Membrane Interactions

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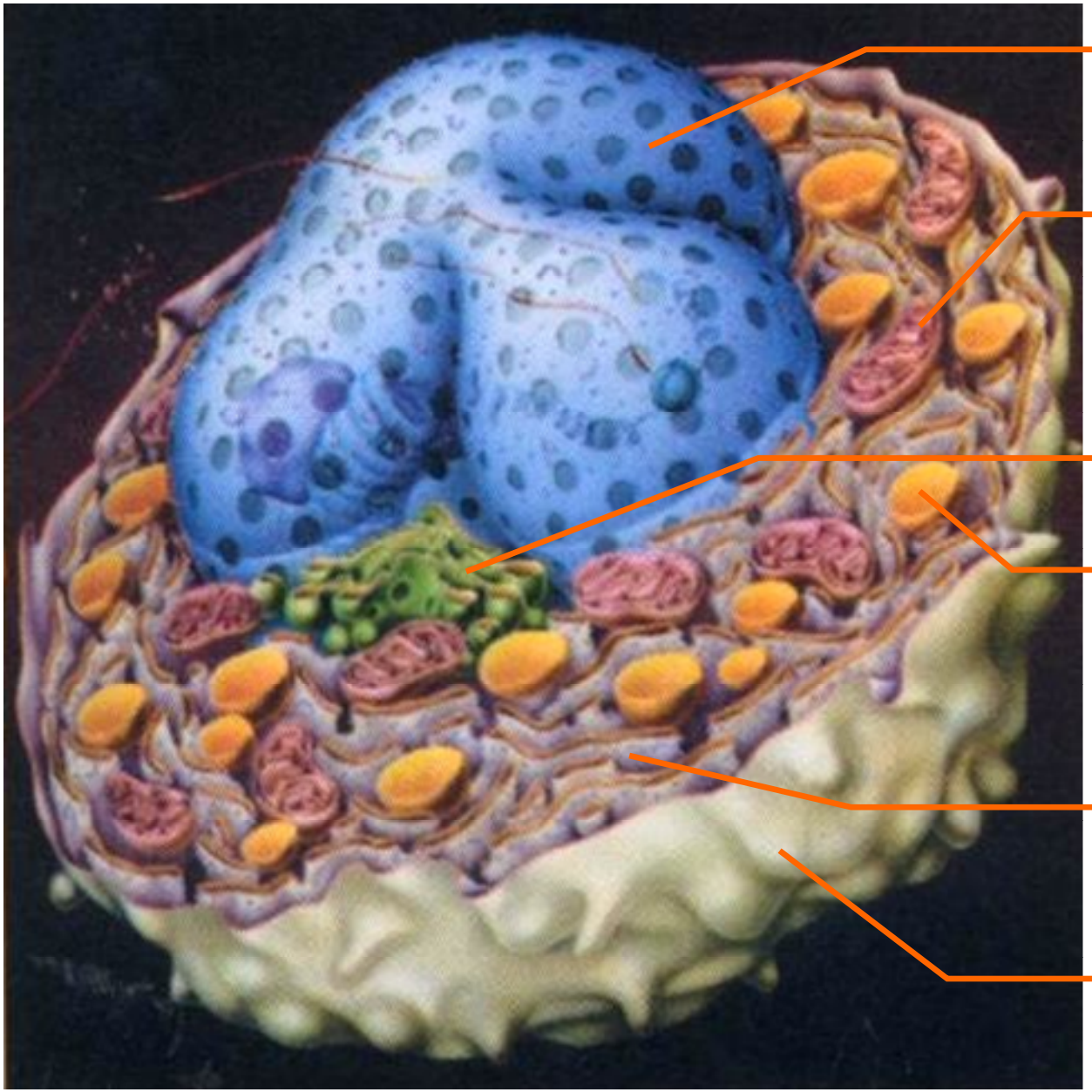
CS Background

- Process calculi
  - Invented to describe highly concurrent systems.
  - Some (Ambient Calculus) for compartmentalized systems.
- Thesis [Ehud Shapiro]
  - With some crucial adaptations, the basic technology of process calculi can be used to describe biological systems.
  - This provides a conceptual framework for programming and simulation languages for biotechnology.
- BioAmbients [Aviv Regev]
  - Implementation of “Stochastic Ambient Calculus” to emulate biochemical systems.
  - BioAmbients was designed for bio applications, but was an impromptu makeover of Ambient primitives.
  - Want to rethink the “right” set of primitives for the job.

