Using Chemical Reactions in MCell3

1. Volume and Surface Molecules

Volume molecules diffuse in solution and are represented simply as points in space. Hence, they do not have a fixed shape or spatial orientation. Volume molecules can react with each other or with surface molecules.

Surface molecules diffuse on surface mesh elements and thus are oriented in space. They can react with volume molecules or other surface molecules, and can be envisioned as triangular tiles that occupy a grid laid out on each mesh element (Fig. 1). **(Note: diffusion of surface molecules and reactions between surface molecules are presently experimental features in MCell3).**

All volume and surface molecules used in a simulation must be defined by a user-supplied name and diffusion coefficient. The names must be unique, and the distinction between volume and surface molecules is made by specifying either a 3-D or 2-D diffusion coefficient, respectively. For example:

```
DEFINE_MOLECULES {
        VR1 { DIFFUSION_CONSTANT_3D = value_1 }
        ...
        VRn { DIFFUSION_CONSTANT_3D = value_2 }

        SR1 { DIFFUSION_CONSTANT_2D = 0 }
        ...
        SRn { DIFFUSION_CONSTANT_2D = 0 }

        VP1 { DIFFUSION_CONSTANT_3D = value_3 }
        ...
        VPn { DIFFUSION_CONSTANT_3D = value_4 }

        SP1 { DIFFUSION_CONSTANT_2D = 0 }
        ...
        SPn { DIFFUSION_CONSTANT_2D = 0 }
}
```

In the foregoing abbreviated MDL example, *n* different volume and surface molecules have been given generic names of VR*i* (volume reactant, *i* = index number), SR*i* (surface reactant), VP*i* (volume product), and SP*i* (surface product). Diffusion constant *values* are given in units of $cm^2 \cdot sec^{-1}$, and in this case all of the surface molecules are stationary because each has a diffusion coefficient of zero.

2. General Rules for Reaction Stoichiometry

- **There can be one or two named molecules on the reactant side of each reaction statement.** By definition, a single reactant constitutes a unimolecular (first order, see tutorial) reaction, and two reactants constitute a bimolecular (second order, see tutorial)

reaction. It is also possible to use a surface object on the reactant side to constrain the directionality of surface reactions, and this is discussed in Section 4 below.

- **Unimolecular reactions can have either a volume or surface reactant molecule.** Thus, in simplified generic form:

VR1 -> (products) [*rate_constant_value*]	/* A volume reactant is converted to some product(s). The *rate_constant_value* has units of inverse time, specifically sec^{-1}. */
SR1 -> (products) [*rate_constant_value*]	/* A surface reactant is converted to some product(s). */

- **Bimolecular reactions can have two volume reactants, two surface reactants, or one volume reactant plus one surface reactant.** Additional simplified examples:

VR1 + VR2 -> (products) [*rate_constant_value*]	/* A bimolecular association in solution. The *rate_constant_value* has units of inverse concentration per unit time, $(moles/liter)^{-1} \cdot sec^{-1}$. */
SR1 + SR2 -> (products) [*rate_constant_value*]	/* A bimolecular association on a surface. Rate constant units??? */
VR1 + VR1 -> (products) [*rate_constant_value*]	/* Self-association in solution. */
SR1 + SR1 -> (products) [*rate_constant_value*]	/* Self-association on a surface. */
VR1 + SR1 -> (products) [*rate_constant_value*]	/* A volume reactant binding to a surface reactant. */

- **Numerical coefficients are not allowed before reactant names.** Three or more molecular reactants would constitute a diffusion-reaction process in which all of the molecules hit each other and react simultaneously at the same point in space. Such processes are physically untenable (highly improbable) compared to alternative step-wise mechanisms in which the molecules meet in pairs.

- **An unlimited number of volume and/or surface products may be generated. Numerical coefficients are not allowed, but product names may be repeated to create multiple copies of a molecule.** The following are examples, again in simplified generic form:

VR1 -> VP1 (+ …VP*n*)	/* Unimolecular conversion of a volume reactant into a single volume product, or dissociation into multiple products */
VR1 -> VP1 + VP1	/* Unimolecular conversion of a volume reactant into two copies of a volume product */
SR1 -> SP1 (+ …SP*n*)	/* Unimolecular conversion of a surface reactant into a single surface product, or dissociation into multiple products */

SR1 -> SP1 + SP1	/* Unimolecular conversion of a surface reactant into two copies of a surface product */
VR1 + VR2 -> VP1 (+ …VP*n*)	/* Bimolecular association of two volume reactants; optional production of additional volume molecules */
SR1 + SR2 -> SP1 (+ …SP*n*)	/* Bimolecular association of two surface reactants; optional production of additional surface molecules */
VR1 + SR1 -> SP1	/* Bimolecular association of a volume reactant and a surface reactant to form a surface product; typically a binding reaction */
SR1 -> SP1 (+ ...SPn) + VP1 (+ …VP*n*)	/* Unimolecular conversion of a surface reactant to one or more surface products and volume products; typically an unbinding reaction */
VR1 + SR1 -> SP1 (+ ...SPn) + VP1 (+ …VP*n*)	/* Bimolecular association of a volume reactant and a surface reactant with production of one or more surface and volume molecules */
VR + SR -> VP1 (+ …VPn)	/* Binding association of a volume reactant and a surface reactant with destruction of the surface molecule and production of one or more volume molecules */

- **The same molecule name can appear as a reactant and as a product. This allows self-association, regeneration, and autoproduction reactions:**

VR1 + VR1 -> VP1 (+ …VP*n*)	/* Bimolecular self-association of a volume reactant; optional production */
SR1 + SR1 -> SP1 (+ …SP*n*)	/* Bimolecular self-association of a surface reactant; optional production */
vol_mol -> VP1 + vol_mol	/* Creation of a volume product by a regenerated volume molecule */
sur_mol -> VP1 + sur_mol	/* Creation of a volume product by a regenerated surface molecule */
VR1 + vol_mol -> VP1 + vol_mol	/* Conversion of a volume reactant into a volume product, mediated by a regenerated volume molecule */
VR1 + surf_mol -> VP1 + surf_mol	/* Conversion of a volume reactant into a volume product, mediated by a regenerated surface molecule */
vol_mol -> vol_mol + vol_mol	/* Autoproduction of a volume molecule */
sur_mol -> sur_mol + sur_mol	/* Autoproduction of a surface molecule */
VR1 + vol_mol -> vol_mol + vol_mol	/* Autoproduction of a volume molecule from a volume reactant */

```
VR1 + sur_mol -> sur_mol + sur_mol   /* Autoproduction of a surface molecule from a
                                       volume reactant */
SR1 + sur_mol -> sur_mol + sur_mol   /* Autoproduction of a surface molecule from a
                                       surface reactant */
```

