# Introduction to Microphysiological Simulations Using MCell

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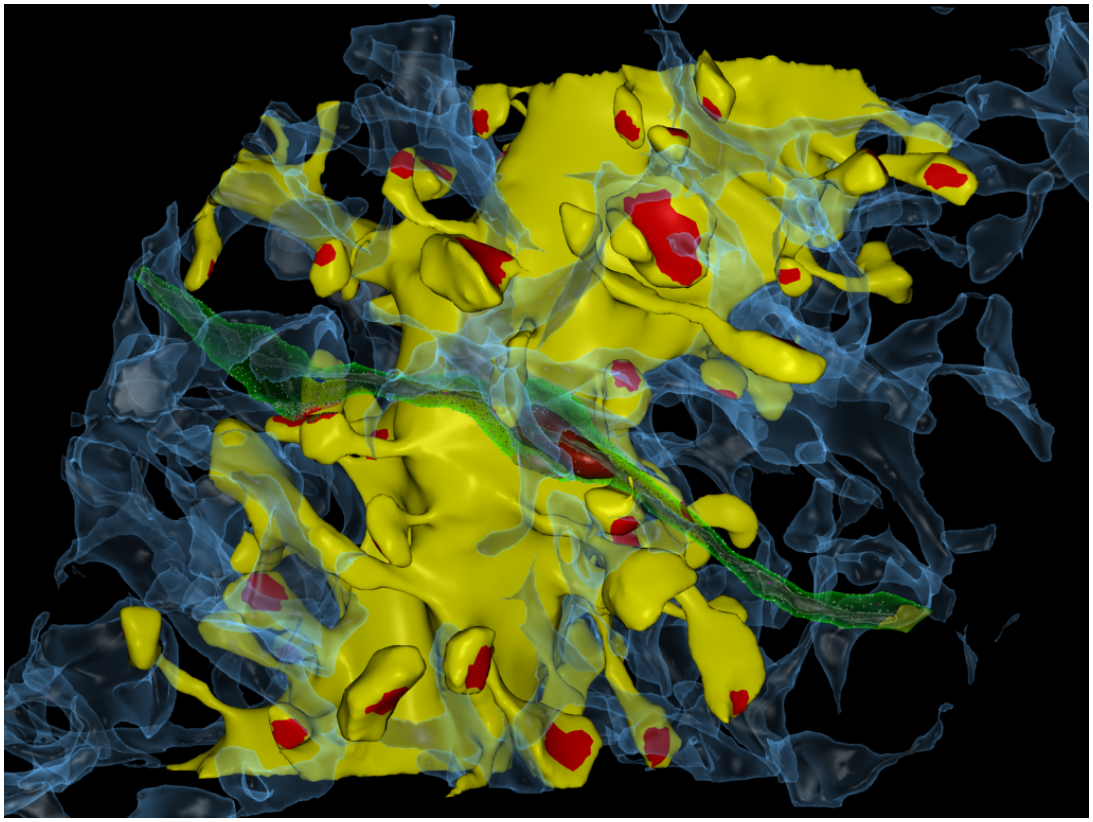
# MCell, a Modeling Tool for Cellular Microphysiology

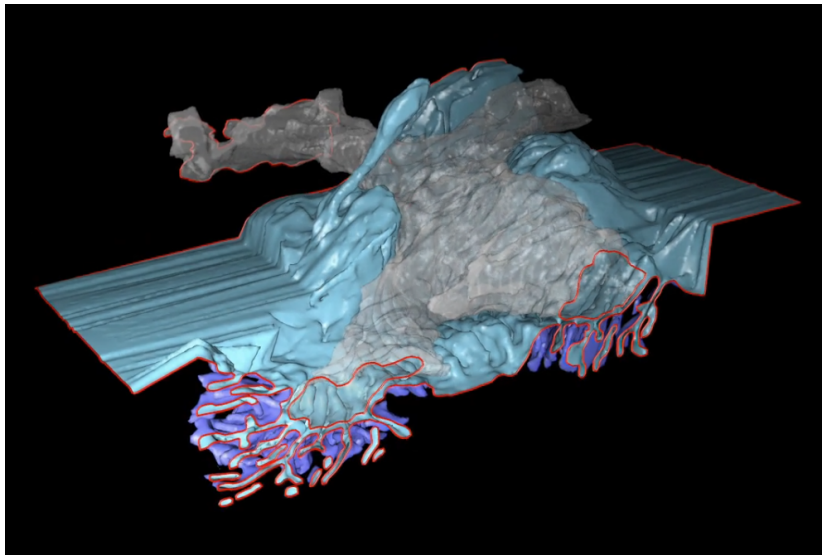
MCell is a Monte Carlo reaction-diffusion simulator for modeling cellular microphysiology in arbitrarily complex 3D spatial geometries.

Computational Microphysiology: The simulation of biological systems at micron to millimeter length scales (subcellular to cellular) using realistic 3D geometries over biological timescales from *ns* to *ms* to *s*.

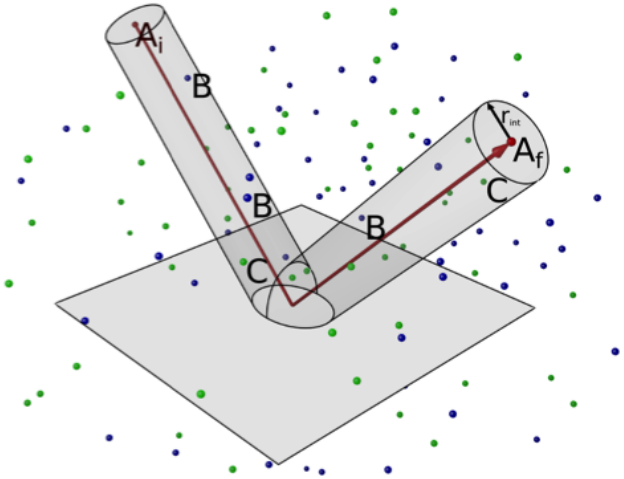


# Main Components of an MCell Model

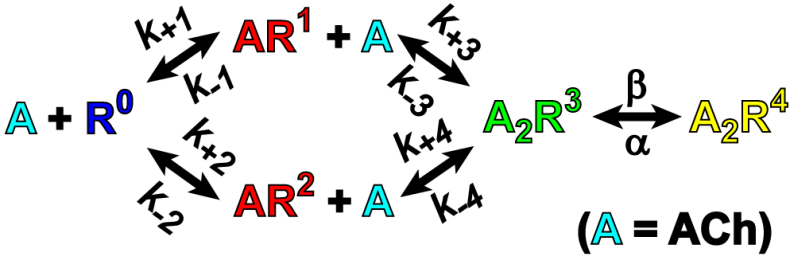
## 1. Realistic 3D Geometry

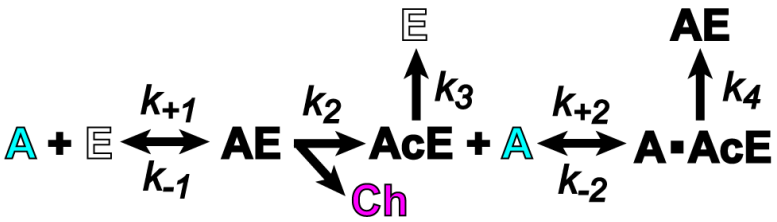


## 2. Random Walk Diffusion




## 3. Stochastic Biochemical State Transition



# Software Pipeline for Building MCell Models

Obtain or Create Model Mesh Geometry

↓

Annotate Meshes

↓

Specify Non-Spatial Model Parameters

↓

Simulate Model

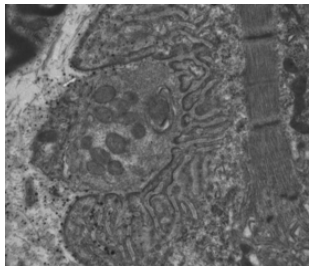
↓

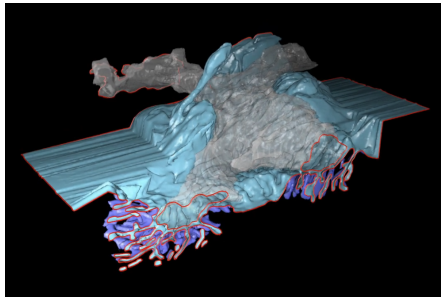
Visualize and Analyze Results

# Geometry Creation, Mesh Generation, Annotation

Model geometries for MCell simulations can be obtained via:

1. Reconstruction of model mesh geometry from electron microscopy data





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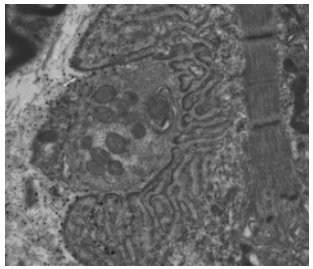
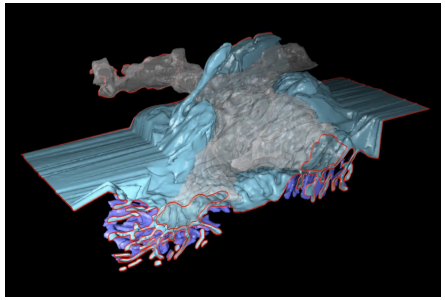
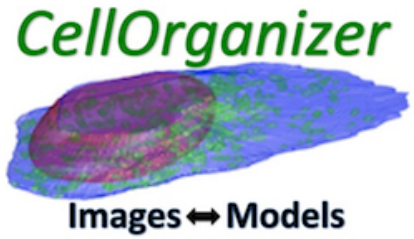
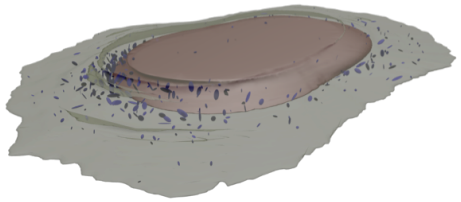




2. Generative models of cell organization from fluorescence microscopy imaging (**Day 3**)



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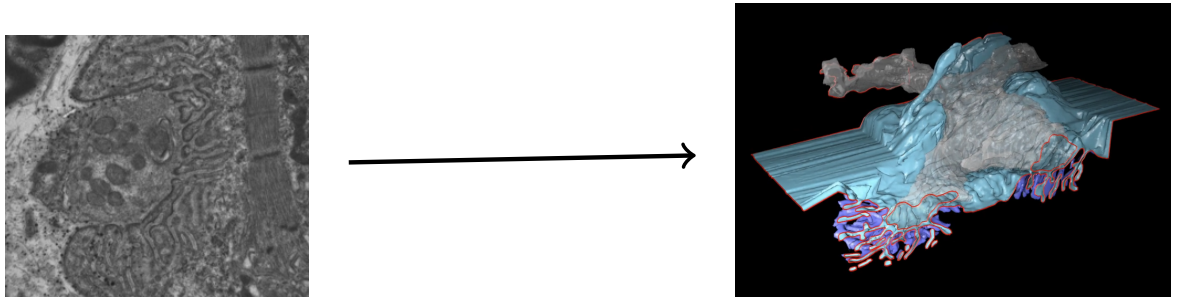

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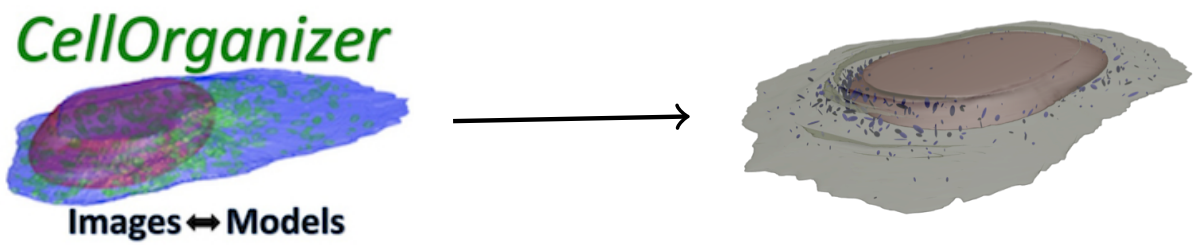
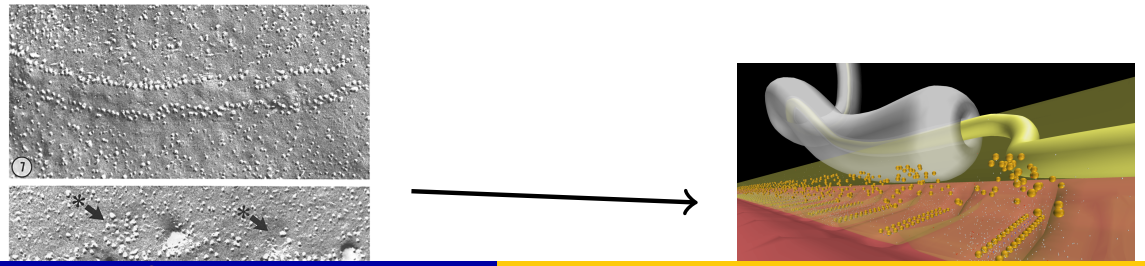
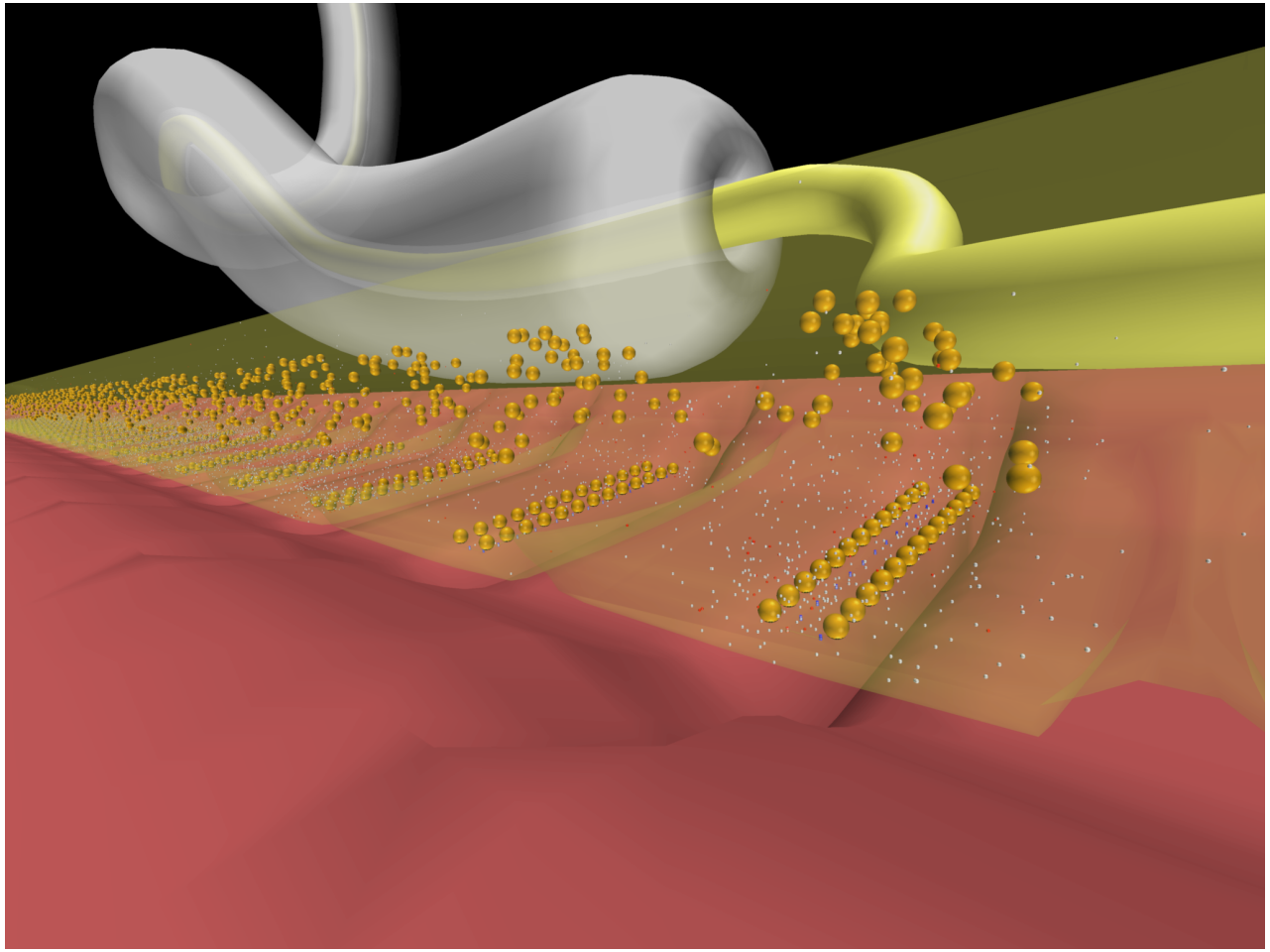



3. *In silico* geometry construction based on average geometry (**Day 1**)



# *In silico* Geometry Construction

Show 24 active zone model



# Software Pipeline to Build an MCell Model

Obtain or Create Model Mesh Geometry

↓

Annotate Meshes

↓

**Specify Non-Spatial Model Parameters**

↓

Simulate Model

↓

Visualize and Analyze Results

# Non-spatial Model Parameters

Beyond a geometry specification, MCell models typically also contain

- Molecules: can diffuse in space (volume molecules) or on mesh surfaces (surface molecules); requires knowledge of diffusion coefficients, concentrations/densities, locations.
- Reactions: requires knowledge of elementary reaction pathways (uni and bimolecular) and the corresponding reaction rate constants.
  Complex reaction networks can be described using rule based approaches via **BioNetGen** and then be imported into MCell models via CellBlender (**Day 2**).
- Output Specification: request output for visualization and analysis purposes; may require definition of additional geometry objects such as counting or sampling boxes.