Eukaryotic Cell

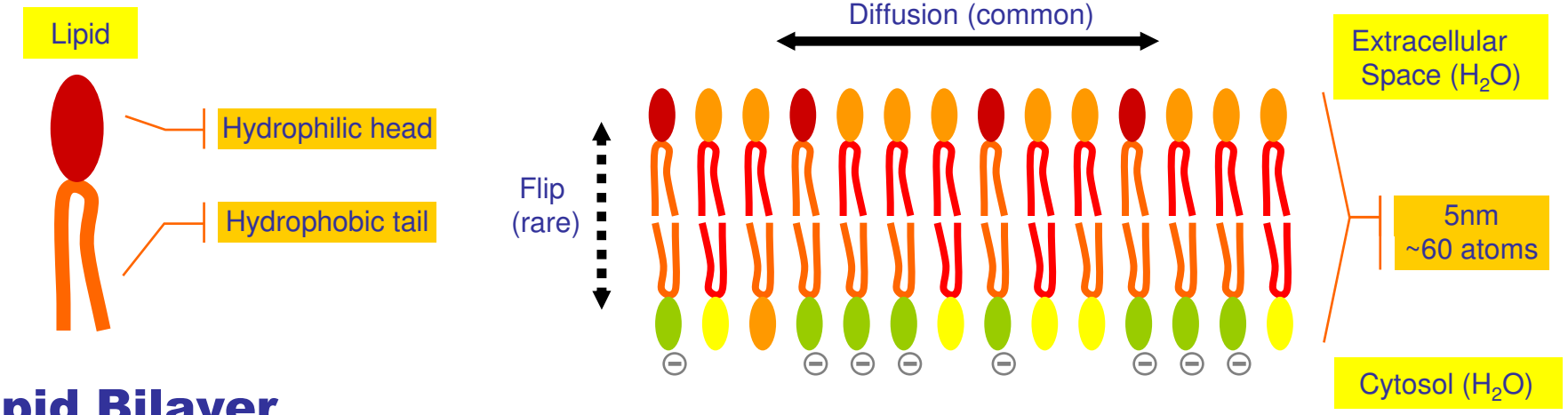
Membranes everywhere



Membrane-based Systems

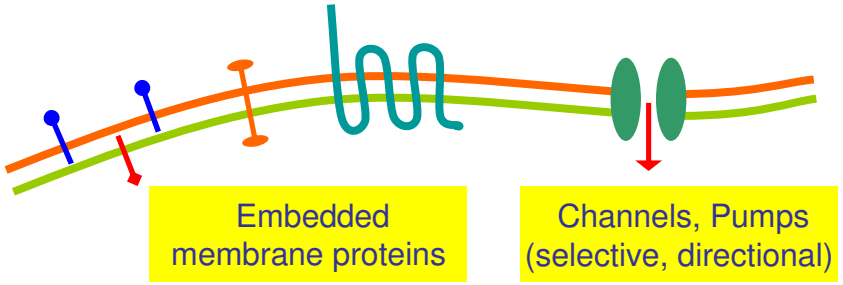
- Many cellular processes operate on membranes, through membranes, via membrane transformations, and via active membrane transport. It's *very far* from a "chemical soup":
  - **For a cell to function properly, each of its numerous proteins must be localized to the correct cellular membrane or aqueous compartment. [MCB p.675]**
- What is the dynamics of these complex configurations of membranes? (Still poorly understood in biology.)
- We *MUST* use abstractions, to avoid combinatorial explosion (*c.f.* protein folding, quantum phenomena).
- Emerging area of *Systems Biology* (~ above molecules, ~ study of biological processes).

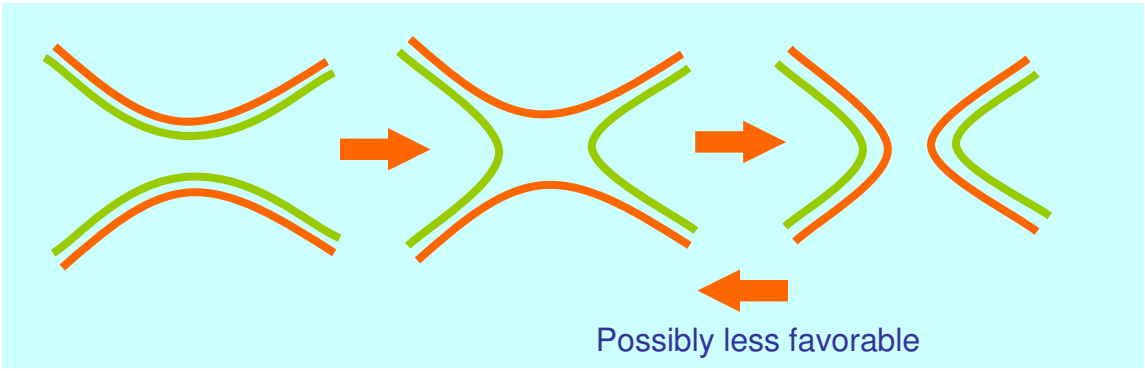
Membranes are Oriented Surfaces

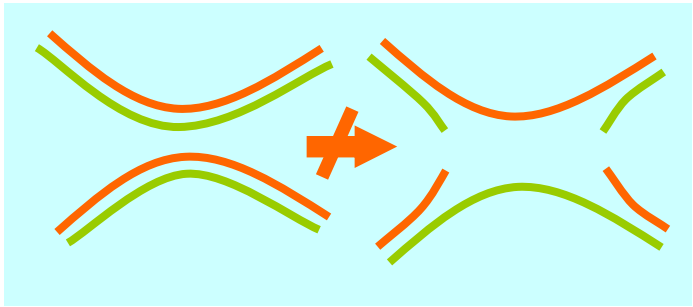


Lipid Bilayer

Self-assembling
Largely impermeable
Asymmetrical (in real cells)
Embedded proteins
Two-dimensional fluid

