MATHEMATICAL MODEL

We review the model constructed in [2] with no cargo transport and no back fusion. We have three compartments 1,2 and 3. We have 6 GTPases A, B, C, D, E, F. We have six relevant SNAREs X, Y, Z, U, V, W. We assume that the amount of X SNAREs is equal to the amount of U SNAREs. So does the Y and V SNAREs, Z and W SNAREs.

1. The Variables

(1) Let N_2^A be the number of vesicles originated in compartment 2 with GTPase A. There are 6 such variables, namely $N_1^B, N_1^E, N_2^A, N_2^D, N_3^C, N_3^F$.
(2) Let S_i be the size of compartment i. There are 3 such variables.
(3) Let X_i be the amount of SNARE X in compartment i. There are 9 such variables, namely X_i, Y_i, Z_i $(i = 1, 2, 3)$.
(4) N_{x2}^A be the amount of SNARE X in the vesicles originated in compartment 2 with GTPase A. There are 18 such variables, namely

$$N_{x1}^B, N_{y1}^B, N_{z1}^B, N_{x1}^E, N_{y1}^E, N_{z1}^E, N_{x2}^A, N_{y2}^A, N_{z2}^A, N_{x2}^D, N_{y2}^D, N_{z2}^D, N_{x3}^C, N_{y3}^C, N_{z3}^C, N_{x3}^F, N_{y3}^F, N_{z3}^F.$$

The following are dependent variables derived from above. Let

(1) $x_i = X_i/S_i$ be the concentration of X in compartment i. y_i, z_i are defined similarly.
(2) $x_2^A = N_{x2}^A/N_2^A$ be the average concentration of X in vesicles originated in compartment 2 with GTPase A. There are 18 such variables.

Let k_x^B be the dissociation constant of SNARE X with GTPase B. There are 18 dissociation constants. Define the saturation functions:

$$s_{x1}^B = \frac{x_1/k_x^B}{1 + 2x_1/k_x^B + 2y_1/k_y^B + 2z_1/k_z^B}.$$

There are 18 saturation functions.

We have 6 budding constants $w^A, w^B, w^C, w^D, w^E, w^F$. Let κ be the fusion rate constant. There are 6 fusion frequencies $f_2^B, f_2^C, f_1^A, f_1^F, f_3^D, f_3^E$ and

$$f_2^B = 2\kappa(x_1^B x_2 + y_1^B y_2 + z_1^B z_2).$$

2. Nonlinear Differential Equations

We can now write down the system of differential equations according to [2]:

$$\frac{dS_1}{dt} = -w^B S_1 - w^E S_1 + f_1^A S_1 N_2^A + f_1^F S_1 N_3^F.$$

$$\frac{dN_1^B}{dt} = w^B S_1 - f_2^B S_2 N_1^B.$$

$$\frac{dX_1}{dt} = -w^B S_1 s_{x1}^B - w^E S_1 s_{x1}^E + f_1^A S_1 N_{x2}^A + f_1^F S_1 N_{x3}^F.$$

$$\frac{dN_{x1}^B}{dt} = w^B S_1 s_{x1}^B - f_2^B S_2 N_{x1}^B.$$

There are total of 36 equations. Notice that these equations are linearly dependent, namely

$$S_1 + S_2 + S_3 + N_1^B + N_1^E + N_2^A + N_2^D + N_3^C + N_3^F = constant; \tag{1}$$

$$X_1 + X_2 + X_3 + N_{x1}^B + N_{x1}^E + N_{x2}^A + N_{x2}^D + N_{x3}^C + N_{x3}^F = constant. \tag{2}$$

There are 4 relations.

3. The Equilibrium: Sizes

Following [1], we compute the equilibrium. We set

$$-w^B S_1 - w^E S_1 + f_1^A S_1 N_2^A + f_1^F S_1 N_3^F = 0; \tag{3}$$

$$w^B S_1 - f_2^B S_2 N_1^B = 0; \tag{4}$$

$$-w^B S_1 s_{x1}^B - w^E S_1 s_{x1}^E + f_1^A S_1 N_{x2}^A + f_1^F S_1 N_{x3}^F = 0; \tag{5}$$

$$w^B S_1 s_{x1}^B - f_2^B S_2 N_{x1}^B = 0. \tag{6}$$

Substituting Equation (4) into Equation (6), we obtain $s_{x1}^B = N_{x1}^B / N_1^B = x_1^B$. So all the concentrations like x_1^B can be expressed as functions of x_i, y_i and z_i. So all fusion frequencies like f_2^B can also be expressed as functions of x_i, y_i and z_i. From Equation (4), we have

$$N_1^B = \frac{w^B S_1}{f_2^B S_2}.$$

Now take x_i, y_i, z_i and S_i as unknowns. Equations (3 5) become

$$(w^B + w^E) S_1 = w^A S_2 + w^F S_3, \tag{7}$$

$$(w^B s_{x1}^B + w^E s_{x1}^E) S_1 = s_{x2}^A S_2 w^A + w^F S_3 s_{x3}^F. \tag{8}$$

