WHAT IS IT?

Eukaryotic cells (those found in all higher organisms) contain
multiple compartments that each perform distinct functions. The
endoplasmic reticulum (ER) is a major site of protein production.
These proteins are transported in small spherical membrane-
bounded vesicles to the Golgi complex for sorting, a process that
determines the proteins' final destinations. Some of the fine
details of sorting are not yet known, such as the exact mechanism
by which proteins become selectively attached to specific domains
in the Golgi membrane bilayer. These regions subsequently bud off
to become vesicles destined for the cell's outer plasma membrane.

The goal of this project is to produce a minimal model that
demonstrates the emergence of protein sorting in the Golgi, given
a set of simpler lipid and protein movement behaviors that depend
on relative size. The current individual-based model is an early
prototype that shows one way to achieve protein sorting.

The model exhibits:
1. The self-organization of lipids into domains, including
thicker cholesterol-rich lipid rafts.
2. The selective association of protein trans-membrane domains
(TMDs) with different lipid domains based on thickness, resulting
in protein sorting.
3. The continuous budding off of vesicles from regions containing
lipid rafts with associated sorted proteins as cargo, and
replacement of this material through the docking of less self-
organized vesicles.
4. Achievement of a steady-state in which the pathways of lipid
self-organization, protein sorting, and vesicle budding and
docking, collectively maintain a homeostatic organization.

HOW IT WORKS

Lipids are modeled as NetLogo patches. There are two types of
lipids, 1-stearoyl-2-oleoyl-phosphatidylcholine (sopcType), and a
1 to 1 combination of cholesterol and Sopc (cholSopcType). Each
lipid type is a different thickness and is displayed in a
different color:

lipidType	lipidThickness	lipidColor
sopcType	3.0 nm	green
cholSopcType	3.3 nm	red

The only possible operation for a lipid is to swap itself with an
immediate neighbor of a different type. In a real cell, a fluid
lateral diffusion occurs as lipids of all types constantly
randomly swap places with other lipids in their local
neighborhood.

Here is the algorithm used by each lipid patch at each time step (adjust-domain-size-continuous):

If I am a CholSopc lipid Then
   If 0 of my 8 neighbors is a CholSopc lipid Then
     With probability ProbIf0, swap with a random one of my Sopc neighbors
   If 1 of my 8 neighbors is a CholSopc lipid Then
     With probability ProbIf1, swap with a random one of my Sopc neighbors

   …
   (same idea for 2, 3, 4, 5, and 6)
   …
   If 7 of my 8 neighbors is a CholSopc lipid Then
     With probability ProbIf7, swap with a random one of my Sopc neighbors
   If all 8 of my 8 neighbors are CholSopc lipids Then do nothing

If I am a Sopc lipid Then
   If fewer than 2 Of my 8 neighbors are Sopc lipids Then
     Swap with a random one of my CholSopc neighbors

Proteins are modeled as a breed of NetLogo turtles, that interact over time with the lipid patches. A protein's only attribute is a hydrophobic trans-membrane domain (TMD), which can be either short (light blue) or long (very dark blue). The TMD seeks to embed itself within a region of lipid bilayer whose thickness is compatible with its TMD length. A long TMD-protein seeks the thicker cholesterol-rich CholSopc lipid rafts. A short TMD-protein seeks the thinner cholesterol-free Sopc lipid regions.

At each time step, all proteins follow the same set of rules in deciding whether to stay where they are or possibly move to a neighboring patch that may lead to a region of optimal lipid thickness. Here is the algorithm (seek-optimal-site):

If my TMD is partly exposed to water (i.e. my hydrophobic length > the thickness of the lipid in which I am embedded) Then
   If a random one of my lipid neighbors is even thinner Then
     With very low probability P_ProbGtGt, move to that patch
   If a random one of my lipid neighbors is the same thickness Then
     With some probability P_ProbGtEq, move to that patch
   If a random one of my lipid neighbors is thicker Then
     With relatively high probability P_ProbGtLt, move to that patch

If my TMD is already optimal (i.e. my hydrophobic length = the thickness of the lipid in which I am embedded) Then
   If a random one of my lipid neighbors is thinner Then
     With very low probability P_ProbEqGt, move to that patch

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   If a random one of my lipid neighbors is the same thickness
Then
     With some probability P_ProbEqEq, move to that patch
   If a random one of my lipid neighbors is thicker Then
     With relatively low probability P_ProbEqLt, move to that
patch

If my TMD has room to spare ((i.e. my hydrophobic length < the
thickness of the lipid in which I am embedded) Then
   If a random one of my lipid neighbors is thinner Then
     With relatively high probability P_ProbLtGt, move to that
patch
   If a random one of my lipid neighbors is the same thickness
Then
     With some probability P_ProbLtEq, move to that patch
   If a random one of my lipid neighbors is even thicker Then
     With relatively low probability P_ProbLtLt, move to that
patch
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Lipid rafts gradually emerge out of an initial random
configuration and through the local actions of individual lipid
patches, as described above. Lipid rafts are regions consisting
largely of patches containing lipids of cholSopcType. They are
high in cholesterol (Chol). These constructs emerge without being
explicitly mentioned anywhere in the rules.