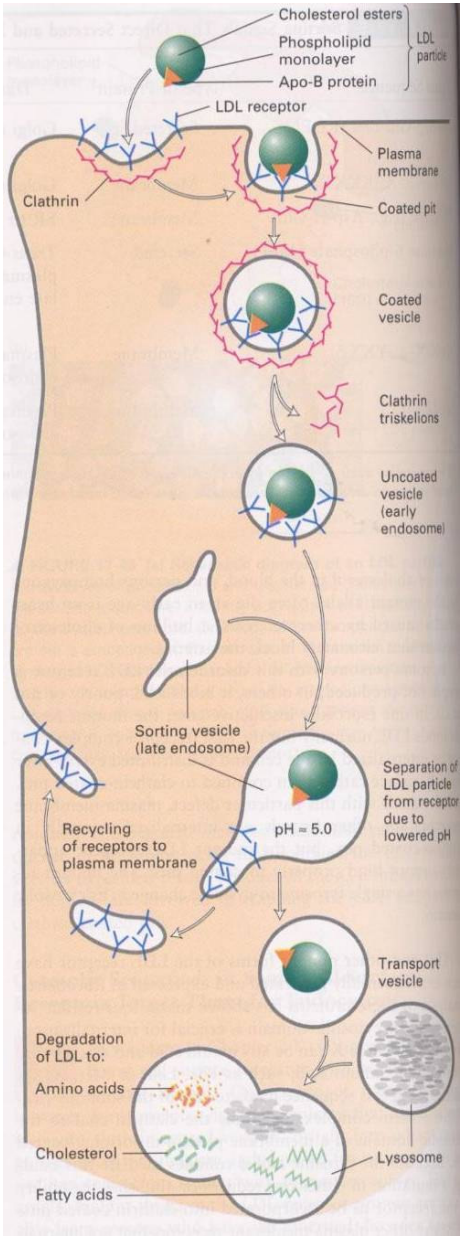






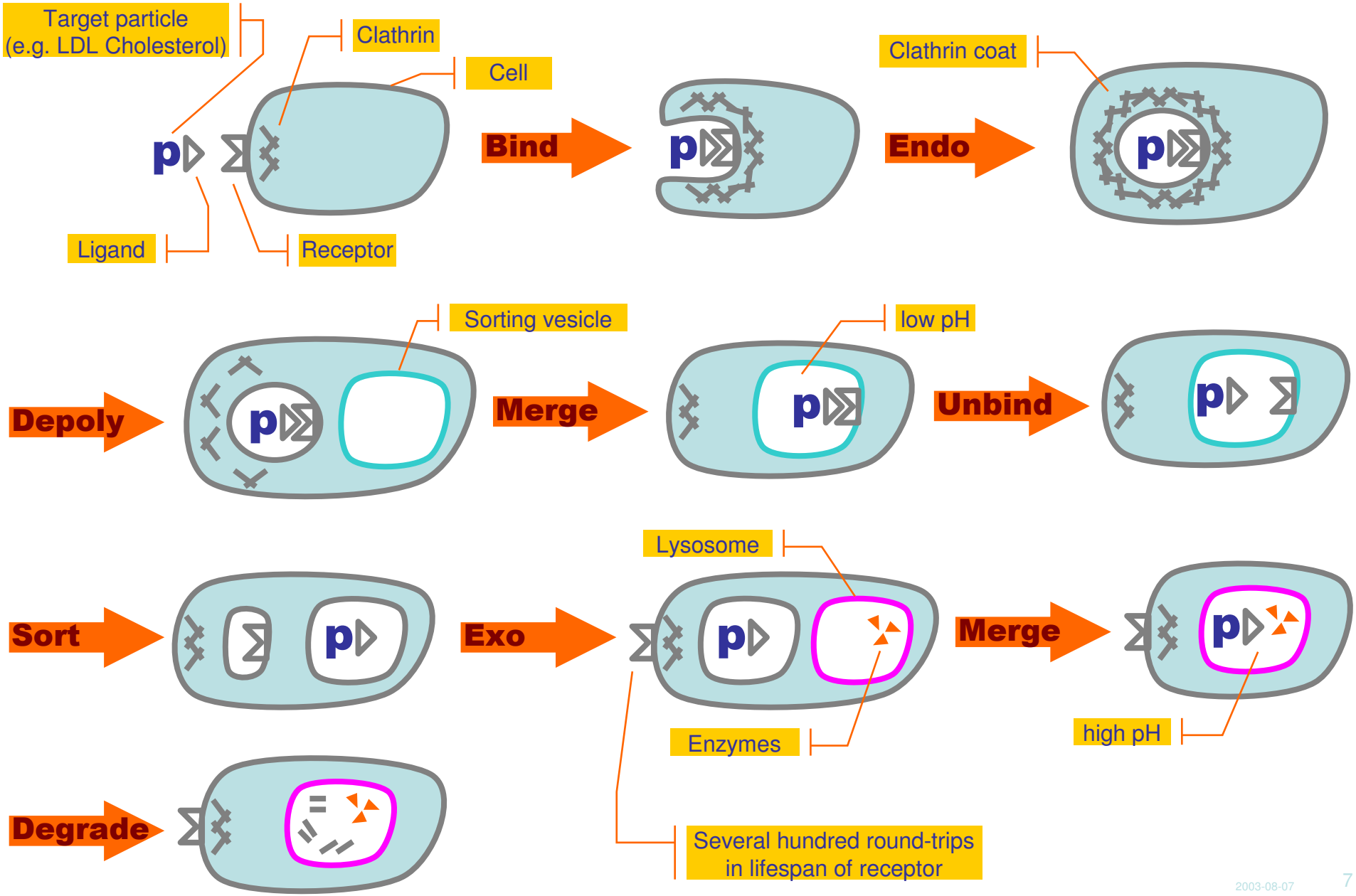
A Biological Algorithm

- LDL-Cholesterol Degradation
  - A cast of many thousands (molecules) just to get one molecule from A to B.
  - Membranes are key to the algorithm, we want to model *them*, not their individual molecules.
- How do people know all that?
  - They take pictures, see all stages of the algorithm in the same snapshot.
  - Stop genes, see what stages survive; build temporal sequence of stages.
  - Identify key molecules. Model them and play with them to see what they do.
  - Many steps still murky. Not possible to model them in detail even if wanted to.



Receptor-Mediated Degradation Pathway

(Abstract view)

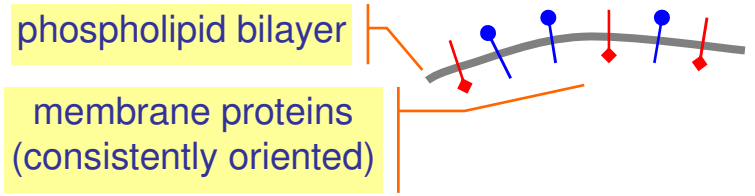


Aims

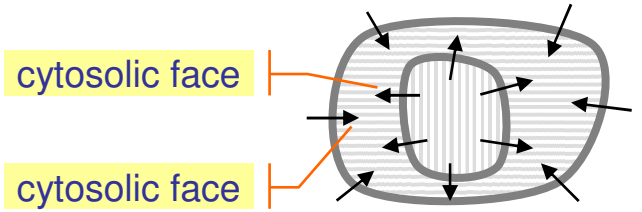
- Describing biological processes.
  - Avoid “biobabble” diagrams.
  - Write bioalgorithms in something closer to a language.
- Options
  - One could represent reactions a different levels of abstraction.
  - Start too low = get lost in a mess of details.
  - Start too high = ignore too many details.
- Strategy (for now)
  - 1) Start too high (but learn basic gameplay).
  - 2) Move one level down.
- Approaches
  - Algebras (shown here)
  - Rewriting systems (sketched here, also Gamma, P-Systems, etc.)
  - Calculi of bulk reactions (in progress)
  - Calculi of individual reactions (BioSPi, BioAmbients etc.)

1: Systems of Oriented Membranes

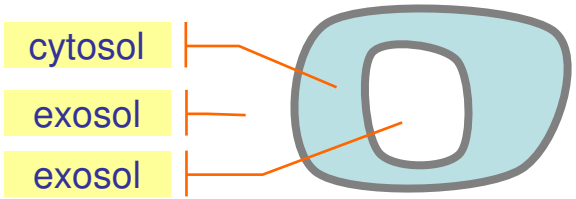
Membranes are closed non-intersecting curves, with an orientation[1].



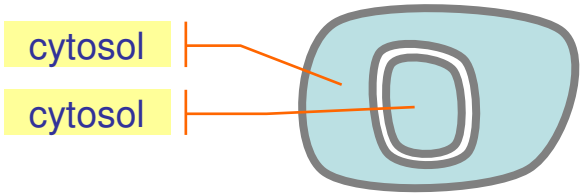
Each membrane has two faces. A cytosolic (~*inner*) face and an exoplasmic (~*outer*) face. Nested membranes alternate orientation. (E.g. cytosolic faces always face each other.)



This alternation is illustrated by using two colors: blue (cytosol[2]) and white (exosol[3]). *Inside/outside* are confusing terms.



Double membranes (e.g. the nuclear membrane) can be used for blue-in-blue components.



(1) A membrane is built from a phospholipid bilayer that is asymmetrical. Moreover, all real membranes are heavily sprinkled with proteins: "each type of integral membrane protein has a single specific orientation with respect to the cytosolic and exoplasmic faces of a cellular membrane, and all molecules of any particular integral membrane protein share this orientation. This absolute asymmetry in protein orientation confers different properties on the two membrane faces." MCB p162.
(2) Short for Cytoplasmic Solution. (3) Short for Exoplasmic Region (I am making this one up).