Set $w^B = w^C = w^D = w^E = w^F = 1$ and $w^A = 0.01$. We have

$$2S_1 = 0.01 S_2 + S_3, \qquad 2S_3 = S_1 + S_2, \qquad 1.01 S_2 = S_1 + S_3.$$

Set $S_1 = 1$. We have $S_2 = \frac{3}{1.02}, S_3 = \frac{2.01}{1.02}$.

4. Equilibrium: Concentration of SNAREs in Vesicles

Set $k_x^B = k_x^E = k_z^F = k_z^C = k_y^A = k_y^D = 100$ and the rest to be 1. Observe that

$$s_{x1}^B = S_{x1}^E = \frac{0.01 x_1}{1 + 0.02 x_1 + 2 y_1 + 2 z_1};$$

$$s_{x2}^A = s_{x2}^D = \frac{x_2}{1 + 2x_2 + 0.02 y_2 + 2 z_2}; \qquad s_{x3}^F = s_{x3}^C = \frac{x_3}{1 + 2 x_3 + 2 y_3 + 0.02 z_3}.$$

Equation (8) becomes

$$s_{x1}^B (w^B + w^E) S_1 = S_{x2}^A S_2 w^A + s_{x3}^C S_3 w^F.$$

We also have

$$s_{x2}^A (w^A + w^D) S_2 = s_{x1}^B S_1 w^B + s_{x3}^C S_3 w^C; \qquad s_{x3}^C (w^F + w^C) S_3 = s_{x1}^B S_1 w^E + s_{x2}^A S_2 w^D.$$

S_i and w^* are all known. We have

$$\begin{pmatrix} 2 & -\frac{0.03}{1.02} & -\frac{2.01}{1.02} \\ 1 & -\frac{3.03}{1.02} & \frac{2.01}{1.02} \\ 1 & \frac{3}{1.02} & -\frac{4.02}{1.02} \end{pmatrix} \begin{pmatrix} s_{x1}^B \\ s_{x2}^A \\ s_{x3}^C \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}.$$

so $s_{x1}^{B} = s_{x2}^{A} = s_{x3}^{C}$. Put

(9) $$s_x = s_{x1}^{B,E} = s_{x2}^{A,D} = s_{x3}^{C,F} = x_1^{B,E} = x_2^{A,D} = x_3^{C,F}.$$

Similar equations hold for SNAREs Y and Z. Put

(10) $$s_y = s_{y1}^{B,E} = s_{y2}^{A,D} = s_{y3}^{C,F} = y_1^{B,E} = y_2^{A,D} = y_3^{C,F};$$

(11) $$s_z = s_{z1}^{B,E} = s_{z2}^{A,D} = s_{z3}^{C,F} = z_1^{B,E} = z_2^{A,D} = z_3^{C,F}.$$

5. The Equilibrium: Concentration of SNAREs in Compartments

Now we will have to find x_i, y_i, z_i. Equation (9) becomes

(12) $$\frac{0.01x_1}{s_x} = 1+0.02x_1+2y_1+2z_1 \qquad \frac{x_2}{s_x} = 1+2x_2+0.02y_2+2z_2; \qquad \frac{x_3}{s_x} = 1+2x_3+2y_3+0.02z_3.$$

Similarly, we have

(13) $$\frac{y_1}{s_y} = 1+0.02x_1+2y_1+2z_1, \qquad \frac{0.01y_2}{s_y} = 1+2x_2+0.02y_2+2z_2; \qquad \frac{y_3}{s_y} = 1+2x_3+2y_3+0.02z_3.$$

(14) $$\frac{z_1}{s_z} = 1+0.02x_1+2y_1+2z_1; \qquad \frac{z_2}{s_z} = 1+2x_2+0.02y_2+2z_2; \qquad \frac{0.01z_3}{s_z} = 1+2x_3+2y_3+0.02z_3.$$