3. Orientation of Surface Molecules

In an MCell model of a biological system, surface molecules are often used to represent transmembrane proteins. A real protein in a cell membrane generally has distinct extracellular and intracellular structural domains, and a protein in an organelle membrane generally has distinct cytoplasmic and lumenal domains. Thus a protein's location in a membrane orients the molecule with respect to the membrane and the surrounding diffusion spaces, and in some cases it is possible for a protein's membrane orientation to flip, e.g., the extracellular and intracellular domains may be exchanged (Fig. 2). A diffusing ligand (molecule) in solution may bind to the protein, and typically will bind to a particular site on one of the protein's structural domains (e.g., a binding site that currently faces the extracellular space). When the ligand unbinds, it may reenter the same diffusion space from which it originated, or, if the protein has flipped orientation or somehow transported the ligand across the membrane, unbinding instead may occur in the diffusion space on the opposite side of the membrane.

In order to simulate such spatial properties of molecular interactions, surface molecules in MCell are given an orientation and have distinct (albeit virtual) structural domains. Since domain labels such as "extracellular" or "cytoplasmic" do not apply in all cases, the simple terms *top* and *bottom* are used instead. When a molecule is placed on a surface, it is given a particular position on a particular mesh element (triangle), and the *top* domain may be on the front or the back of the triangle. Therefore, there are two possible orientations, TOP_FRONT or TOP_BACK. The front and back of the triangle are defined by the order in which the triangle's vertices are listed when the mesh is created (Fig. 3). In general, adjacent mesh elements are expected to have adjacent front and back sides, so that the entire mesh object has a consistent front and back. DReAMM can be used to visualize mesh objects using different colors for the front and back, and also can be used to reverse individual mesh elements if necessary (links to DReAMM tutorials). In addition, directional icons such as arrows or receptor protein glyphs can be used to visualize the orientation of surface molecules (Fig. 4).

Initial orientations are assigned when surface molecules are added to mesh elements. At the beginning of a simulation, molecules can be added as a constituent of an entire mesh object, or as a constituent of a restricted mesh region. The number of molecules to be added is either specified explicitly using the NUMBER keyword, or is determined indirectly by specifying an average DENSITY (μm^{-2}) of molecules over the surface. In addition, molecules can be released onto a mesh region during a simulation (see Section ??? for examples). In any case, the initial orientation of surface molecules is specified as TOP_FRONT, TOP_BACK, or RANDOM, where RANDOM means that TOP_FRONT or TOP_BACK is assigned at random on a molecule-by-molecule basis (Fig. 5). It is important to realize, however, that the orientation of surface molecules may be changed by a reaction during a simulation, just as an actual membrane protein's orientation can change.

4. Spatial Properties of Surface Reactions

When volume molecules diffuse and react with surface molecules, and/or are produced by a surface molecule, then the directionality of the reaction must be specified. That is, does the reaction occur when the volume molecule encounters the top, bottom, or either domain of the surface molecule? And, similarly, does a newly produced volume molecule appear from the top, bottom, or either domain of the surface molecule?

To handle these (and other) possibilities, volume and surface molecules are labeled in reaction statements to indicate *membership in a reaction group* as well as their *relative alignment or directionality within the group*. In addition, a surface object (?? actually a surface class ??) may be included on the reactant side of the statement to further constrain the directionality of the interaction.

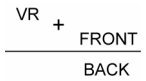
Tick marks (apostrophes and commas) are used to label molecule and surface names in reaction statements. The rules for group membership and alignment are:

- If molecules and the surface (if applicable) have the *same number* of ticks, then they are in the *same group*. *Different* numbers of ticks indicate *different* groups. For example, in the reaction (VR' + SR'' + surface' -> SP''), VR and the surface are in the same group, but SR and SP are in a different group.

- Within a group, *matching tick marks* (all apostrophes or commas) indicate that the molecules and surface (if applicable) are *aligned*. *Different* tick marks instead indicate that they are *opposed*. For example, in the reaction (VR' + SR, + surface' -> SP,) all three molecules and the surface are in the same group, but VR is aligned with the surface and opposed to SR and SP, and so on.

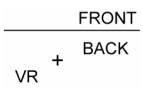
- If a volume molecule and a surface are *aligned*, then the volume molecule is on the FRONT side of the surface. If a volume molecule and a surface are *opposed*, then the volume molecule is on the BACK side of the surface.

  For example, (VR' + surface') could be used as part of a reaction in which VR dissolves into a membrane (VR is partitioned between aqueous and lipid phases), and can be diagrammed as:



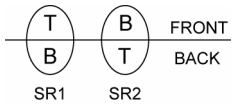
  The horizontal line indicates the surface (membrane) with its indicated FRONT and BACK sides. In this case, since VR and the surface are aligned, reaction is only possible if and when the volume reactant hits the FRONT of the surface. It is important to recognize that VR molecules in a simulation may also have access to the BACK of the surface, but the syntax (VR' + surface') precludes any reactions if and when VR hits the BACK.

  On the other hand, in (VR' + surface,) the molecule and surface are opposed, and so the diagram would be:

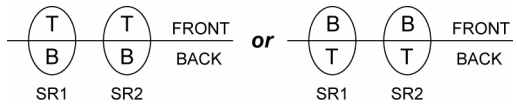


In this case reaction would only be possible if and when VR hits the BACK of the surface.

- If a surface molecule and a surface are *aligned*, then the TOP of the surface molecule is on the FRONT side of the surface, i.e, the molecule has an orientation of TOP_FRONT. Conversely, if they are opposed, then the TOP of the molecule is on the BACK of the surface and the orientation is TOP_BACK. Thus, in the following diagram, SR1 and the surface are aligned, while SR2 and the surface are opposed:

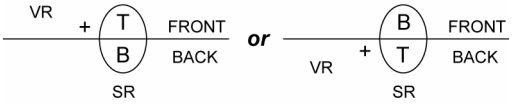


- If two surface molecules are *aligned*, then their TOPs are on the *same* side of the surface, whether it is the FRONT or the BACK. In the foregoing example, SR1 and SR2 are opposed to each other. In the following example, however, they are aligned in two different possible configurations:



On the left side of the diagram above, SR1 and SR2 are aligned with each other and are also aligned with the surface. On the right side they are aligned with each other but are opposed to the surface.