What Systems to Allow

Color Alternation Postulate

Blue and white areas alternate.

Color Duality Postulate

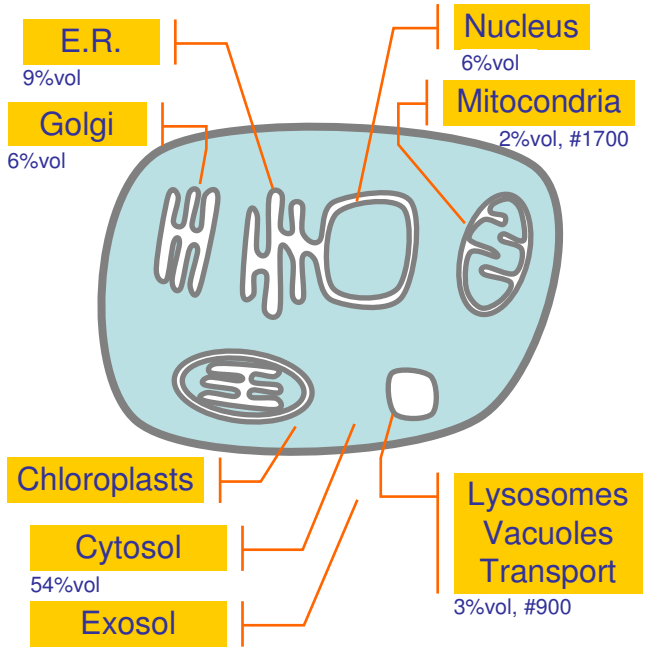
The color-dual of a reaction is a reaction.

Color Alternation Invariant

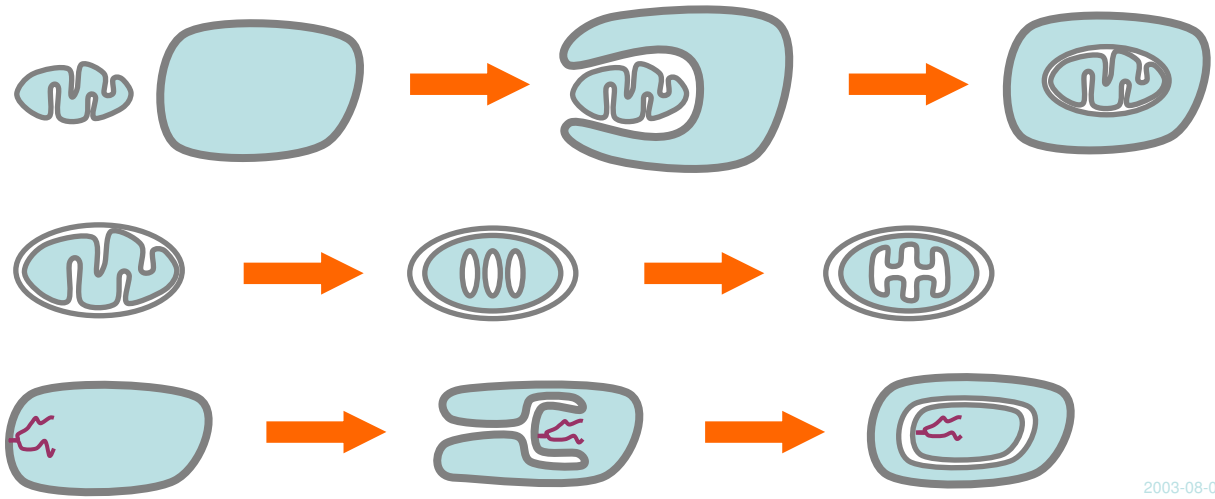
Color alternation is preserved by reactions.
(With localized violations: e.g., digestion.)

Color Stability Invariant

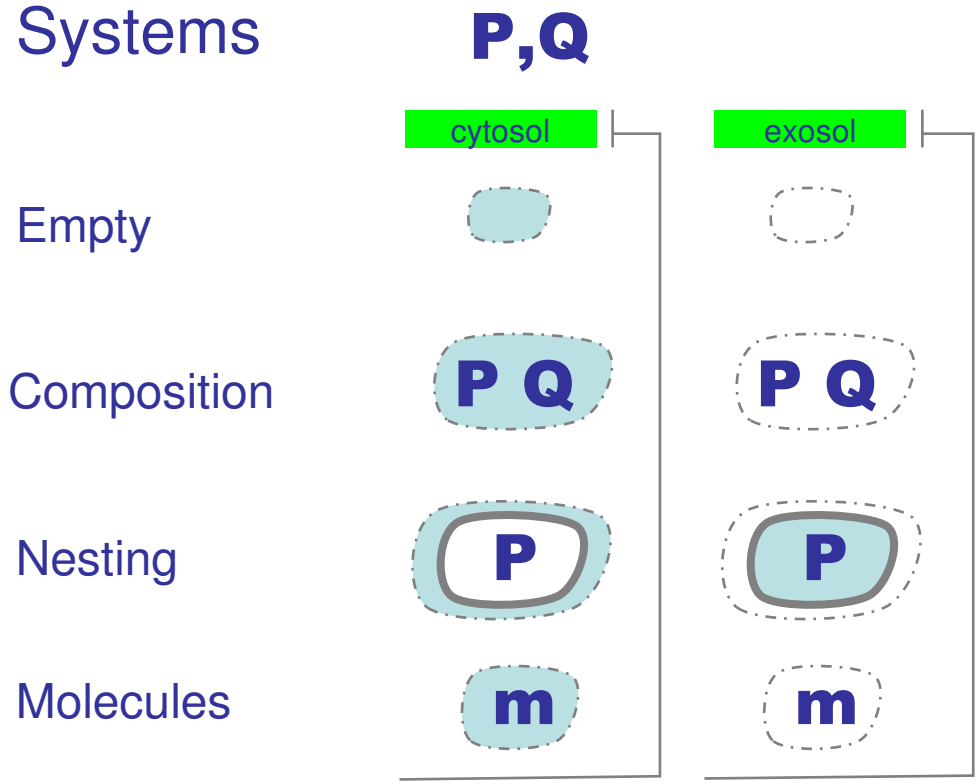
Reactions do not swap the background.
Reactions do not swap whole subsystems.