# Software Pipeline to Build an MCell Model

Create Geometry

↓

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Simulate Model

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Visualize and Analyze Results

# Simulate Your Model

MCell simulations are run on the command line or from within CellBlender.

```
# mcell my_model.mdl
```

`my_model.mdl` contains the complete model description as Model Description Language (MDL).

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# mcell my_model.mdl
```

`my_model.mdl` contains the complete model description as Model Description Language (MDL).

```
# mcell -seed 10 my_model.mdl
```

# Software Pipeline to Build an MCell Model

Create Geometry

↓

Generate Meshes

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Annotate Meshes

↓

Specify Non-Spatial Model Parameters

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Simulate Model

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Visualize and Analyze Results

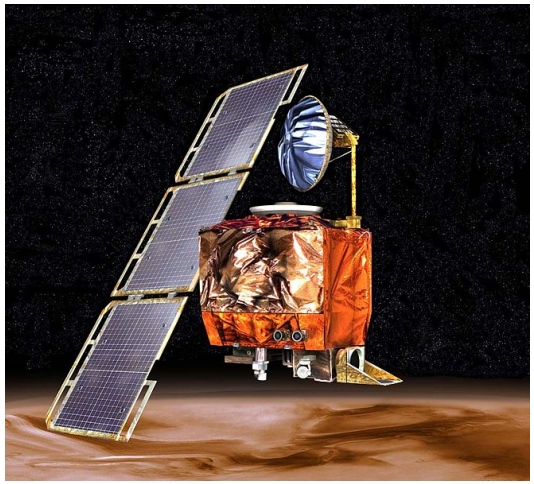
# Visualize and Analyse Results

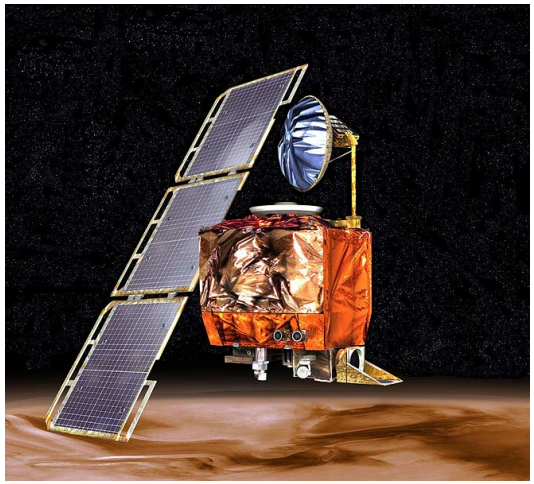
MCell provides two kinds of output (you specify how much of each, what molecules, etc.):

- Visualization Output for viewing via CellBlender, contains the location and orientation of surface and volume molecules.
- Reaction data output, contains time series of
  - volume molecule counts in specified regions of the model
  - surface molecule counts on specified regions of the model
  - reaction counts
  - hits or crossings of specific surface regions by surface and/or volume molecules
  - ...

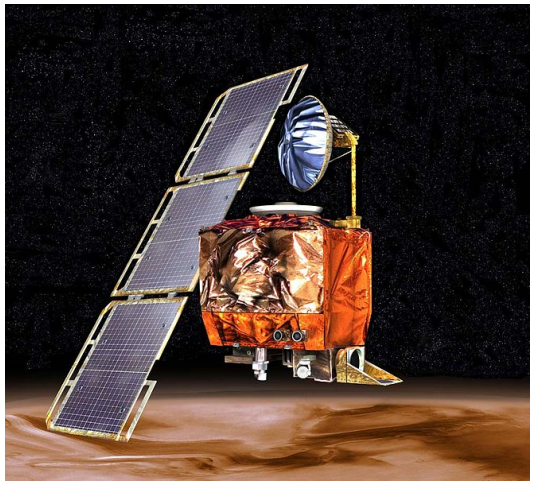
  Reaction data can be plotted with CellBlender and also be analyzed using external tools, e.g. `R`, `python`, `octave`, `MATLAB`, etc..

# MCell - Basic Definitions and Units





Mars Climate Orbiter, September 23, 1999



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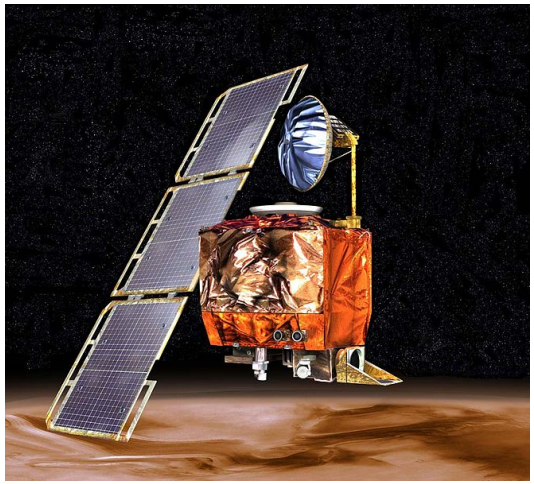
The MCO MIB has determined that the root cause for the loss of the MCO spacecraft was the failure to use metric units in the coding of a ground software file [...] The output from the SM_FORCES application code as required by a MSOP Project Software Interface Specification (SIS) was to be in metric units of Newtonseconds (N-s). Instead, the data was reported in English units of pound-seconds (lbf-s). [...] An erroneous trajectory was computed using this incorrect data.



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Don't let your MCell model become the next MCO!

# MCell - Basic Definitions and Units

- Spatial dimensions are in units of microns ($\mu m, 10^{-6} m$).
- Time is in units of seconds.
- Diffusion coefficients are in units of $cm^2 s^{-1}$.
- Uni-molecular reaction rate constants are in $s^{-1}$.
- Bi-molecular reaction rate constants between two volume or a volume and surface molecule are in $Mol^{-1} s^{-1}$.
- Bi-molecular reaction rate constants between two surface molecules are in $\mu m^2 \#^{-1} s^{-1}$.
- Each simulation runs for a specified number of iterations.
- The duration of an iteration is one timestep.

# Your First Model - MDL

MCell models are described using Model Description Language (MDL) (see
`http://www.mcell.org/documentation/qrg/index.html`
for a comprehensive list of keywords.)

MDL commands are written in ALL CAPS and consist of

- simple statements of the form

```
MDL_COMMAND = <value>
```

- statement blocks enclosed in curly braces describing a certain aspect of the simulation (geometry and release object definition, molecule definition)

```
MDL_BLOCK { <block content> }
```

where `<block content>` are other `MDL_COMMAND`s or `MDL_BLOCK`s.

Each MCell simulation needs to define the simulation *timestep* (TIME_STEP) and the number of *iterations* (ITERATIONS).

**first_model.mdl**

```
/* define variables for timestep
   and iterations */
iters = 100
dt    = 1e-6