- If a volume molecule and a surface molecule are *aligned*, then the volume molecule and the TOP of the surface molecule are on the *same* side of the surface, whether it is the FRONT or the BACK. Thus (VR' + SR') can be diagrammed in two different ways:



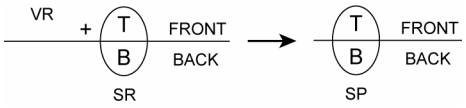
Therefore, in the example above VR can react with the TOP of SR whether SR is in the TOP_FRONT or TOP_BACK orientation. To restrict reaction to one specific orientation, the surface must be added, e.g., (VR' + SR' + surface') would correspond to the left alternative above, while (VR, + SR, + surface') would correspond to the right.

- The foregoing examples have illustrated use of alignment only for reactants, but the same rules apply to products as well. In summary:

    - If (VR is aligned with SR), and (SR is aligned with VP), then (VR is aligned with VP).
    - If (SR is aligned with SP), and (SR is aligned with VP), then (SP is aligned with VP).
    - If (SR is aligned with SP), and (SP is aligned with VP), then (SR is aligned with VP).

  For example, the binding reaction (VR' + SR' + surface' -> SP') would be diagrammed

as:



In this case all of the molecules and the surface are aligned, and the reaction can only occur when and if the VR hits the TOP of the SR when and if it is in the TOP_FRONT orientation.

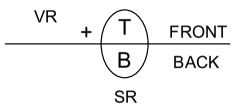
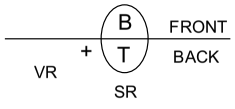
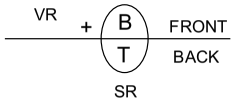
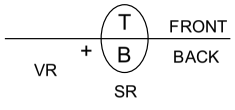
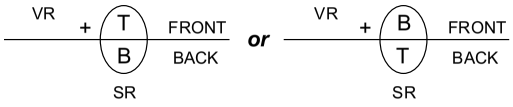
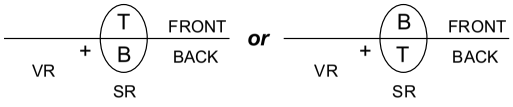
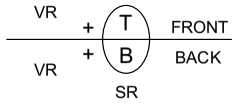
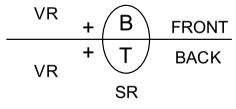
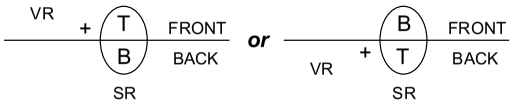
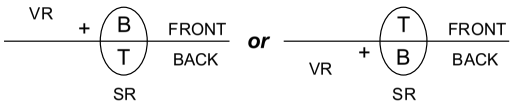
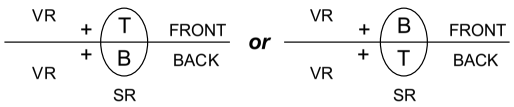
- If a pair of molecules and/or the surface belong to *different groups* (i.e., have different numbers of ticks), then *the directionality of reaction is randomized unless membership in another group exists and dictates otherwise*. In summary:

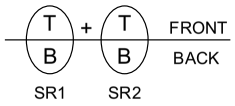
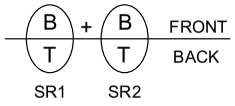
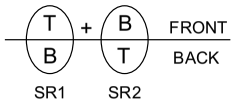
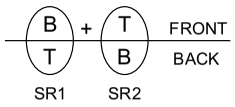
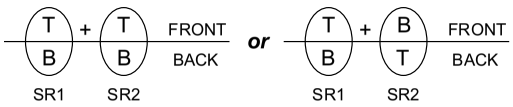
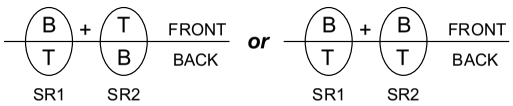
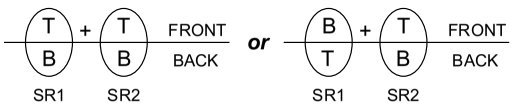
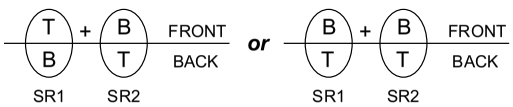
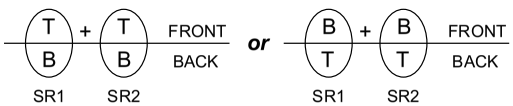
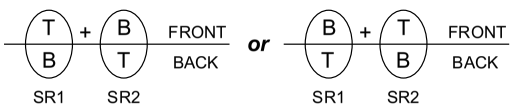
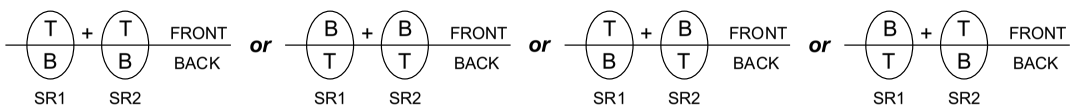
    - If a VR is in a unique group, then reaction can occur on either side of the surface and with the TOP or BOTTOM of a SR.
    - If a VP is in a unique group, then it is produced on either side of the surface with equal probability.
    - If a SR is in a unique group, then reaction can occur whether it is in the TOP_FRONT or TOP_BACK orientation.
    - If a SP is in a unique group, then it is produced in TOP_FRONT or TOP_BACK orientation with equal probability.