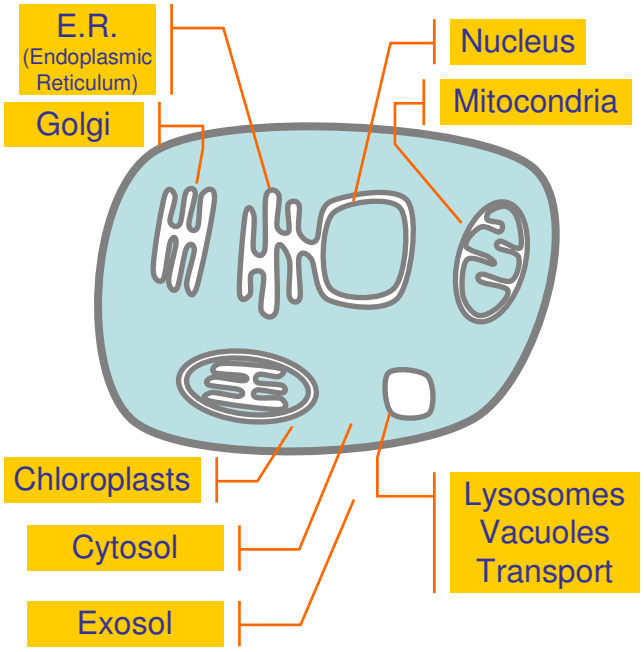


Evolutionary explanations



Oriented Membrane Systems





A *well-colored* system **P** has proper color alternation.
The *polarity* of **P** is the color of its background, also drawn as:

P a system **P** of blue polarity ("**P** swims in cytosol")

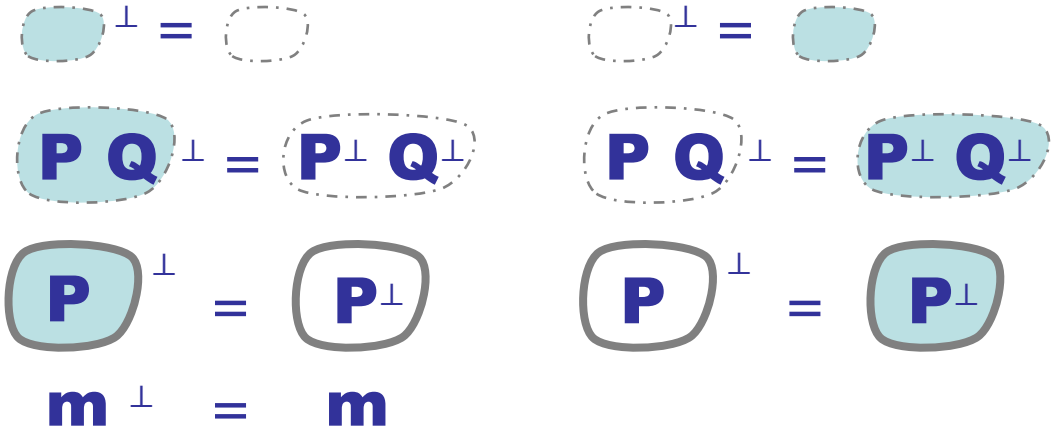
P a system **P** of white polarity ("**P** swims in exosol")

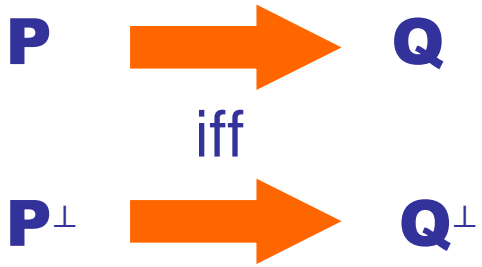
Reactions

Directed reaction
P,**Q** same polarity

Reversible reaction
P,**Q** same polarity

Dual Reactions





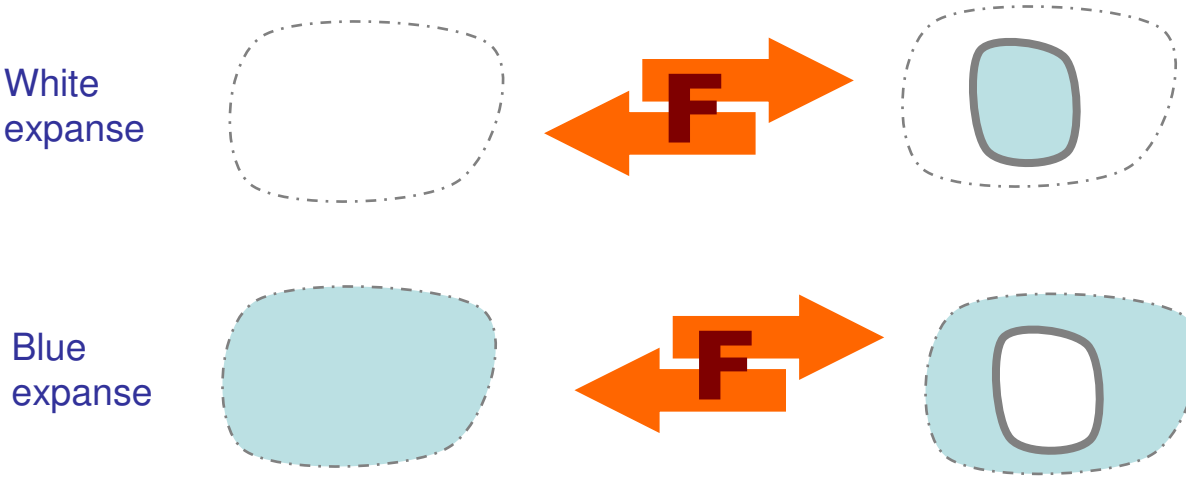
Reactions in Context

by duality

by duality

✓ Frothe/Fizz Reaction

The spontaneous appearance/disappearance of empty bubbles (of the correct orientation).



Preserves color alternation and stability.

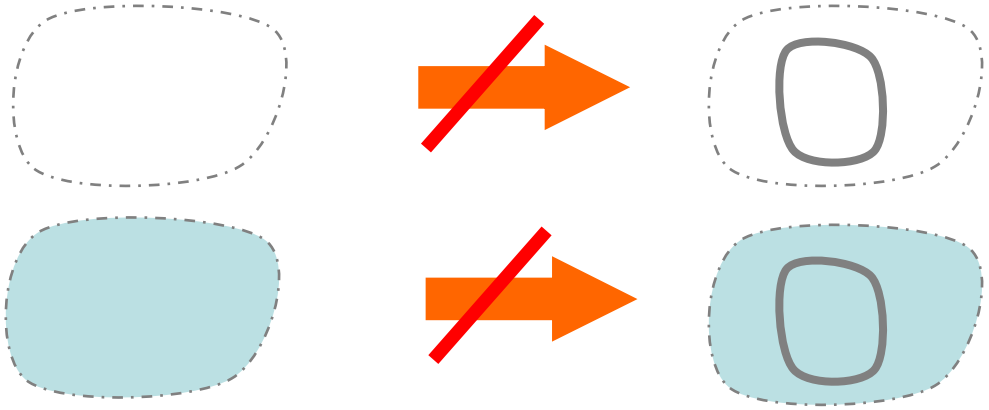
* Phospholipid molecules automatically assemble into closed membranes.