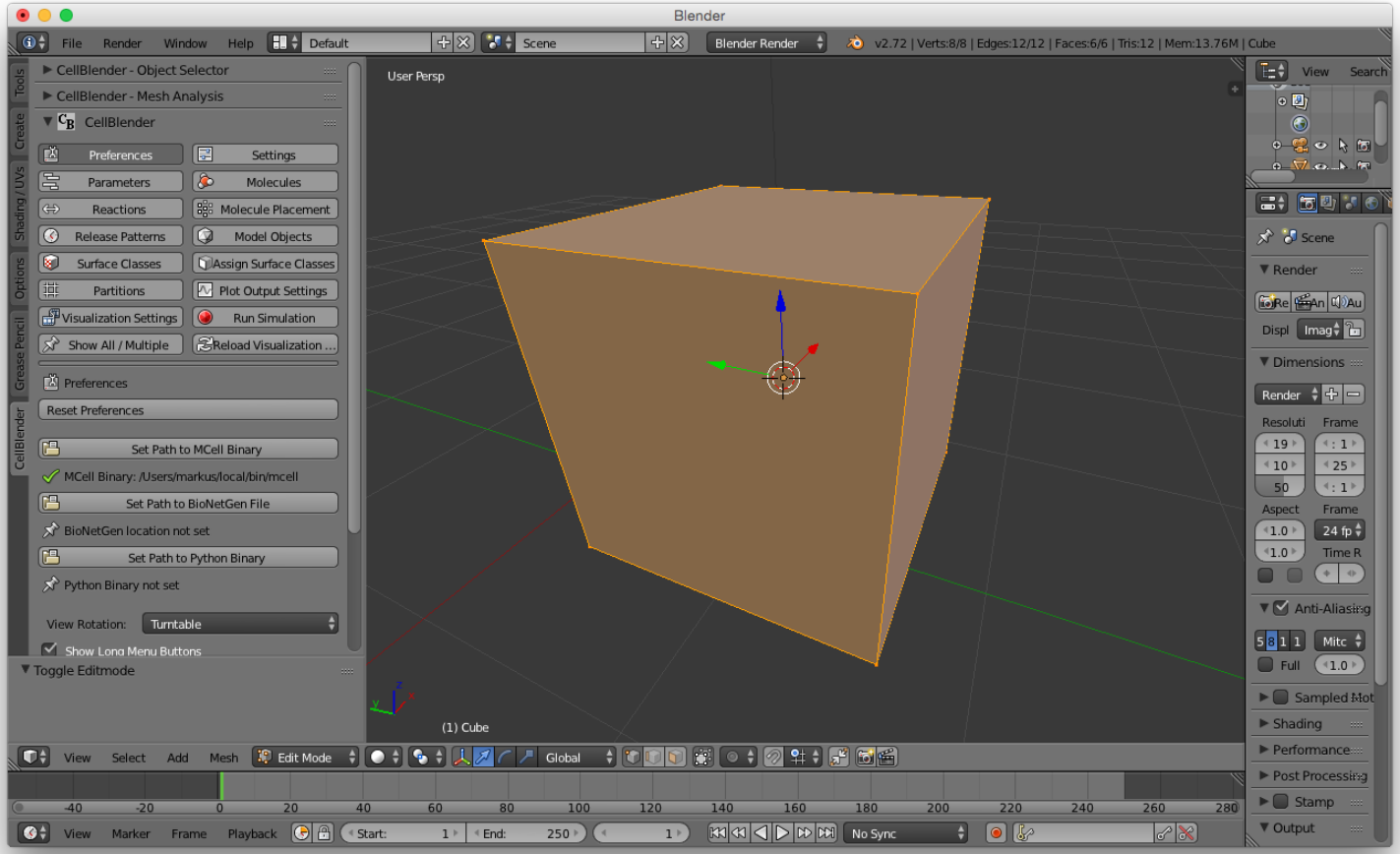
/* use variable to set actual keywords */
ITERATIONS = iters
TIME_STEP = dt
```

Notes:

- Within MDL you can define arbitrary variables (such as `iters`, `dt`).
- MDL is case sensitive - do not use ALL_CAPS for variables to avoid clashes with MCell keywords.
- You can use C-style comments (`/* */` and single line `//`).

# Your First Model - Defining Geometry

Next, we use CellBlender to construct a mesh which defines the 3D geometry of our model. We create a simple cube shaped object and export it in MDL format, `Cube.mdl`.



Then we add `Cube.mdl` to our MDL file ....

**first_model.mdl**

```
iters = 100
dt    = 1e-6
ITERATIONS = iters
TIME_STEP = dt

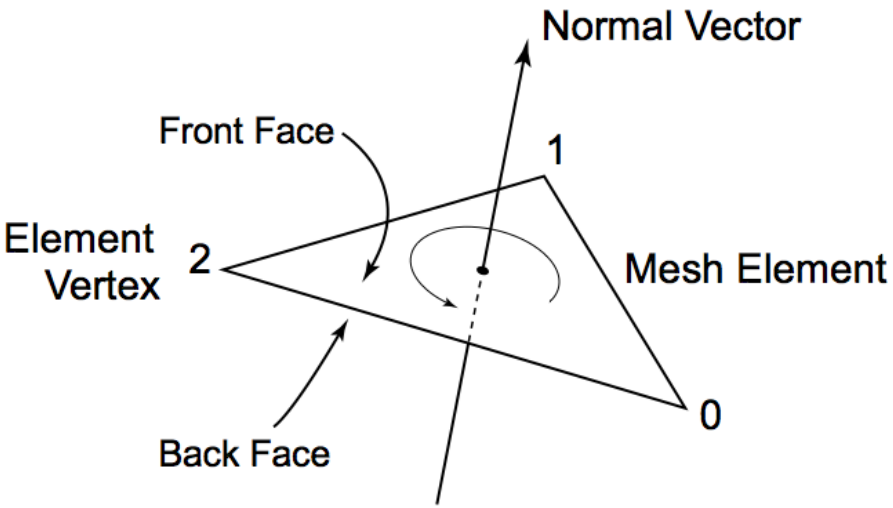
INCLUDE_FILE = "./Cube.mdl"
```

Notes:

- MDL files can include other MDL files which is very useful for organizing them, e.g., according to model component (geometry description, molecule definitions, etc.).
- Inclusion is lexical and thus the order of `INCLUDE` statements does matter.

## Cube.mdl

```
Cube POLYGON_LIST
{
  VERTEX_LIST
  {
    [ 1, 0.999999940395355, -1 ]
    [ 1, -1, -1 ]
    [ -1.00000011920929, -0.999999821186066, -1 ]
    [ -0.999999642372131, 1.00000035762787, -1 ]
    [ 1.00000047683716, 0.999999463558197, 1 ]
    [ 0.999999344348907, -1.00000059604645, 1 ]
    [ -1.00000035762787, -0.999999642372131, 1 ]
    [ -0.999999940395355, 1, 1 ]
  }
  ELEMENT_CONNECTIONS
  {
    [ 4, 0, 3 ]
    [ 4, 3, 7 ]
    [ 2, 6, 7 ]
    [ 2, 7, 3 ]
    [ 1, 5, 2 ]
    [ 5, 6, 2 ]
    [ 0, 4, 1 ]
    [ 4, 5, 1 ]
    [ 4, 7, 5 ]
    [ 7, 6, 5 ]
    [ 0, 1, 2 ]
    [ 0, 2, 3 ]
  }
  DEFINE_SURFACE_REGIONS
  {
    top
    {
      ELEMENT_LIST = [8, 9]
    }
  }
}
```



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  VERTEX_LIST
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  }
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    [ 4, 0, 3 ]
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    [ 1, 5, 2 ]
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    [ 0, 4, 1 ]
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    [ 4, 7, 5 ]
    [ 7, 6, 5 ]
    [ 0, 1, 2 ]
    [ 0, 2, 3 ]
  }
  DEFINE_SURFACE_REGIONS
  {
    top
    {
      ELEMENT_LIST = [8, 9]
    }
  }
}
```

Notes:

- Our Cube object is a `POLYGON_LIST` object, the most general way of specifying a geometrical shape within MDL.
- MCell also provides geometric primitives to define object geometry and molecule `RELEASE_SITE`s.
- `DEFINE_SURFACE_REGIONS` allows one to group subsets of triangles into surface regions.
- Meshes are by default reflective to all diffusing volume molecules but can be made absorptive or transparent via *surface classes*.

... and then make it part of the actual simulation model by adding it to the `INSTANTIATE`ed main object.

### first_model.mdl

```
iters = 100
dt    = 1e-6
ITERATIONS = iters
TIME_STEP = dt

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}
}
```

first_model.mdl

```
...

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}
}

...
```

Notes:

- Geometry objects can be combined into "meta" objects (here a single one called `World`).
- Within meta objects new geometry objects can be created, or exisiting objects can be copied and transformed (translation, rotation, scaling).
- Meta objects can be nested, i.e. contain other meta objects.

# Your First Model - Defining Molecules

Molecules are defined within a `DEFINE_MOLECULES` block. Our cube model will contain two volume molecules `Vol1`, `Vol2` and a surface molecule `Surf`.

**first_model.mdl**

```
iters = 100
dt    = 1e-6
ITERATIONS = iters
TIME_STEP = dt


DEFINE_MOLECULES {
  Vol1 {DIFFUSION_CONSTANT_3D = 1E-6}
  Vol2 {DIFFUSION_CONSTANT_3D = 1E-6}
  Surf  {DIFFUSION_CONSTANT_2D = 1E-7}
}

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}
}
```

Notes:

- Volume and surface molecules are distinguished via providing either a 3D or 2D diffusion coefficient.
- the units of the diffusion coefficient are $cm^2 s^{-1}$
- molecules in MCell are point particles

# Your First Model - Adding Molecules

Up to this point we only **defined** the molecules in our simulation but we haven't **released** any!