In the model, as a lipid raft grows in size, there is an
increasing probability that a circular region of the membrane
containing a raft will bud off to become a separate vesicle. The
material that buds off is replaced by lipids in vesicles that
dock with the membrane. A similar mechanism takes place in a real
biological cell. Vesicles from the endoplasmic reticulum (ER)
dock with the Golgi. Vesicles that are higher in cholesterol
content later bud off from the Golgi and find their way to the
plasma membrane on the outside of the cell.

An extended neighborhood is specified using the NetLogo in-radius
<number> primitive. The number of patches, including the current
patch, that are within one radius unit, is 5. 13 patches are
within a radius of 2, and 149 patches are within a radius of 7.
The model uses a default radius of 7 (BudRadius) to specify a
region large enough to, with some probability, bud off.

Every n time steps (default: 1), a random patch is sampled to see
if the number of lipids with lipidType = cholSopcType within this
extended neighborhood exceeds some threshold (BudRadius). If so,
a vesicle buds off. In the model this means that CholSopc lipids
change their state to Sopc, and all proteins that were within
this region cease to exist. The "lost" CholSopc lipids and
proteins are recreated at random locations in the membrane,
simulating the docking of vesicles from the ER. The result is a

reduction in order that counteracts the fine-grained order-
increasing behavior of individual lipids described previously.

HOW TO USE IT

Set the PercentCholesterolSopc slider to a value between 0% and
100% cholesterol. The default for the Golgi is 20%.

Set the NumberOfProteins slider to a value between 100 and 5000.
The default is 2000.

Set the ChromosomeNum to 1 or 2. This determines the
probabilities of position-swapping and movement for lipids and
proteins. It is called a chromosome because it's a list of values
that could be optimized using a genetic algorithm. With a value
of 1, behavior is somewhat more exploratory. With a value of 2
(the default), the lipids and proteins tend to maintain current
good locations.

Set the BudRadius to a value from 1 to 10, but typically between
5 and 8. The default is 7.

Press the setup button. You will see a random initial
configuration. Look at the Command Center window for information
on the colors used.

Press the Go button.

THINGS TO NOTICE

The thicker CholSopc lipids will gradually cluster together to
form lipid rafts, red domains within the green Sopc lipid. The
long-TMD proteins (darker color) will mostly sort themselves into
the thicker lipid rafts, while the short-TMD proteins (lighter
color) will be retained in the Sopc.

Watch the graph. It shows the percentage of each type of protein
(short-TMD and long-TMD) embedded within CholSopc lipids, a rough
measure of protein sorting. Note that this measure does not
discriminate between solitary CholSopc patches and CholSopc found
in lipid raft regions. After about 800-900 time steps, some 90%
of long-TMD proteins (the darker curve) will be embedded in
CholSopc, while only about 4% of short-TMD proteins (the lighter
curve) will be embedded in CholSopc.

Also at around 800-900 time steps, budding will start to occur.
Sufficiently large lipid rafts will bud off as vesicles carrying
whatever lipids and proteins were within a BudRadius radius of
the approximate center of the lipid raft. The budding will appear
as a circular region in a different shade of green. The same
number of CholSopc lipid and protein units will be randomly
distributed over the entire NetLogo grid, representing docking of

new vesicles from the ER. The new CholSopc lipids will appear
yellow, but are otherwise the same as the red ones.

By some 4000 time steps, the long-TMD protein curve will be
trending downward. Because of the randomness introduced by many
cycles of budding and docking, more and more of the long TMD
proteins become transiently associated with individual CholSopc
lipid patches that are not part of a cluster. These CholSopc are
constantly moving so a high proportion of the long TMD are
constantly being moved back into Sopc patches. The slow downward
trend will continue for many thousands of time steps.

The overall pattern on the graph for the default starting
conditions, is hyperbolic growth, followed by exponential decay.

THINGS TO TRY
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(1) Change the ChromosomeNum to 1, while keeping the other values
at their defaults. Press setup and go. The behavior is quite
different. Watch the effect of this change on clustering, and
watch the graph.

(2) For a much faster moving simulation, but one in which it will
be hard to see the clustering, set values as follows:
ChromosomeNum = 1, BudRadius = 5, NumberOfProteins = 500. Also
you will need to change the size of the NetLogo grid, to the
NetLogo default of 35 by 35. Press the "more ..." button just
above the grid. Set "Screen Edge X" to 17, "Screen Edge Y" to 17,
and "Patch Size" (pixels) to 9.0. Press OK. This configuration
produces clustering into lipid rafts, budding, and a flat curve.

EXTENDING THE MODEL

Add additional intermediate protein TMD lengths, and try to get
the longer sizes sorted into the lipid rafts.

NETLOGO FEATURES

This model does not yet work with 2.x versions of NetLogo. It has
only been tested with NetLogo 1.3.1.

RELATED MODELS

There are no other models I am aware of that deal with protein
sorting.

CREDITS AND REFERENCES

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