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.
- For any cell i, let N_i denote the *internalized* total substrate.

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

$$\begin{aligned} \frac{\partial}{\partial t} \int_\Omega \rho \, \mathrm{d}V &= \sum_{\text{cells } i} \int_\Omega \mathbb{1}_i(\mathbf{x}) \Big(S_i \left(\rho_i^T - \rho \right) - U_i \rho \Big) \, \mathrm{d}V & (1) \\ &\approx \sum_{\text{cells } i} V_i \int_\Omega \delta \left(\mathbf{x} - \mathbf{x}_i \right) \Big(S_i \left(\rho_i^T - \rho \right) - U_i \rho \Big) \, \mathrm{d}V. & (2) \end{aligned}$$

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:

$$\begin{aligned} \frac{dn_i}{dt} = \frac{\partial}{\partial t} \int_{\Omega_i} \rho \, \mathrm{d}V &\approx V_i \Big(S_i \left(\rho_i^T - \rho(\mathbf{x}_i) \right) - U_i \rho(\mathbf{x}_i) \Big) & (3) \\ &= V_i \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big). & (4) \end{aligned}$$

(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,

$$\begin{aligned} W_i \frac{d\rho_i}{dt} &\approx V_i \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big) & (5) \\ \implies \frac{d\rho_i}{dt} &\approx \frac{V_i}{W_i} \Big(S_i \left(\rho_i^T - \rho_i \right) - U_i \rho_i \Big) & (6) \end{aligned}$$

2.1 BioFVM implementation

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:

$$\begin{aligned} \frac{\rho_i(t + \Delta t) - \rho_i(t)}{\Delta t} &\approx \frac{V_i}{W_i} \Big(S_i \left(\rho_i^T - \rho_i(t + \Delta t) \right) - U_i \rho_i(t + \Delta t) \Big) & (7) \\ \implies \rho_i(t + \Delta t) &\approx \frac{\rho_i(t) + c_1}{c_2}, & (8) \end{aligned}$$

where

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

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

This is the algorithm in

```
void Basic_Agent::simulate_secretion_and_uptake( Microenvironment* pS, double dt )
```

The constants c_1 and c_2 are set in `void Basic_Agent::set_internal_uptake_constants( double dt )`.

2.2 Net extracellular substrate change

Now, let's determine the change in total substrates in this implementation. First,

$$n_i(t+\Delta t) - n_i(t) = W_i \rho_i(t+\Delta t) - W_i \rho_i(t) \tag{11}$$

$$= W_i \left(\frac{\rho_i(t) + c_1}{c_2} - \rho_i(t) \right) \tag{12}$$

$$= W_i \left(\frac{\rho_i(t) + c_1 - c_2 \rho_i(t)}{c_2} \right) \tag{13}$$

$$= W_i \left(\frac{(1-c_2)\rho_i(t) + c_1}{c_2} \right) \tag{14}$$

$$\tag{15}$$

Notice that this can be calculated completely using constants that are already computed and used in BioFVM.

2.3 Algorithm

We will use the following operations in the cell secretion/uptake function. (In the actual implementation, perform this on the entire vector of substrates, and use element-wise operations. i.e., Hadamard products and quotients.)

1. `change = 1 // 1`
2. `change -= c2 // 1-c2`
3. `change *= substrates // (1-c2)*rho`
4. `change += c1 // (1-c2)*rho + c1`
5. `change /= c2 // ((1-c2)*rho + c1)/c2`
6. `change *= voxel_volume // W_i*((1-c2)*rho + c1)/c2`

This is the net change in total substrates in Ω_i. For conservation, the net chnage in cell i is equal and opposite. Thus

7. `internalized_substrates -= change`

3 Additional option(s)

If you set `Basic_Agent::use_internal_densities_as_targets = true`, then whenever the internal constants are changed, it sets

$$\rho_i^* = \frac{N_i}{V_i} \tag{16}$$

This criterion would be appropriate for non-active, diffusive secretion from the cell.

Please note that if $\rho_i^* < \rho_i$, there is nothing in the mathematical form to prevent diffusion of the substrate back into the cell. You can prevent that by setting

```
Basic_Agent::prevent_reverse_secretion = true
```

If this option is set (and as of Version 1.5.0, we default to true), then we replace ρ_i^* by

$$\rho_i^* H(\rho_i^* - \rho_i)$$