## first_model.mdl

```
...

DEFINE_MOLECULES {
  Vol1 {DIFFUSION_CONSTANT_3D = 1E-6}
  Vol2 {DIFFUSION_CONSTANT_3D = 1E-6}
  Surf {DIFFUSION_CONSTANT_2D = 1E-7}
}

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}

  vol1_rel RELEASE_SITE {
      SHAPE = World.Cube
      MOLECULE = Vol1
      NUMBER_TO_RELEASE = 2000
  }
  surf1_rel RELEASE_SITE {
      SHAPE = World.Cube[top]
      MOLECULE = Surf'
      NUMBER_TO_RELEASE = 2000
  }

}
```

- Volume and surface molecules can be released within `RELEASE_SITE` blocks.

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```
...

DEFINE_MOLECULES {
  Vol1 {DIFFUSION_CONSTANT_3D = 1E-6}
  Vol2 {DIFFUSION_CONSTANT_3D = 1E-6}
  Surf {DIFFUSION_CONSTANT_2D = 1E-7}
}

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}

  vol1_rel RELEASE_SITE {
      SHAPE = World.Cube
      MOLECULE = Vol1
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  }
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}
```

- Volume and surface molecules can be released within `RELEASE_SITE` blocks.
- For volume molecules the `SHAPE` keyword needs to reference a **closed** geometry object (qualified starting from the instantiated top level object) in which to release the molecules.

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```
...

DEFINE_MOLECULES {
  Vol1 {DIFFUSION_CONSTANT_3D = 1E-6}
  Vol2 {DIFFUSION_CONSTANT_3D = 1E-6}
  Surf {DIFFUSION_CONSTANT_2D = 1E-7}
}

INCLUDE_FILE = "./Cube.mdl"

INSTANTIATE World OBJECT {
  Cube OBJECT Cube{}

  vol1_rel RELEASE_SITE {
      SHAPE = World.Cube
      MOLECULE = Vol1
      NUMBER_TO_RELEASE = 2000
  }
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}
```
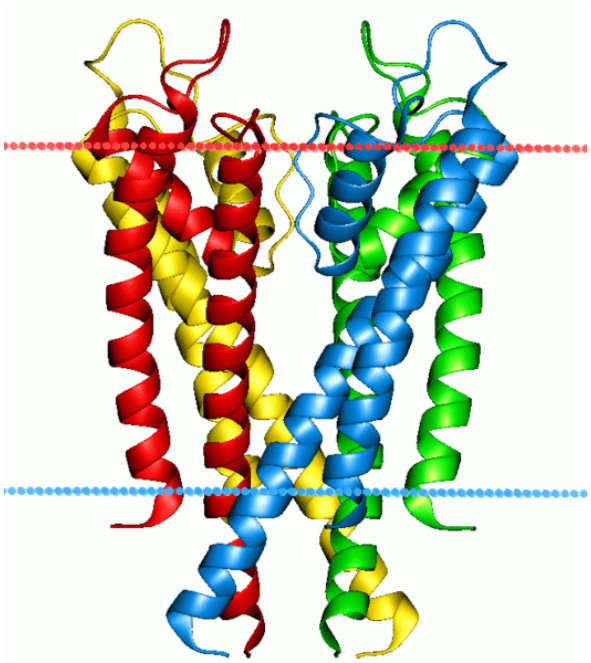

- Volume and surface molecules can be released within `RELEASE_SITE` blocks.
- For volume molecules the `SHAPE` keyword needs to reference a **closed** geometry object (qualified starting from the instantiated top level object) in which to release the molecules.
- For surface molecules the `SHAPE` keyword defines a surface region on a geometry object (here `top` on `World.Cube` via the `GeometryObject[<region specifier>]` syntax).

# Digression - Surface Molecules



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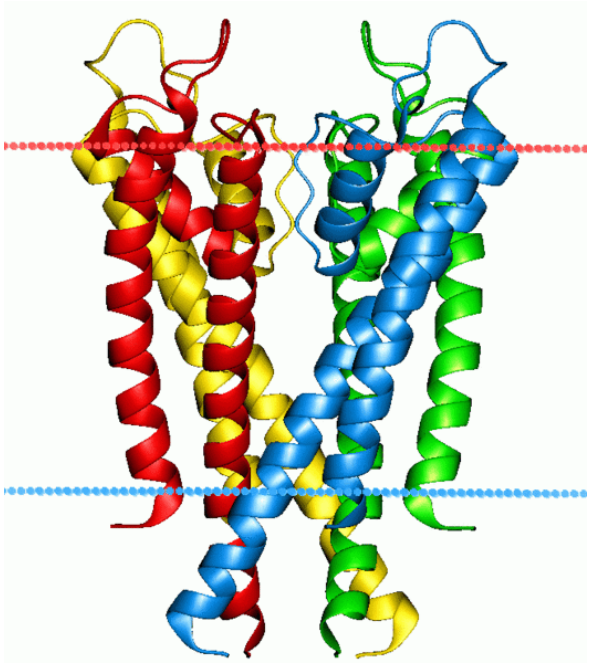
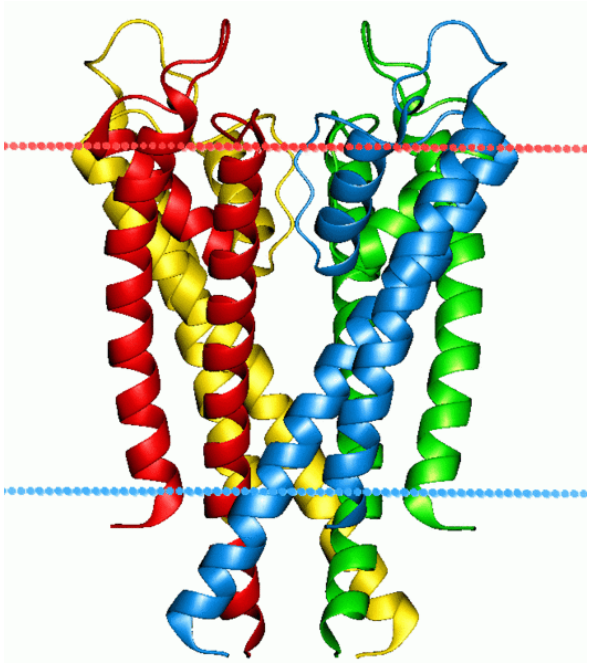


KcsA (image from Wikipedia)

# Digression - Surface Molecules

top



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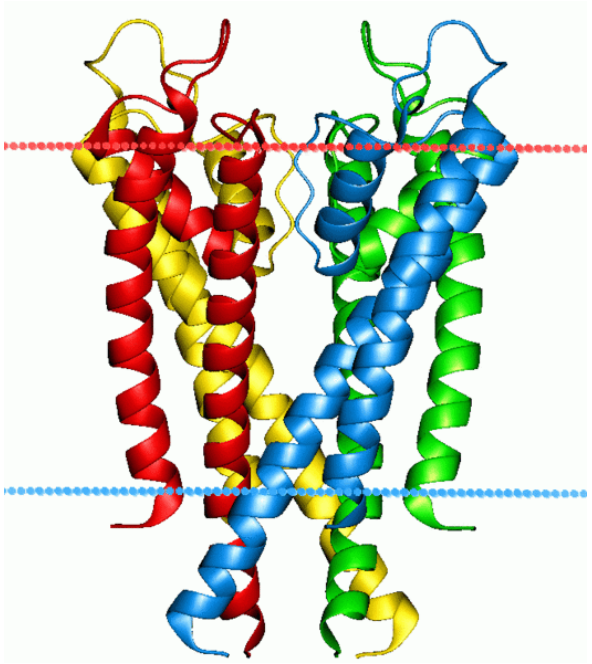

bottom

KcsA (image from Wikipedia)

- Surface molecules have a **top** and **bottom** domain.