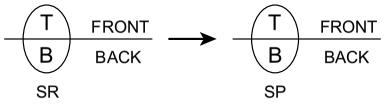
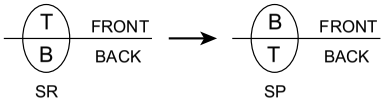
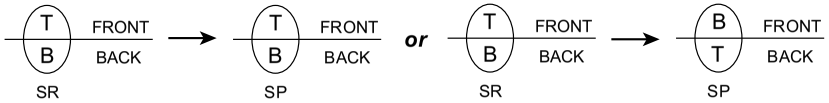
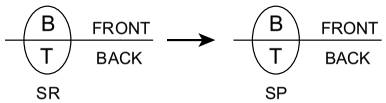
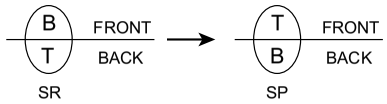
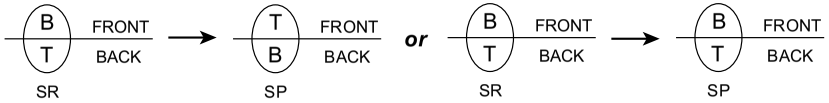
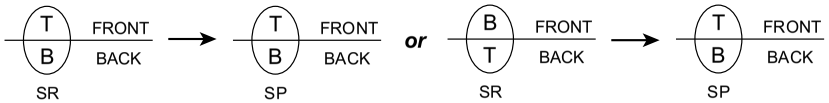
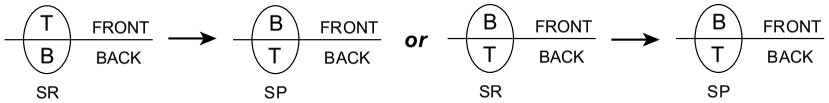
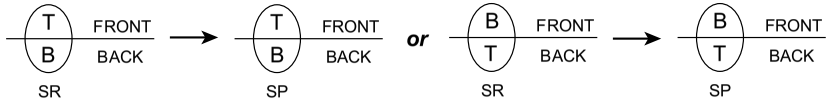
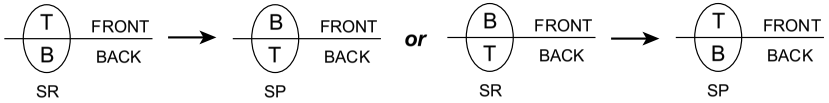
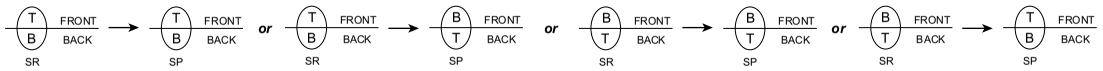
All of the foregoing rules are illustrated in Tables 1 – 5, which show diagrams and reaction syntax for all elementary combinations of reactants, products, alignment and orientation. Each example of syntax is shown in two equivalent forms produced by inverting all of the tick marks. Since alignment depends only on having the same *type* of tick mark, inverting all the tick marks in a reaction leaves all of the alignment relationships unchanged.

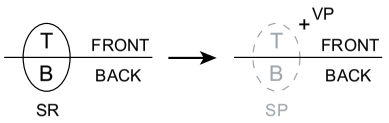
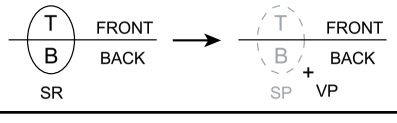
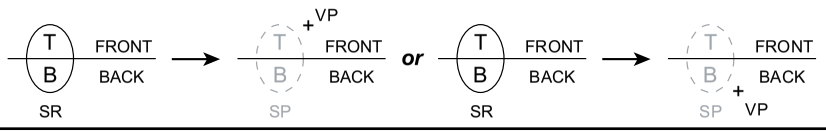
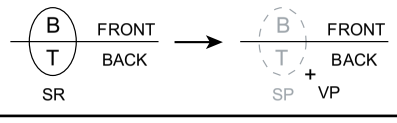
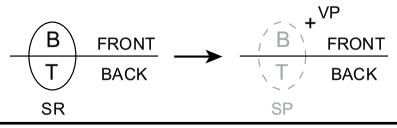
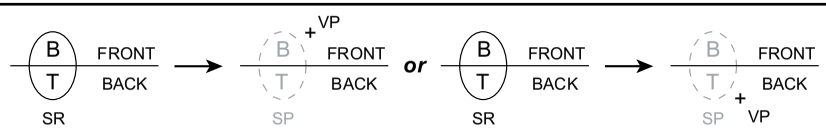
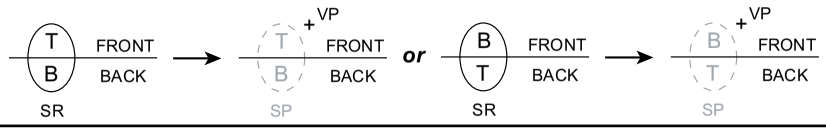
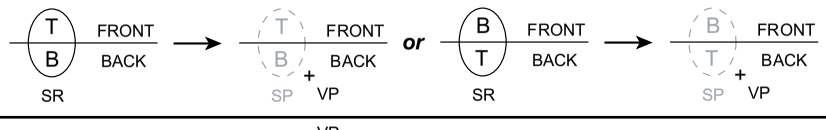
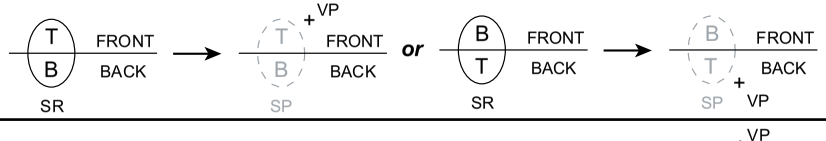
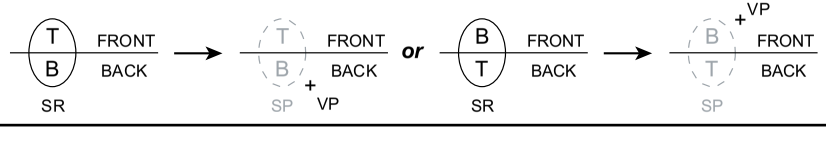
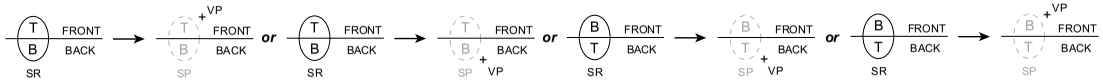
To write MDL reaction statements for more complex reactions than those shown in Tables 1 – 5, start with a diagram of the desired interaction. Make sure to include the correct initial orientations of the surface molecules and the possible locations of diffusing species, i.e., whether they have access to one or both sides of the surfaces. Then, simply match the elementary steps of the reaction with the corresponding diagrams in Tables 1 – 5 and then begin writing the corresponding syntax. Below are some examples for common biological reactions used in MCell simulations:

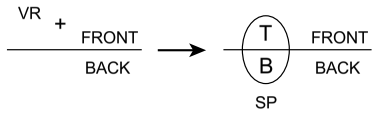
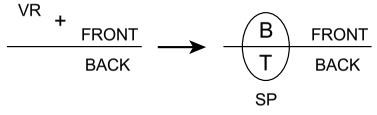
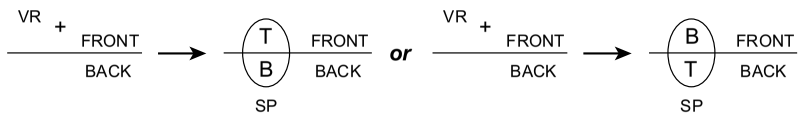
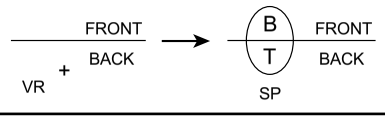
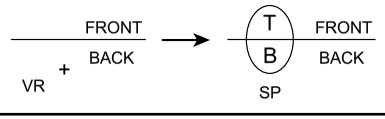
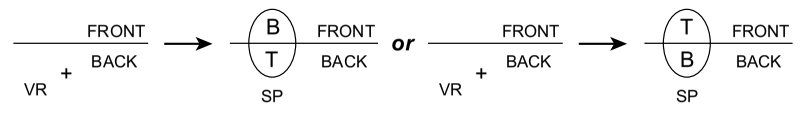
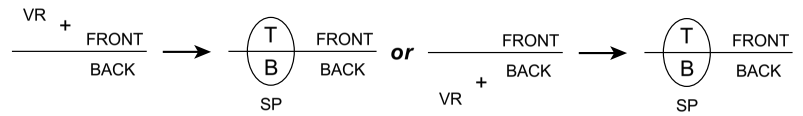
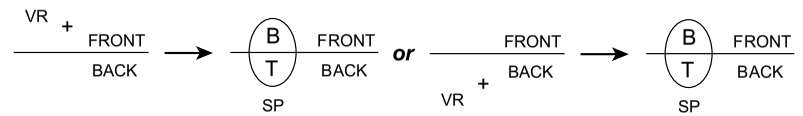
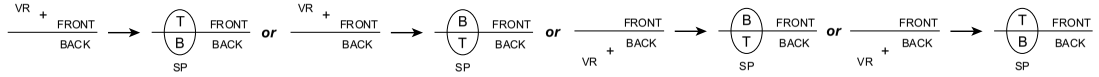
(receptor, transporter, etc.)

Bimolecular Reaction with Volume and Surface Reactants	*VR*	*SR*	*Syntax Examples*
	FRONT	TOP_FRONT	VR' + SR' + surface' VR, + SR, + surface,
	BACK	TOP_BACK	VR, + SR, + surface' VR' + SR' + surface,
	FRONT	TOP_BACK	VR' + SR, + surface' VR, + SR' + surface,
	BACK	TOP_FRONT	VR, + SR' + surface' VR' + SR, + surface,
	FRONT	EITHER	VR' + SR" + surface' VR, + SR,, + surface,
	BACK	EITHER	VR, + SR" + surface' VR' + SR,, + surface,
	EITHER	TOP_FRONT	VR" + SR' + surface' VR,, + SR, + surface,
	EITHER	TOP_BACK	VR" + SR, + surface' VR,, + SR' + surface,
	ALIGNED		VR' + SR' VR, + SR,
	OPPOSED		VR' + SR, VR, + SR'
	ANY		VR' + SR" VR, + SR,,

Bimolecular Reaction with Two Surface Reactants	*SR1*	*SR2*	*Syntax Examples*
	TOP_FRONT	TOP_FRONT	SR1' + SR2' + surface' SR1, + SR2, + surface,
	TOP_BACK	TOP_BACK	SR1, + SR2, + surface' SR1' + SR2' + surface,
	TOP_FRONT	TOP_BACK	SR1' + SR2, + surface' SR1, + SR2' + surface,
	TOP_BACK	TOP_FRONT	SR1, + SR2' + surface' SR1' + SR2, + surface,
	TOP_FRONT	EITHER	SR1' + SR2" + surface' SR1, + SR2,, + surface,
	TOP_BACK	EITHER	SR1, + SR2" + surface' SR1' + SR2,, + surface,
	EITHER	TOP_FRONT	SR1" + SR2' + surface' SR1,, + SR2, + surface,
	EITHER	TOP_BACK	SR1" + SR2, + surface' SR1,, + SR2' + surface,
	ALIGNED		SR1' + SR2' SR1, + SR2,
	OPPOSED		SR1' + SR2, SR1, + SR2'
	ANY		SR1' + SR2" SR1, + SR2,,

Unimolecular Reaction with Surface Reactant and Surface Product	*SR*	*SP*	*Syntax Examples*
	TOP_FRONT	TOP_FRONT	SR' + surface' -> SP' SR, + surface, -> SP,
	TOP_FRONT	TOP_BACK	SR' + surface' -> SP, SR, + surface, -> SP'
	TOP_FRONT	EITHER	SR' + surface' -> SP'' SR, + surface, -> SP,,
	TOP_BACK	TOP_BACK	SR' + surface, -> SP' SR, + surface' -> SP,
	TOP_BACK	TOP_FRONT	SR' + surface, -> SP, SR, + surface' -> SP'
	TOP_BACK	EITHER	SR' + surface, -> SP'' SR, + surface' -> SP,,
	EITHER	TOP_FRONT	SR' + surface'' -> SP'' SR, + surface,, -> SP,,
	EITHER	TOP_BACK	SR' + surface'' -> SP,, SR, + surface,, -> SP''
	ALIGNED		SR' -> SP' SR, -> SP,
	OPPOSED		SR' -> SP, SR, -> SP'
	ANY		SR' -> SP'' SR, -> SP,,

