1 Notation

- For any cell i with center $\boldsymbol{x}_i$, 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 $\boldsymbol{x}_i$, let Ω_i denote the voxel containing cell i, with corresponding volume W_i.
- Let $\mathbb{1}_i(\boldsymbol{x})$ be the characteristic function for the cell, so that $\mathbb{1}_i(\boldsymbol{x}) = 1$ inside the cell (inside R_i), and $\mathbb{1}_i(\boldsymbol{x}) = 0$ otherwise.
- Let $V_i = \int_{\mathbb{R}^3} \mathbb{1}_i(\boldsymbol{x}) \, \mathrm{d}V = V_i$ 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

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

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

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

(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.

4 Internal model

Without an internal model, internalized substrate will reflect the total history of all uptaken substrates, or the sum tutoal fo all secreted substrates. In particular, in the case of secretion, the internalized value will be negative to upload mass conservation. (No thing made inside, minus the secreted amount.)

Users can provide their own internal model (e.g., for metabolomics), but we provide a "sensible default." Inside the cell, we model:

$$\frac{dN}{dt} = \overbrace{-uN}^{\text{use}} + \overbrace{c(N^* - n)}^{\text{creation}} \tag{17}$$

$$= -u\rho_I W + s(\rho_I^* - \rho_E)W, \tag{18}$$

where ρ_I is the internal density, and c, u, and ρ_I^* are to be determined. We shall give the rationale for this form in the analysis below.

To determine these parameters, let us consider the total amount of substrate in the cell:

$$\frac{dN}{dt} = \overbrace{U\rho_E W}^{\text{import}} - \overbrace{S\left(\rho_E^* - \rho_E\right)W}^{\text{export}} - \overbrace{u\rho_I W}^{\text{internal use}} + \overbrace{c\left(\rho_I^* - \rho_E\right)W}^{\text{internal creation}} \tag{19}$$

Now, consider the case where there is uptake and use but no creation or secretion. Then

$$\frac{dN}{dt} = U\rho_E W - u\rho_I W = \left(U\rho_E - u\rho_I\right)W. \tag{20}$$

In quasi-steady (or steady) conditions, we seek u so that $\rho_I \approx \rho_E$. Notice that if $u = U$, then

$$\frac{dN}{dt} = U\left(\rho_E - \rho_I\right)W, \tag{21}$$

and so $\rho_I = \rho_E$ in quasi-steady condition. This model balances import with internal use. Moreover, if we balance all substrate in the environment (assuming without loss of generality only one uptaking cell):

$$\frac{d}{dt}\left(n + N\right) = -U\rho_E W + U\rho_E W - U\rho_I V = -U\rho_I W, \tag{22}$$

and over long times, $\rho_I \approx \rho_E$, so we arrive at the normal situation from BioFVM where the overall loss rate is $-U\rho_E W$.

Next, consider the case of only creation and export. In that case,

$$\frac{dN}{dt} = -S(\rho_E^* - \rho_E)W + s(\rho_I^* - \rho_E)W. \tag{23}$$

Suppose we follow our prior motivation and set $s = S$. Then

$$\frac{dN}{dt} = S\left(-\rho_E^* + \rho_E + \rho_I^* - \rho_E\right)W = S\left(-\rho_E^* + \rho_I^*\right)W. \tag{24}$$

If we choose $\rho_I^* = \rho_E^*$, then

$$\frac{dN}{dt} = 0 \tag{25}$$

and so we have successfully balanced creation and export. This the motivation for the functional form $s(\rho_I^* - \rho_E)$ instead of the more obvious $s(\rho_I^* - \rho_I)$. The biophysical interpretation is that the cell internally creates the substrate until the extenral density reaches the target value.

4.1 Summary:

Returning now to the original notation where $\boldsymbol{\rho}$ is the vector of (extracellular) substrate densities, $\boldsymbol{N}$ is the vector of total internalized substrates, then we use (as an internal model), and

$$\frac{d\boldsymbol{N}}{dt} = -\boldsymbol{u} \circ \boldsymbol{N} + \boldsymbol{c} \circ (\boldsymbol{\rho}^* - \boldsymbol{\rho})\, W \tag{26}$$

and we set defaults:

$$\boldsymbol{u} = \boldsymbol{U} \tag{27}$$
$$\boldsymbol{c} = \boldsymbol{S} \tag{28}$$

5 Key cellular processes

When a cell divides, it must distribute its internalized substrates to its daughter cells while maintaining conservation of mass.

In PhysiCell 1.5.0, we do this by dividing the substrate by half in each of the daughter cells.

When a cell dies and is removed by the simulation, multiple things could happen: for some substrates, it may make sense to remove them from the environment entirely, release it entirely at the time of lysis, or slowly release it back into the environment while the cell degrades.

In PhysiCell, we opt for the simplest solution: release (some fraction) of internalized substrates when the basic agent (and hence cell) calls its destructor. Let $0 \leq F \leq 1$ denote the fraction of internalized substrates released at the time of death.

We overwrite the density in the cell's voxel by first noting that there should be conservation of mass:

$$n_i(t + \Delta t) = n_i(t) + F N_i(t) \tag{29}$$
$$\implies V_i \rho_i(t + \Delta t) = V_i \rho_i(t) + F N_i(t) \tag{30}$$
$$\implies \rho_i(t + \Delta t) = \rho_i(t) + \frac{F}{V_i} N_i \tag{31}$$