Now from the first equations in (12 13 14), we have

$$x_1 = \frac{100s_x}{1-2s_x-2s_y-2s_z}, \qquad y_1 = \frac{s_y}{1-2s_x-2s_y-2s_z}, \qquad z_1 = \frac{s_z}{1-2s_x-2s_y-2s_2}.$$

Similarly, from the second and the third equations in (12 13 14), we have

$$x_2 = \frac{s_x}{1-2s_x-2s_y-2s_z}, \qquad y_2 = \frac{100s_y}{1-2s_x-2s_y-2s_z}, \qquad z_2 = \frac{s_z}{1-2s_x-2s_y-2s_z}.$$

$$x_3 = \frac{s_x}{1-2s_x-2s_y-2s_z}, \qquad y_3 = \frac{s_z}{1-2s_x-2s_y-2s_z}, \qquad z_3 = \frac{100s_z}{1-2s_x-2s_y-2s_z}.$$

6. The Equilibrium: Fusion Frequencies

Now we have the fusion rates

$$f_2^B = 2\kappa(s_x x_2 + s_y y_2 + s_z z_2) = \frac{2\kappa(s_x^2 + 100s_y^2 + s_z^2)}{1-2s_x-2s_y-2s_z} = f_2^C;$$

$$f_3^E = 2\kappa(s_x x_3 + s_y y_3 + s_z z_3) = \frac{2\kappa(s_x^2 + s_y^2 + 100s_z^2)}{1-2s_x-2s_y-2s_z} = f_3 D;$$

$$f_1^A = 2\kappa s_x x_1 + s_y y_1 + s_z z_1 = \frac{2\kappa(100s_x^2 + s_y^2 + s_z^2)}{1-2s_x-2s_y-2s_z} = f_1^F.$$

The fusion rate f_2^B, f_3^E, f_2^C dictate the transport of cargo from compartment 1 to compartment 2.

7. The Equilibrium: Determining Concentration of SNAREs from Initial Condition

Lastly, s_x, s_y and s_z can be determined by Equation (2). Notice that the total amount of X SNAREs equals

$$
\begin{aligned}
& x_1 S_1 + x_2 S_2 + x_3 S_3 + s_x (N_1^B + N_1^E + N_2^A + N_2^D + N_3^C + N_3^F) \\
=& \frac{s_x(100S_1 + S_2 + S_3)}{1 - 2s_x - 2s_y - 2s_z} + s_x \Big(\frac{w^B S_1}{f_2^B S_2} + \frac{w^E S_1}{f_3^E S_3} + \frac{w^A S_2}{f_1^A S_1} + \frac{w^D S_2}{f_3^D S_3} + \frac{w^C S_3}{f_2^C S_2} + \frac{w^F S_3}{f_1^F S_1} \Big) \\
=& \frac{s_x(100S_1 + S_2 + S_3)}{1 - 2s_x - 2s_y - 2s_z} + \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(s_x^2 + 100s_y^2 + s_z^2)} \Big(\frac{S_1 + S_3}{S_2} \Big) \\
& + \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(100s_x^2 + s_y^2 + s_z^2)} \Big(\frac{0.01S_2 + S_3}{S_1} \Big) + \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(s_x^2 + s_y^2 + 100s_z^2)} \Big(\frac{S_1 + S_2}{S_3} \Big) \\
=& \frac{s_x(100S_1 + S_2 + S_3)}{1 - 2s_x - 2s_y - 2s_z} + 1.01 \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(s_x^2 + 100s_y^2 + s_z^2)} \\
& + 2 \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(100s_x^2 + s_y^2 + s_z^2)} + 2 \frac{s_x(1 - 2s_x - 2s_y - 2s_z)}{2\kappa(s_x^2 + s_y^2 + 100s_z^2)}
\end{aligned}
\tag{15}
$$

Similar equations can be written down for SNAREs Y and SNAREs Z. Now S_1, S_2, S_3 are known. The total amount of X, Y and Z determine s_x, s_y, s_z. s_x, s_y and s_z can be computed numerically.

References

[1] H. He, N. Kato "Equilibrium Submanifold in a Biological System,", submitted (2009).

[2] R Heinrich and T. Rapoport "Generation of Nonidentical Compartments in Vesicular Transport Systems," *Journal of Cell Biology*, Vol 168, No. 2 2005 (271-280).