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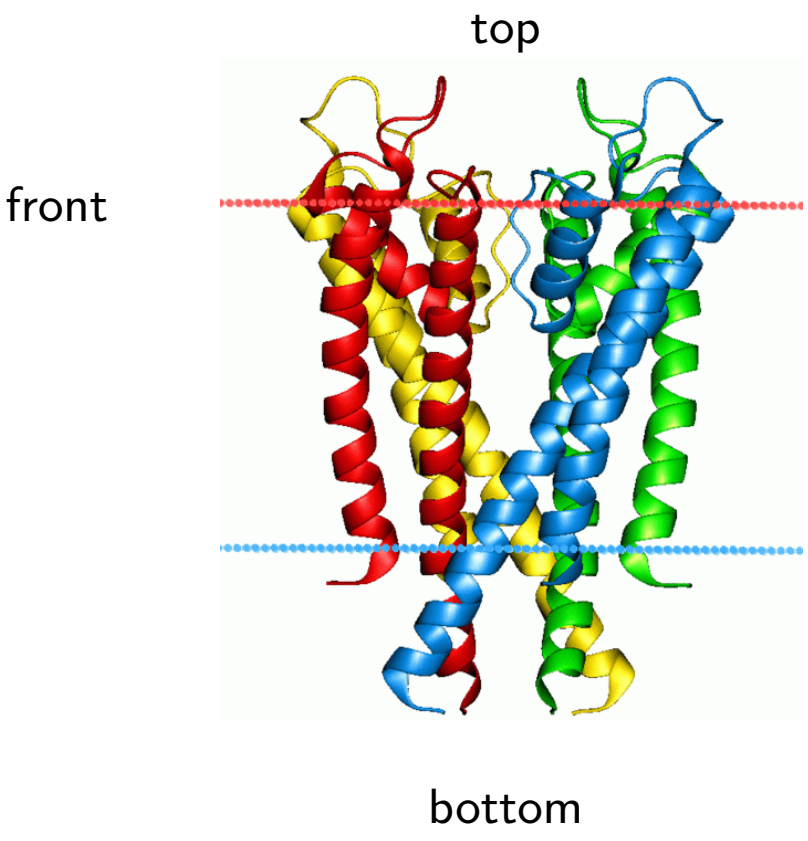


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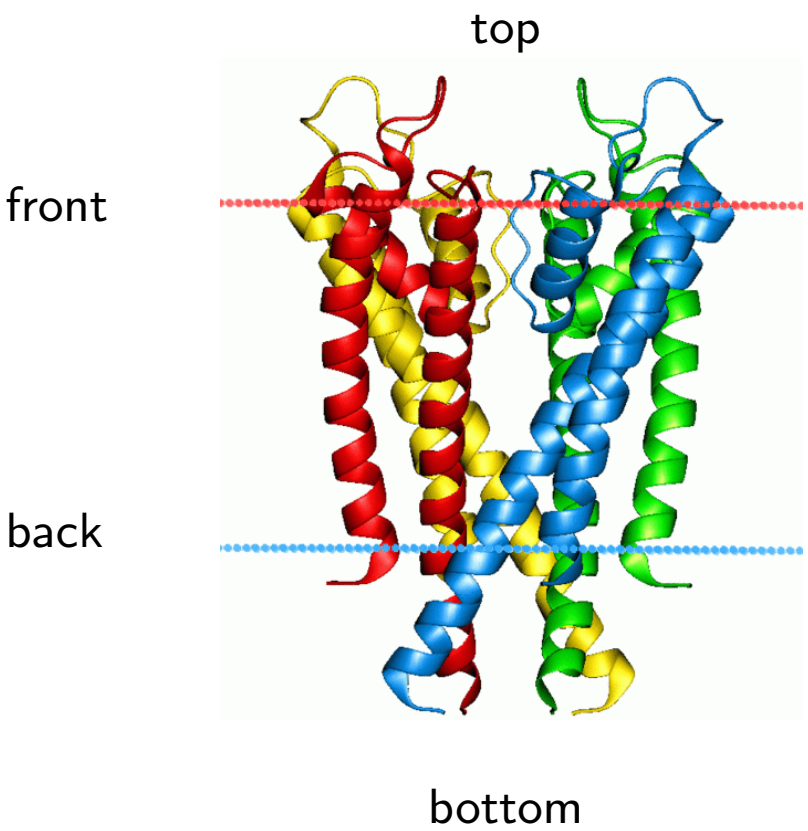
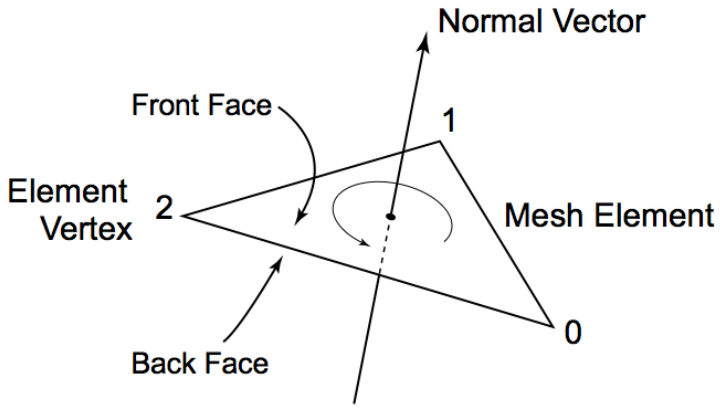


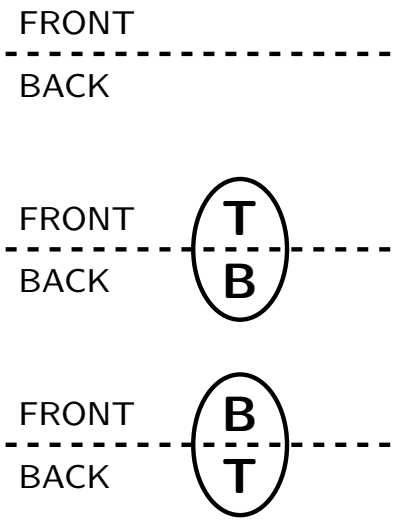

KcsA (image from Wikipedia)

- Surface molecules have a **top** and **bottom** domain.
- Surfaces (membranes) have a **front** and **back**.

# Digression - Surface Molecules

How does MCell handle surface molecule orientation?




- mesh tiles and thus surfaces have a unique front and back according to the *right hand rule*.
  **Note:** Your mesh tiles need to have a consisted orientation!
- surface molecules are either placed with their top at the front or the back of the surface!
- each mesh element is subdivided into (triangular) tiles which can each accommodate only a single surface molecules; surface molecules "acquire" a certain surface area. The tile density can be set via `SURFACE_GRID_DENSITY` (default 10000 $\mu m^{-2}$).

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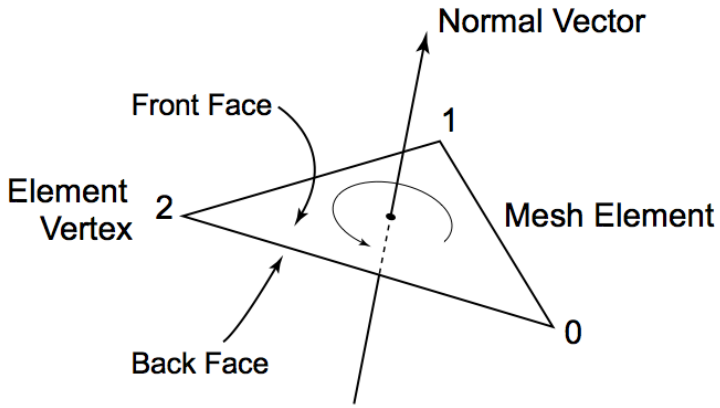


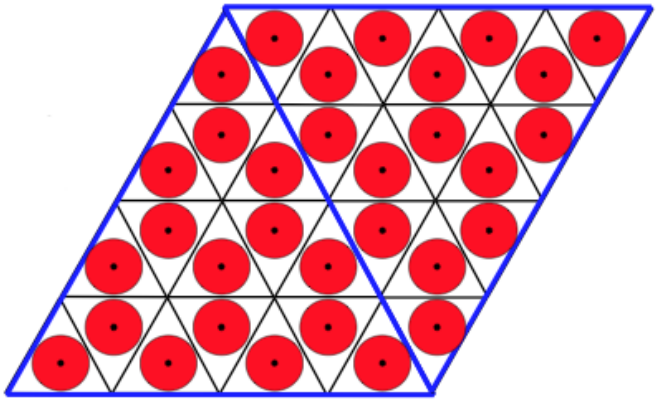

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# Digression - Surface Molecules

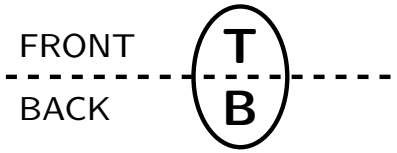
Now we can understand MCell's surface molecule placement syntax.

**first_model.mdl**

```
...

surf1_rel RELEASE_SITE {
  SHAPE = World.Cube[top]
  MOLECULE = Surf'
  NUMBER_TO_RELEASE = 2000
}
...
```

- `Surf'` places the molecule with its top at the FRONT of the surface.



