1 Notation

- For any cell i with center $\mathbf{x}_i$, let R_i denote the region of space occupied by it. Assume that for any other cell j, that $R_i \cap R_j = \emptyset$.
- For any computational mesh with voxels $\{\Omega\}$ and corresponding volumes $\{W\}$, let $\rho(\Omega)$ denote the mean substrate density in voxel Ω, and let $n(\Omega) = \int_\Omega \rho \, \mathrm{d}V$ denote the total amount of substrate in the voxel.

  Note that BioFVM tracks the mean substrate density in each voxel, so $\rho \equiv \rho(\Omega)$ throughout Ω.
- For any voxel Ω_k with an index k, let W_k denote its volume, define $\rho_k = \rho(\Omega_k)$, and define $n_k = n(\Omega_k)$.
- For any cell i with center $\mathbf{x}_i$, let Ω_i denote the voxel containing cell i, with corresponding volume W_i.
- Let $\mathbb{1}_i(\mathbf{x})$ be the characteristic function for the cell, so that $\mathbb{1}_i(\mathbf{x}) = 1$ inside the cell (inside R_i), and $\mathbb{1}_i(\mathbf{x}) = 0$ otherwise.
- Let $V_i = \int_{\mathbb{R}^3} \mathbb{1}_i(\mathbf{x}) \, \mathrm{d}V = V_i$ be the total volume of cell i.

2 Net extracellular substrate change due to the i^{th} cell

Note that in BioFVM the cells' contribution to changes in total substrate in any volume Ω is given by

$$\frac{\partial}{\partial t} \int_\Omega \rho \, \mathrm{d}V = \sum_{\text{cells } i} \int_\Omega \mathbb{1}_i(\mathbf{x}) \Big(S_i \left(\rho_i^T - \rho \right) - U_i \rho \Big) \, \mathrm{d}V \tag{1}$$

$$\approx \sum_{\text{cells } i} V_i \int_\Omega \delta\left(\mathbf{x} - \mathbf{x}_i\right) \Big(S_i \left(\rho_i^T - \rho \right) - U_i \rho \Big) \, \mathrm{d}V. \tag{2}$$

Now, let $\Omega = \Omega_i$ be the voxel containing $\mathbf{x}_i$ as defined above. Then assuming that only cell i is in Ω_i:

$$\frac{dn_i}{dt} = \frac{\partial}{\partial t} \int_{\Omega_i} \rho \, \mathrm{d}V \approx V_i \Big(S_i \left(\rho_i^T - \rho(\mathbf{x}_i) \right) - U_i \rho(\mathbf{x}_i) \Big) \tag{3}$$

$$= V_i \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big). \tag{4}$$

(The case with multiple cells in a single computational voxel generalizes by performing this calculation separately for each cell contained in the voxel.)

Now, because $n_i = \rho_i W_i$, and asssuming W_i is constant or changes very slowly compared to substrate densities,

$$W_i \frac{d\rho_i}{dt} \approx V_i \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big) \tag{5}$$

$$\Longrightarrow \frac{d\rho_i}{dt} \approx \frac{V_i}{W_i} \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big) \tag{6}$$

Now, let's apply a backward Euler scheme as in BioFVM, to determine the net change in total substrate in any time step with duration Δt:

$$\frac{\rho_i(t + \Delta t) - \rho_i(t)}{\Delta t} \approx \frac{V_i}{W_i} \Big(S_i \left(\rho_i^T - \rho_i(t + \Delta t) \right) - U_i \rho_i(t + \Delta t) \Big) \tag{7}$$

$$\Longrightarrow \rho_i(t + \Delta t) \approx \frac{\rho_i(t) + c_1}{c_2}, \tag{8}$$

where

$$c_1 = \Delta t \frac{V_i}{W_i} \left(S_i \rho_i^T \right) \tag{9}$$

$$c_2 = 1 + \Delta t \frac{V_i}{W_i} \left(S_i + U_i \right). \tag{10}$$