N.B. non-empty membranes should not “spontaneously” be created or deleted: usually only very deliberate processes cause that. However, spontaneous frothe/fizz seems be harmless; it means that empty membranes are not observable.

✗ Bad Bubbles

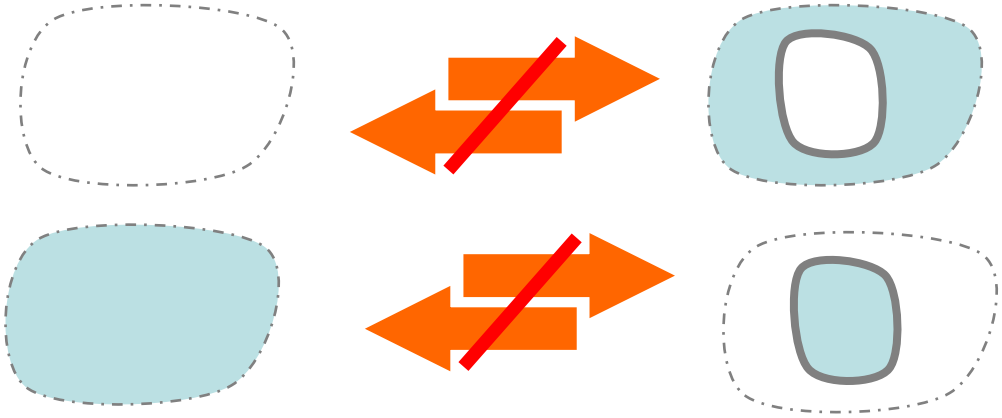
Wrong bubbles:

Violates color alternation.



Bubble catastrophe:

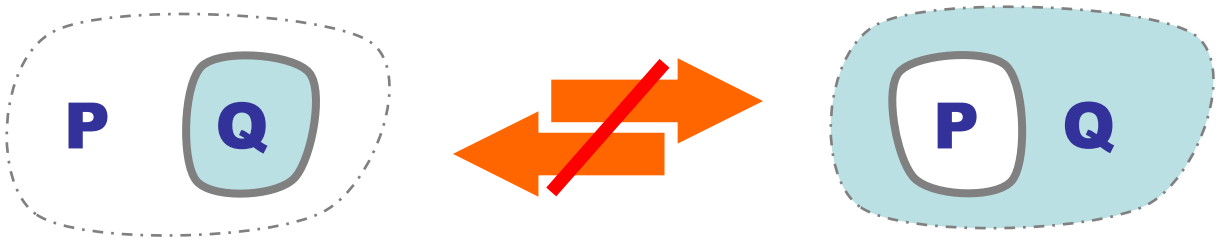
Violates color alternation in context.
Also, ill-colored reaction arrow.



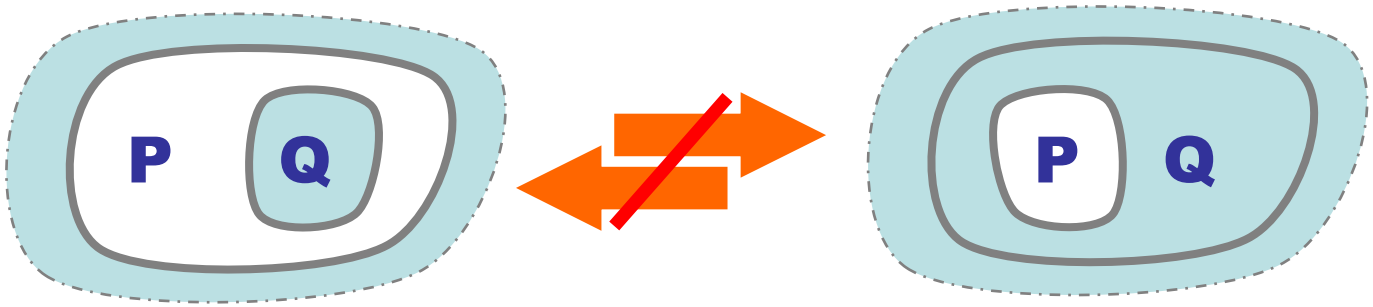
× Flooding

Flooding

Violates color alternation in context.
Also, ill-colored reaction arrow.

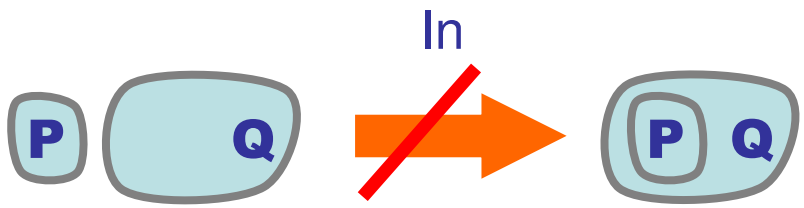


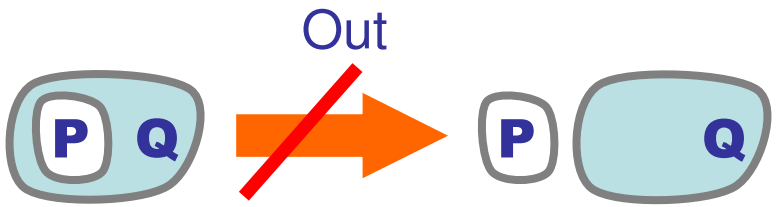
Flooding in context violates color alternation:



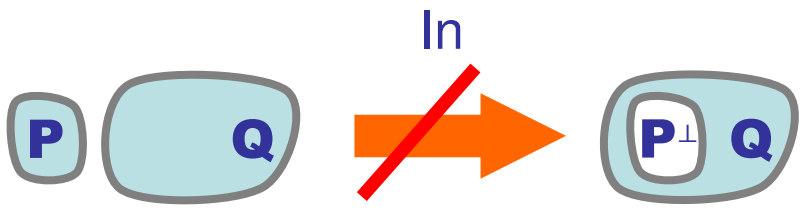
× Ambients

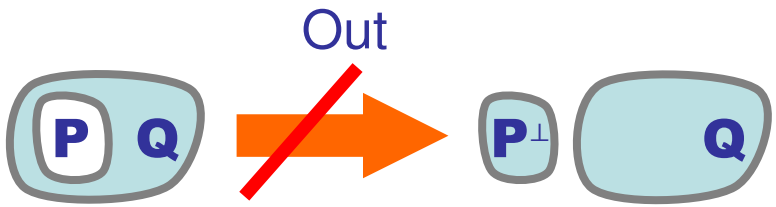
Violate color alternation





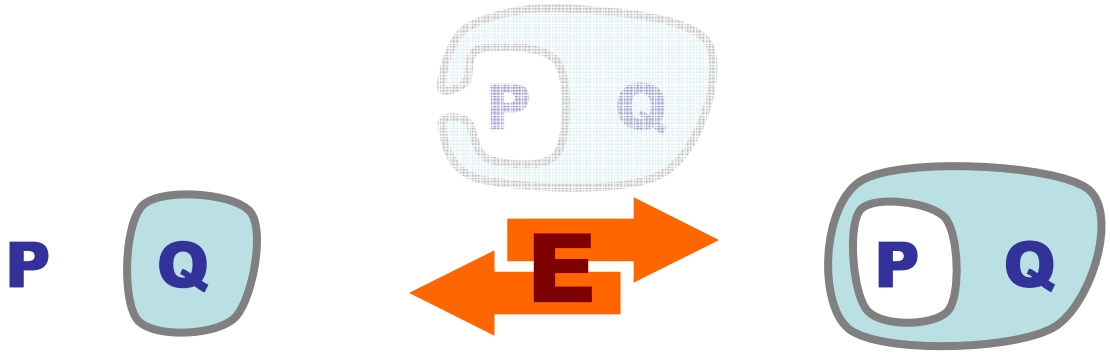
Preserve color alternation, but violate color stability for subsystem P.



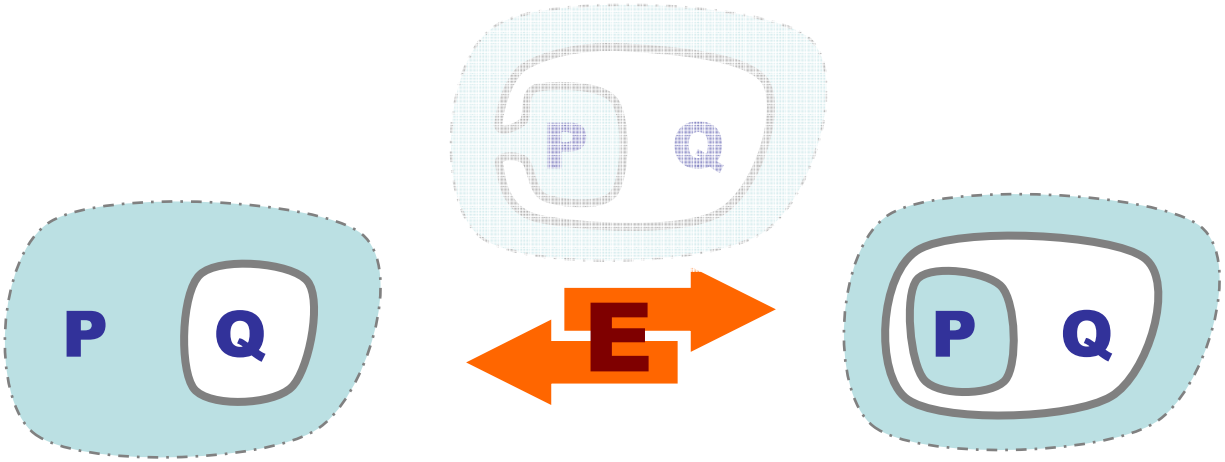


✓ Endo/Exo Reaction

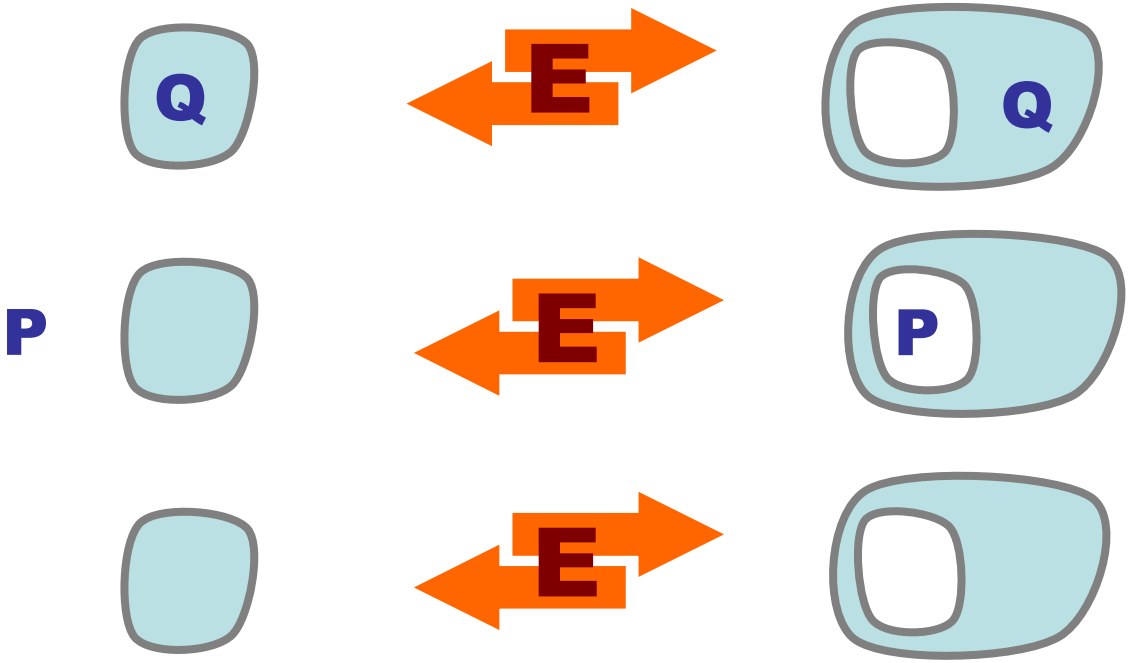
Preserves color alternation and stability.



