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. If this is a concern, I suggest users manually test for that and set the secretion rates to zero accordingly.

Future releases of PhysiCell may automate this testing, but we note that this test should be performed substrate-by-substrate.