Unimolecular Reaction with Surface Reactant and Volume Product	*SR*	*VP*	*Syntax Examples*
	TOP_FRONT	FRONT	SR' + surface' -> VP' (+ SP') SR, + surface, -> VP, (+ SP,)
	TOP_FRONT	BACK	SR' + surface' -> VP, (+ SP') SR, + surface, -> VP' (+ SP,)
	TOP_FRONT	EITHER	SR' + surface' -> VP" (+ SP') SR, + surface, -> VP,, (+ SP,)
	TOP_BACK	BACK	SR, + surface' -> VP, (+ SP,) SR' + surface, -> VP' (+ SP')
	TOP_BACK	FRONT	SR, + surface' -> VP' (+ SP,) SR' + surface, -> VP, (+ SP')
	TOP_BACK	EITHER	SR, + surface' -> VP" (+ SP,) SR' + surface, -> VP,, (+ SP')
	EITHER	FRONT	SR' + surface'' -> VP" (+ SP') SR, + surface,, -> VP,, (+ SP,)
	EITHER	BACK	SR' + surface'' -> VP,, (+ SP') SR, + surface,, -> VP" (+ SP,)
	ALIGNED		SR' -> VP' (+ SP') SR, -> VP, (+ SP,)
	OPPOSED		SR' -> VP, (+ SP') SR, -> VP' (+ SP,)
	ANY		SR' -> VP" (+ SP') SR, -> VP,, (+ SP,)

Volume Reactant Becomes Surface Product	*VR*	*SP*	*Syntax Examples*
	FRONT	TOP_FRONT	VR' + surface' -> SP' VR, + surface, -> SP,
	FRONT	TOP_BACK	VR' + surface' -> SP, VR, + surface, -> SP'
	FRONT	EITHER	VR' + surface' -> SP'' VR, + surface, -> SP,,
	BACK	TOP_BACK	VR, + surface' -> SP, VR' + surface, -> SP'
	BACK	TOP_FRONT	VR, + surface' -> SP' VR' + surface, -> SP,
	BACK	EITHER	VR, + surface' -> SP'' VR' + surface, -> SP,,
	EITHER	TOP_FRONT	VR' + surface'' -> SP'' VR, + surface,, -> SP,,
	EITHER	TOP_BACK	VR' + surface'' -> SP,, VR, + surface,, -> SP''
	EITHER	EITHER	VR' + surface'' -> SP''' VR, + surface,, -> SP,,,

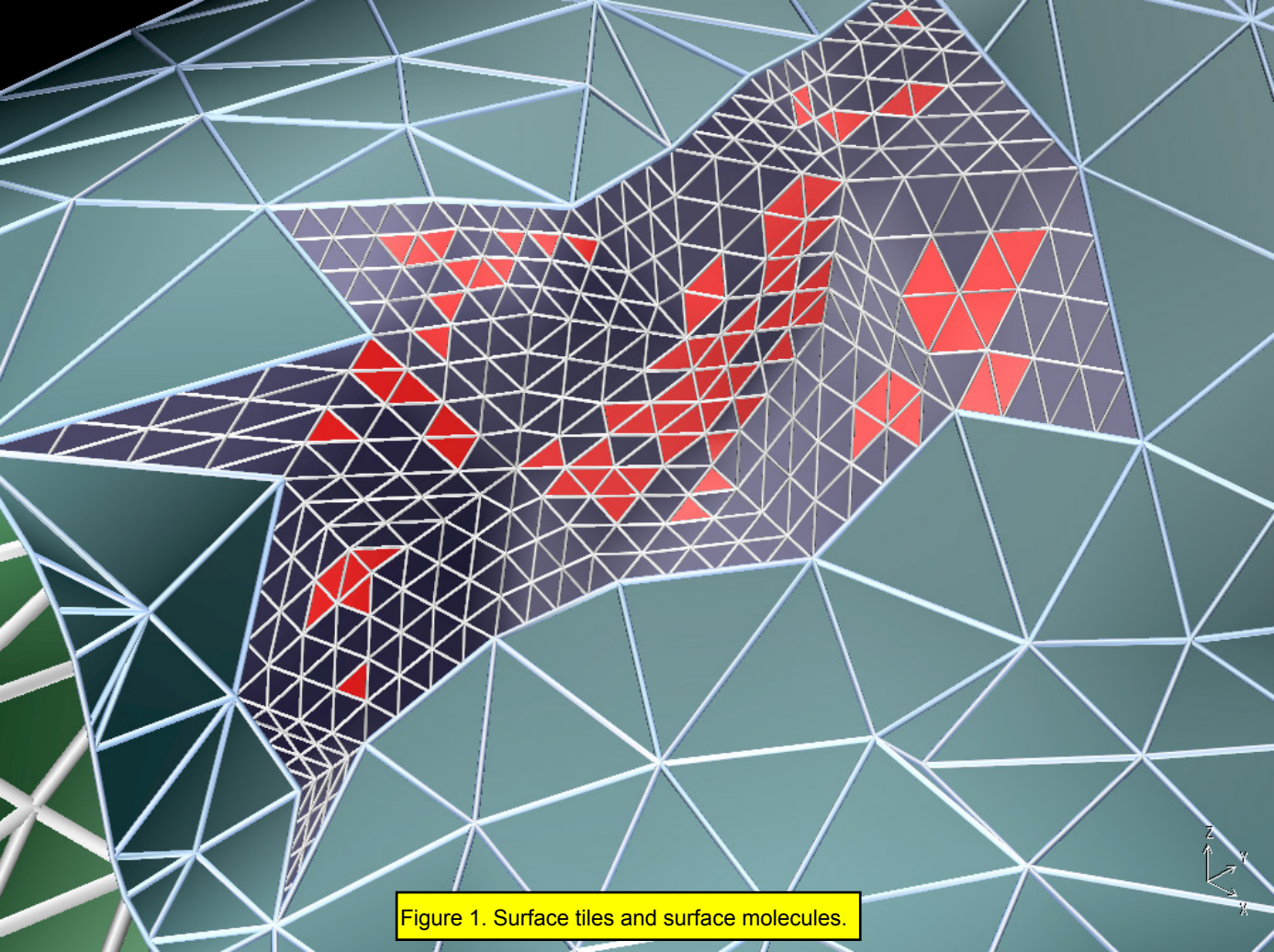


Figure 1. Surface tiles and surface molecules.