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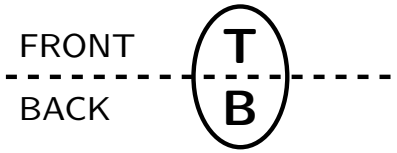
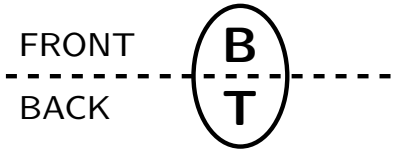



- `Surf,` places the molecule with its top at the BACK of the surface.



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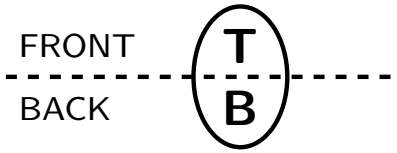
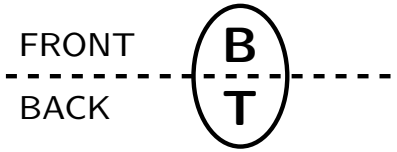
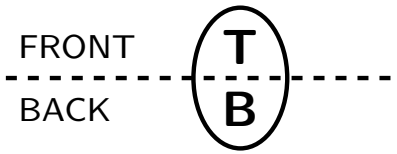



- `Surf,` places the molecule with its top at the BACK of the surface.




- `Surf;` places the molecule with its top randomly at the FRONT or BACK of the surface.

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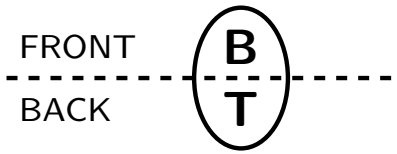

# Your First Model - Defining Reactions

Now that we have defined molecules and placed them in the `World` we can define reactions between them.

**first_model.mdl**

```
...

DEFINE_MOLECULES {
  Vol1 {DIFFUSION_CONSTANT_3D = 1E-6}
  Vol2 {DIFFUSION_CONSTANT_3D = 1E-6}
  Surf {DIFFUSION_CONSTANT_2D = 1E-7}
}

DEFINE_REACTIONS {
  /* creation of Vol2 */
  Vol1        -> Vol2 [1e4]

  /* annihilation of Vol2 */
  Vol2 + Vol2 -> NULL [1e6] : annih

  /* transport of Vol1 across surface
   * via Surf */
  Vol1, + Surf' -> Vol1' + Surf' [1e7]
}
```

- The general reaction syntax is

  `reactant(s) -> product(s) [rate] : name`

- Reactions can be named and then counted.

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- Reactions can be named and then counted.
- The units are
  - $[s^{-1}]$ for unimolecular reactions,
  - $[M^{-1}s^{-1}]$ for bimolecular reactions between two volume or a volume and a surface molecule.
  - $[\mu m^2 \#^{-1} s^{-1}]$ for bimolecular reactions between two surface molecules.
- Make sure your simulation parameters are such that reaction probabilities remain $< 1$.

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What is going on in the reaction involving `Vol1` and `Surf`?

How do we properly write reactions involving surface molecules in MCell?

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- Any reaction involving surface molecules requires orientation specifiers for **each** molecular player (volume and surface) involved.
- The *relative* location of orientation specifiers determines the relative orientation molecules need to have in order for the reaction to proceed.

How do we properly write reactions involving surface molecules in MCell?

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```
...

DEFINE_REACTIONS
  /* creation of Vol2 */
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  /* annihilation of Vol2 */
  Vol2 + Vol2 -> NULL [1e6] : annihi

  /* transport of Vol1 across surface
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```
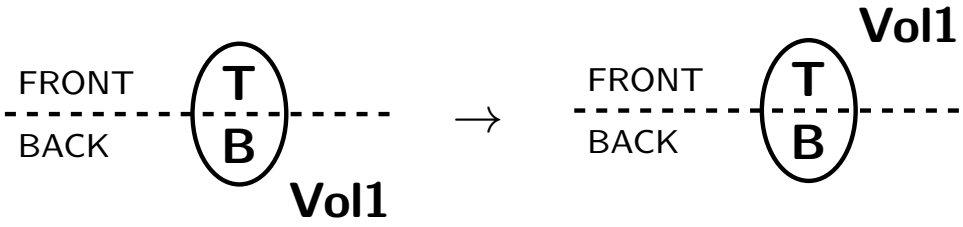

Since `Vol1` and `Surf` have

- opposite specifiers on the reactant side, `Vol1` reacts with the **bottom** of `Surf`.
- matching specifiers on the product side, `Vol1` reacts with the **top** of `Surf`.



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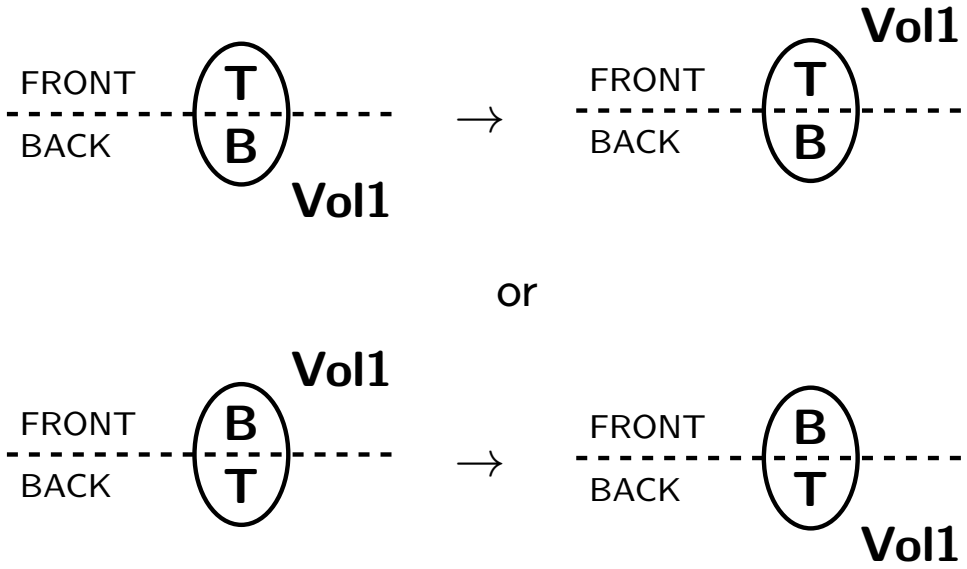

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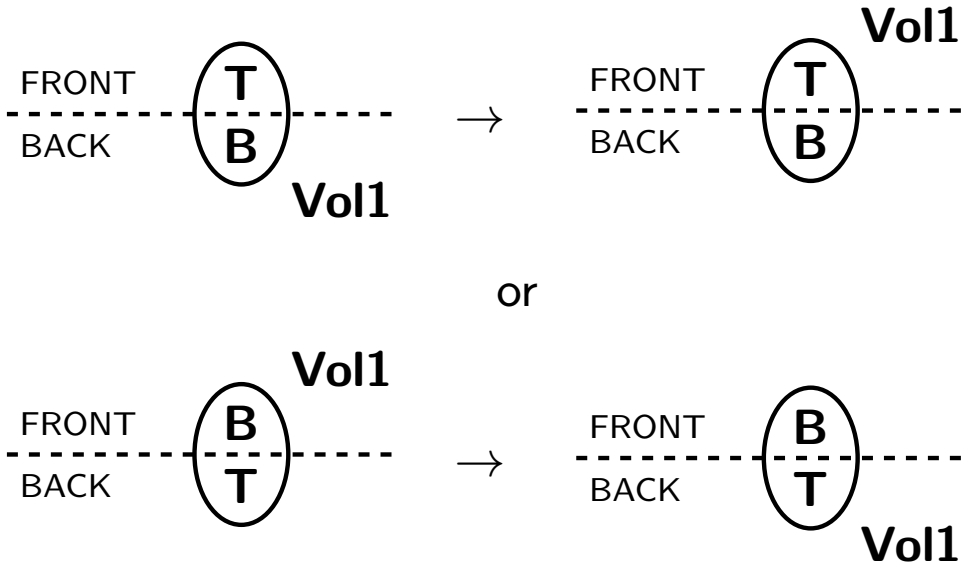
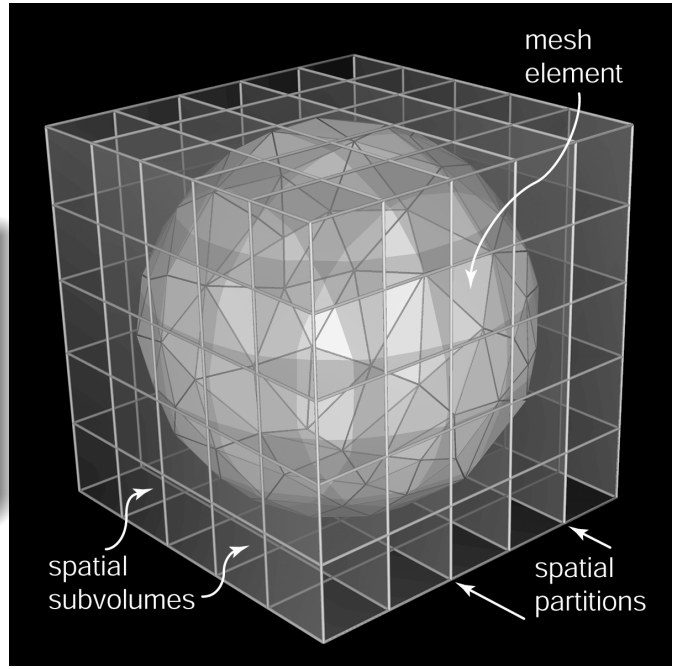



We will learn more about surface reactions later!

