compartment as the outermost compartment in a model. This restriction for the converter 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 BioNetGen 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 BioNetGen file.

Custom geometry file

The geometry file should be created using CellBlender. All compartment names specified in the BioNetGen model file should be mapped to different objects in the geometry file. (To see how the names of compartments are matched between a BioNetGen file and a geometry file, please see example file fceri_ji_comp.bngl and fceri_ji_comp.mdl in the example folder.)

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 BioNetGen file should be mapped to objects in a geometry file. A compartment bloc in compartmental BioNetGen 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 BioNetGen 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 converter 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 converter-provided common name for object surfaces. User should provide consistent size for this compartment in the BioNetGen compartment bloc, i.e., `vol_EC` must be equal to the volume of the shell space. To define the surfaces of the objects, the converter 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

The converter internally calculates diffusion constants for each species in different compartments. The diffusion constant values can be changed by manually editing the output model file.

Diffusion constant for a 2D membrane compartment is calcualted using Saffman and Delbruck equation:

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

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.

Diffusion of a species in a 3D compartment is calculated using Einstein-Stokes equation:

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

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.