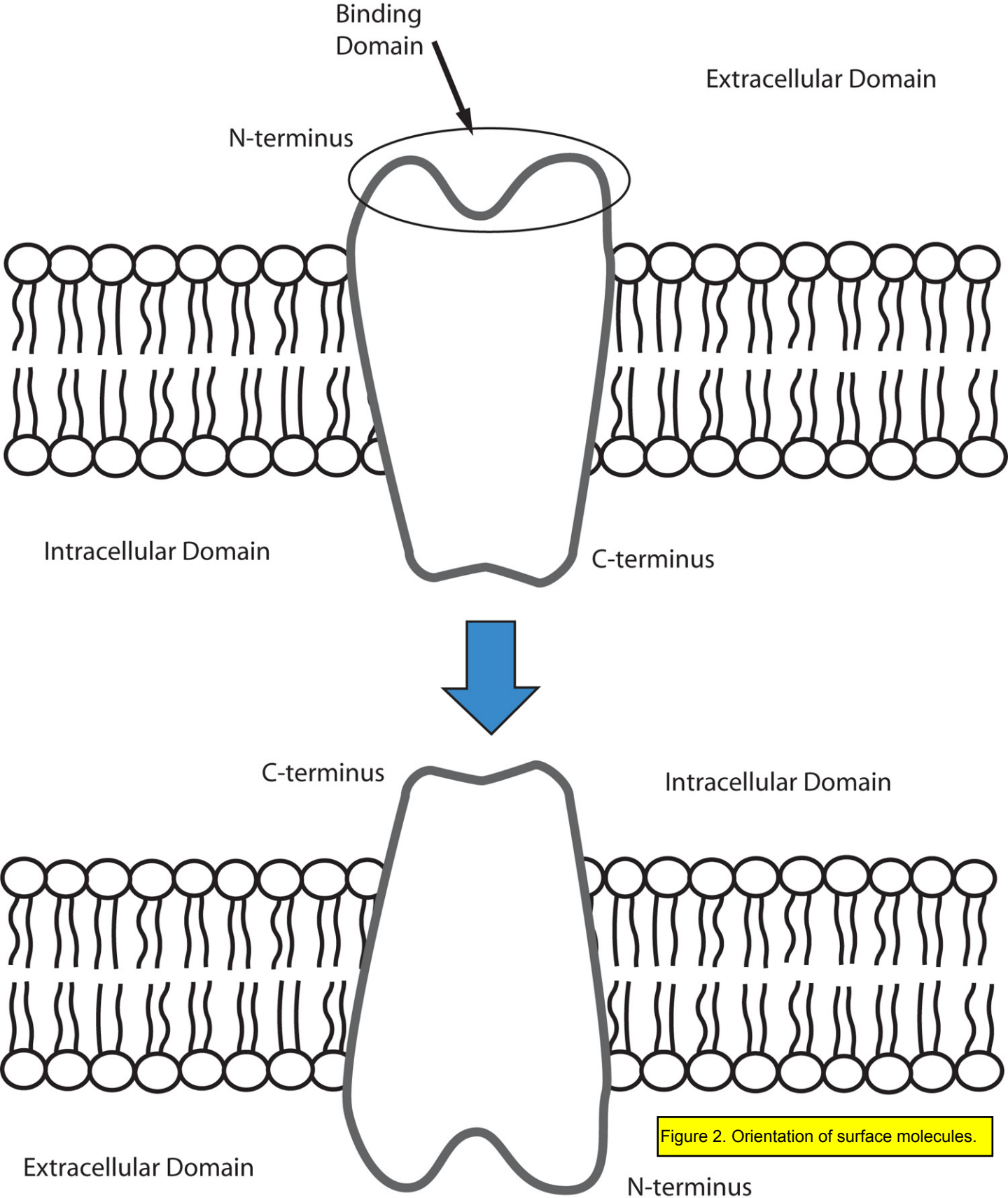


Figure 2. Orientation of surface molecules.