# Digression - Spatial Partitions For Efficiency

**first_model.mdl**

```
  ...
PARTITION_X = [[-1.0 TO 1.0 STEP 0.1]]
PARTITION_Y = [[-1.0 TO 1.0 STEP 0.1]]
PARTITION_Z = [[-1.0 TO 1.0 STEP 0.1]]
  ...
```




- Partitioning into spatial subvolumes is used by MCell to significantly speed up simulations via *divide and conquer*.

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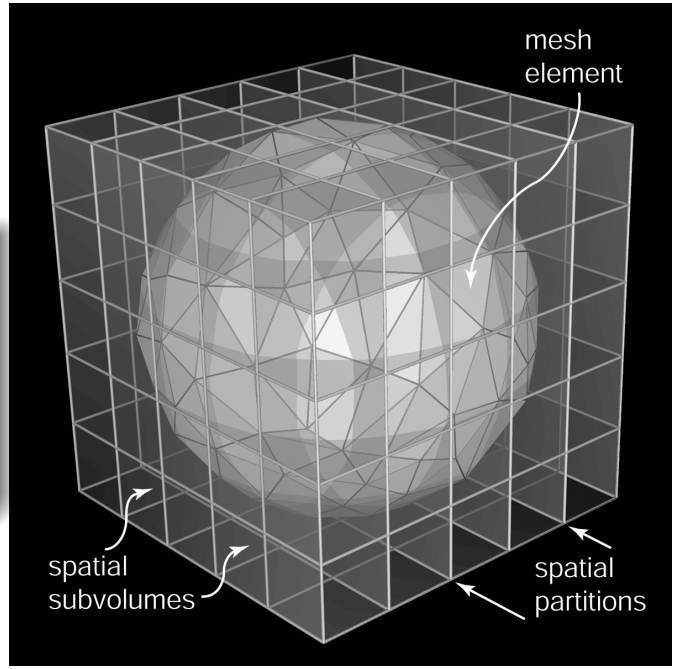


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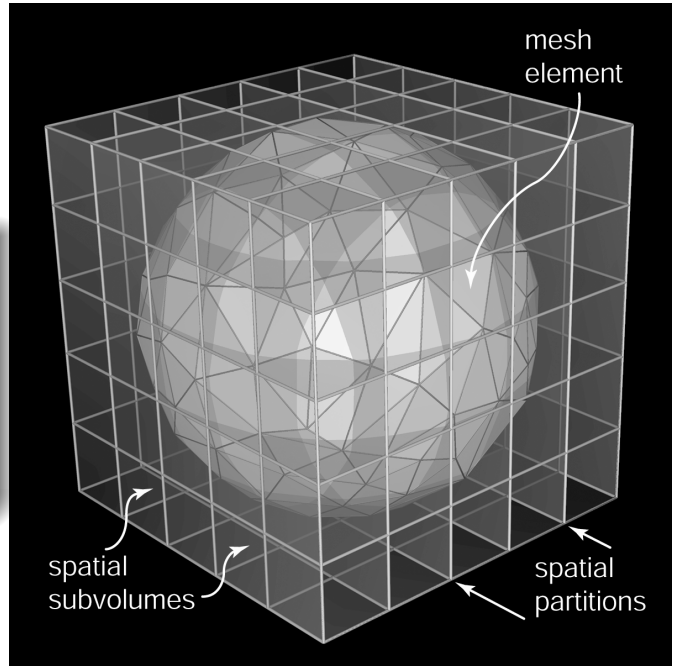


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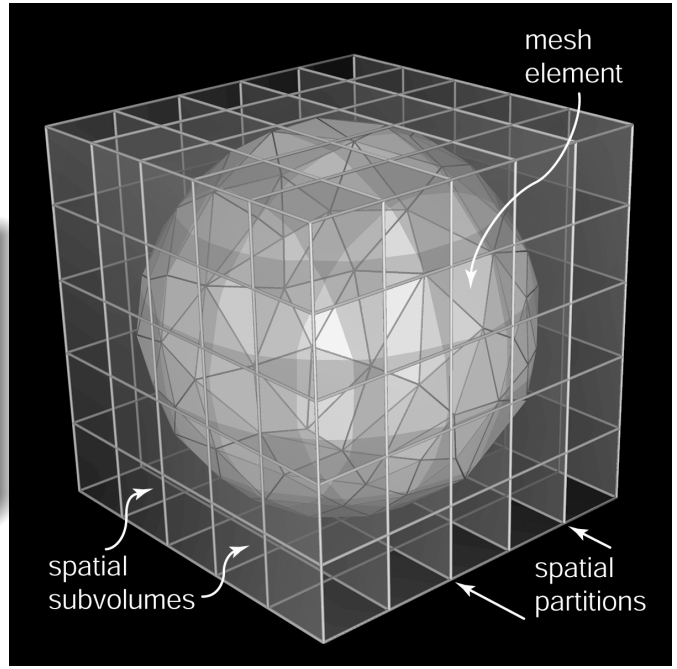


- Partitioning into spatial subvolumes is used by MCell to significantly speed up simulations via *divide and conquer*.
- Especially for larger models experimenting to find the proper partitioning scheme can lead to significant simulation speedup.
- Good partitioning requires hand tuning.
- There is a "sweet spot" between speed up due to an increased number of spatial subvolumes and excessive memory consumption.

# Your First Model - Generate Output

MCell provides to types of output

- Visualization Output for viewing your simulation in CellBlender.
- Reaction Data Output provides counts of molecules, events, reactions etc. in plain text ASCII format for further processing in your favourite tool.

# Your First Model - Reaction Data Output

## first_model.mdl

```
iters = 100
dt    = 1e-6
ITERATIONS = iters
TIME_STEP  = dt

cubeVolume = 1e-15
Na = 6.02214129e23

...

INSTANTIATE World OBJECT {
  Cube OBJECT Cube {}
  ...
}

REACTION_DATA_OUTPUT {
  STEP = dt
  {(COUNT[Vol1,WORLD])/cubeVolume/Na}
    => "./react_data/vol1_conc.dat"

  {COUNT[Vol2,WORLD]}
    => "./react_data/vol2.dat"
}
```

- Reaction data output is requested via a `REACTION_DATA_OUTPUT` block.
- `STEP` defines the interval at which to produce output.
- `COUNT` statements define what events to count and output. The general syntax is

  ```
  {COUNT[name , WORLD]} => "<filename>"     or
  {COUNT[name , object]} => "<filename>"    or
  {COUNT[name , region]} => "<filename>"
  ```

  where `name` is the name of a molecule or reaction.
- Output is typically in two column format

  ```
  ...
  time1   count1
  time2   count2
  time3   count3
  ...
  ```

# Your First Model - Visualization Data Output

**first_model.mdl**

```
iters = 100
dt = 1e-6
ITERATIONS = iters
TIME_STEP  = dt
...


VIZ_OUTPUT {
  VIZ_MOLECULE_FORMAT = CELLBLENDER
  FILENAME = "viz_data"
  MOLECULES {
      NAME_LIST {ALL_MOLECULES}
      ITERATION_NUMBERS {ALL_DATA @ ALL_ITERATIONS}
  }
}
```

- Visualization data output is requested via a `VIZ_OUTPUT` block.
- `VIZ_MOLECULE_FORMAT` defines the format of output the output and should be `CELLBLENDER` for compatibility with CellBlender.
- `FILENAME` defines the name of the master viz header file.
- `NAME_LIST` is a whitespace separated list of molecule names to output. `ALL_MOLECULES` outputs all molecules.
- `ITERATION_NUMBERS` defines what to output (`POSITIONS`, `ORIENTATIONS` or `ALL_DATA`) and when to output as a list of iterations (or `ALL_ITERATIONS`)

Visualization data can be read and visualized by CellBlender.