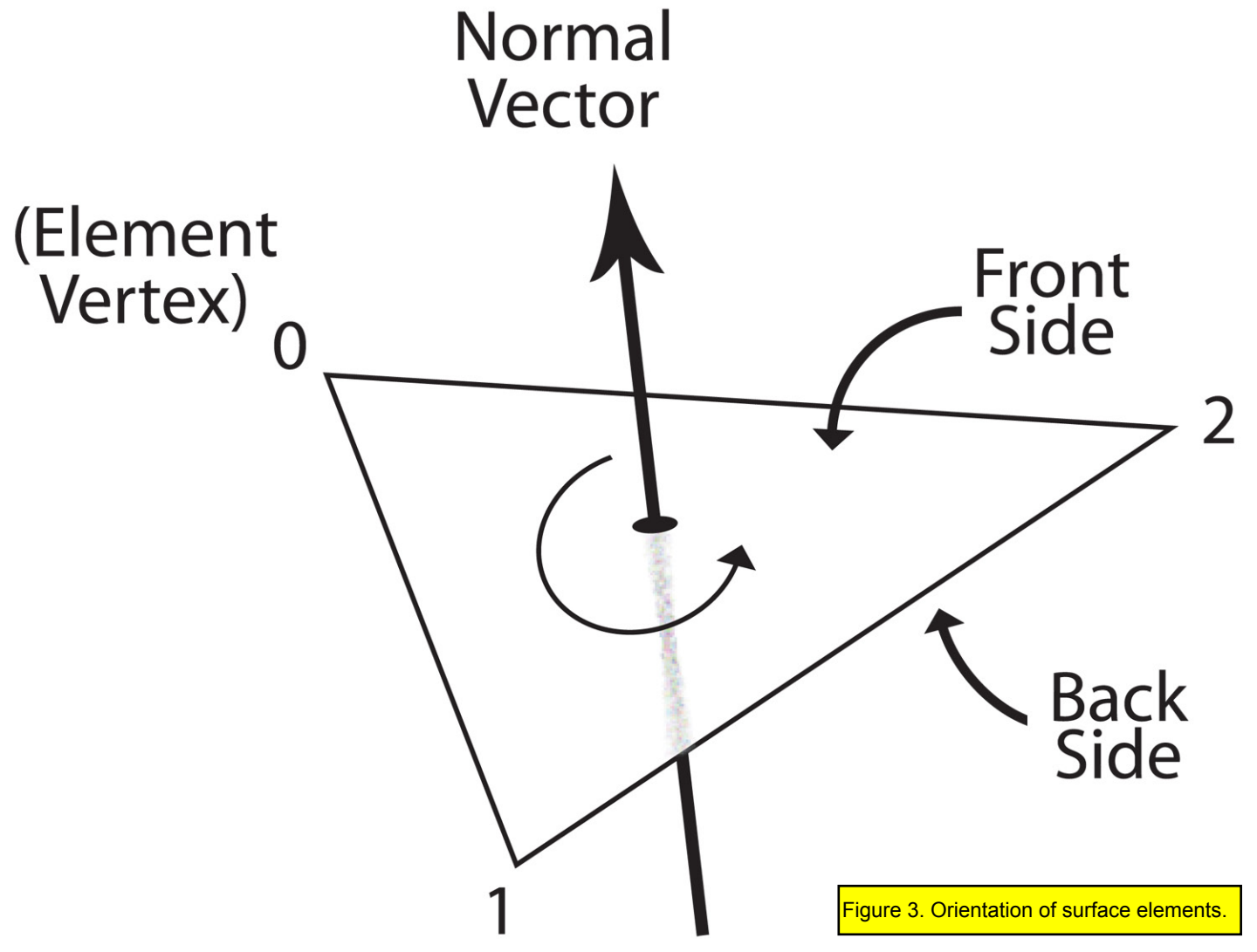


Figure 3. Orientation of surface elements.

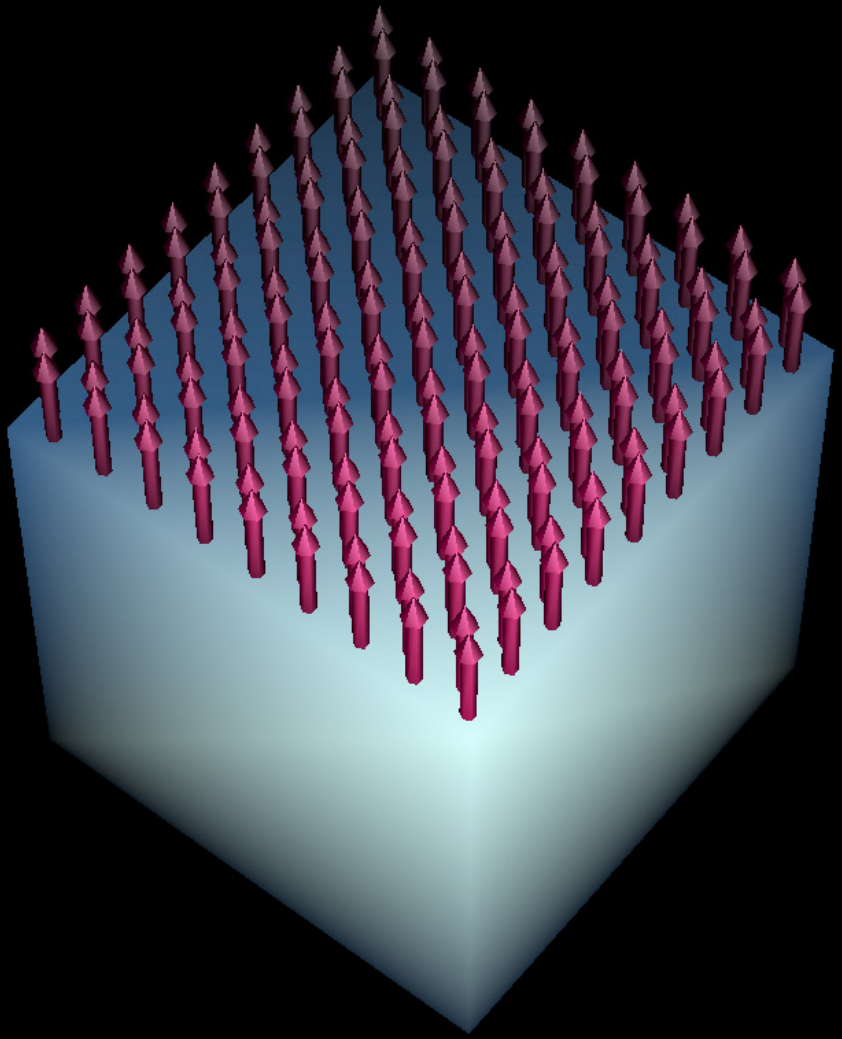


Figure 4. Surface molecules in TOP_FRONT orientation.

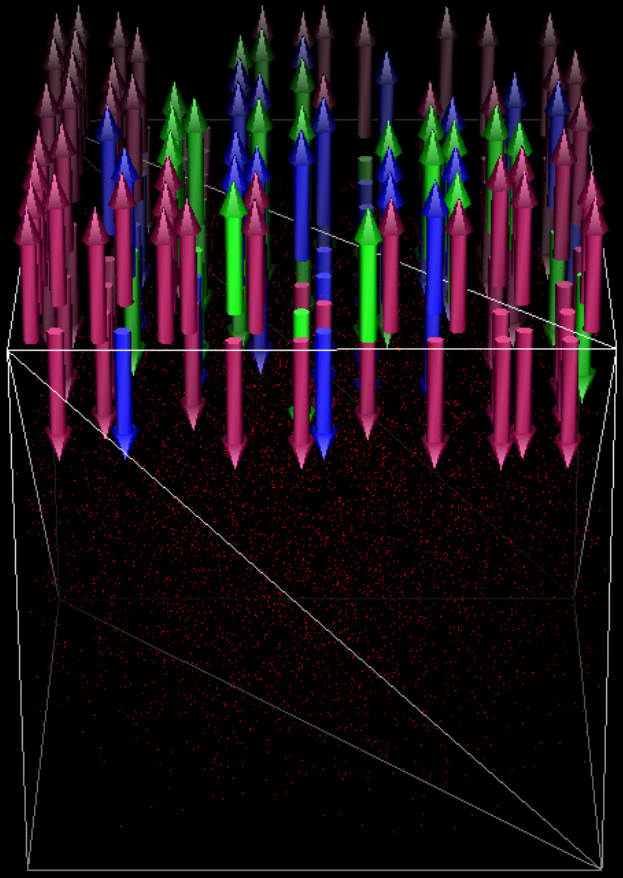


Figure 5. Surface molecules in RANDOM orientation.