Dual:

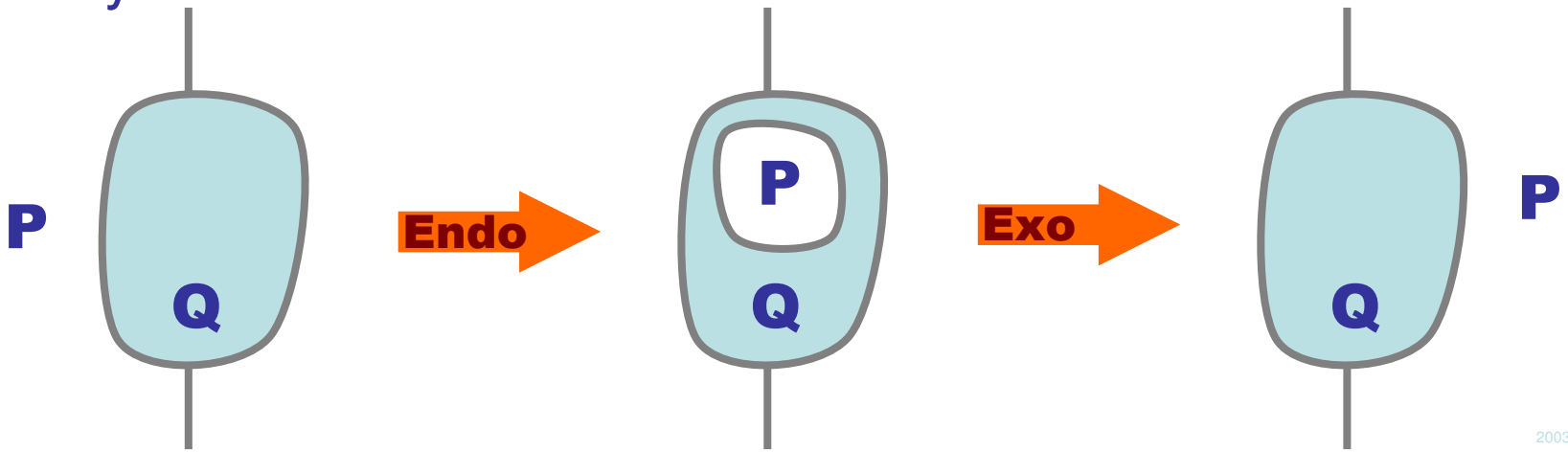


Examples



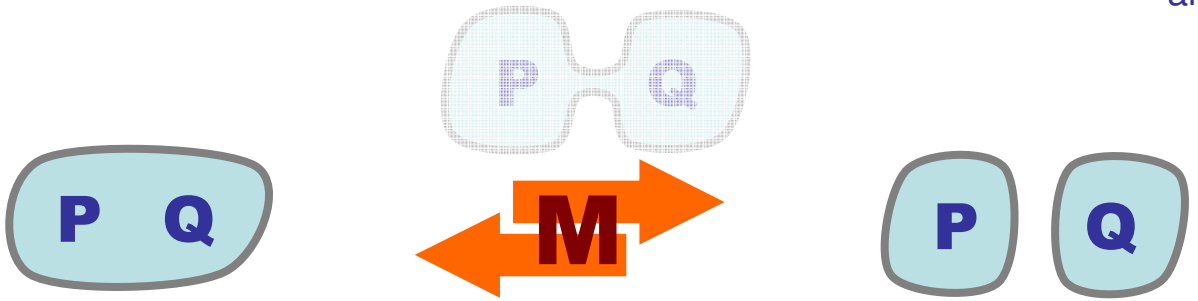
There are various kinds of **Endocytosis**.
Phagocytosis (“cellular eating”) is when a membrane (e.g. a bacterium) is incorporated in a cell.
Pinocytosis (“cellular drinking”) is when a bit of outside fluid is spontaneously incorporated in a cell.
Receptor-mediate endocytosis is when an active receptor-ligand reaction creates a transport vesicle for a molecule.

Transcytosis

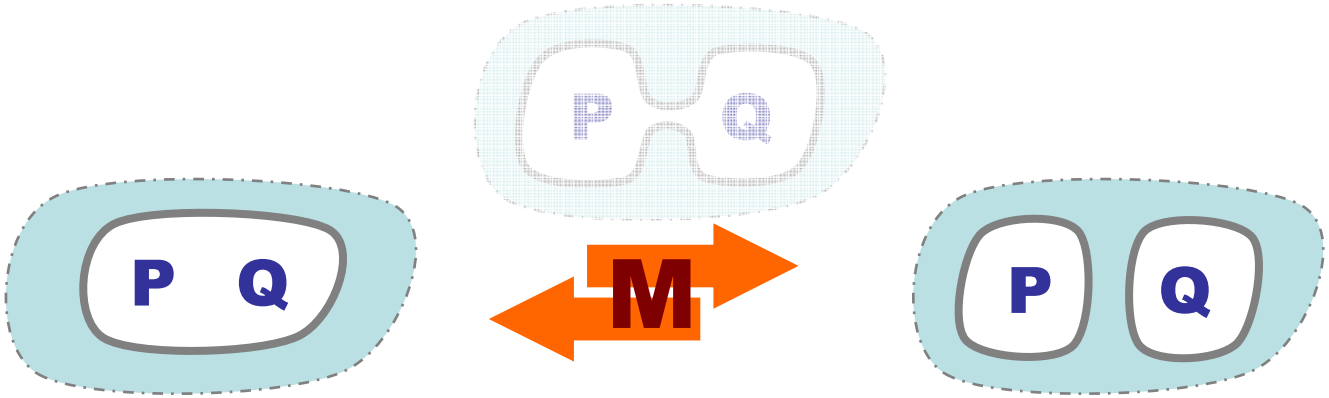


✓ Mito/Mate Reaction

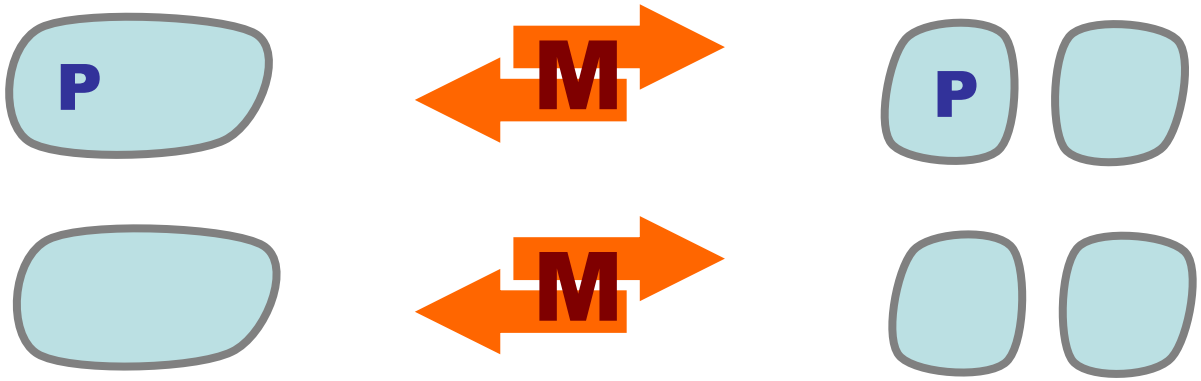
Preserves color alternation and stability.



Dual:



Examples

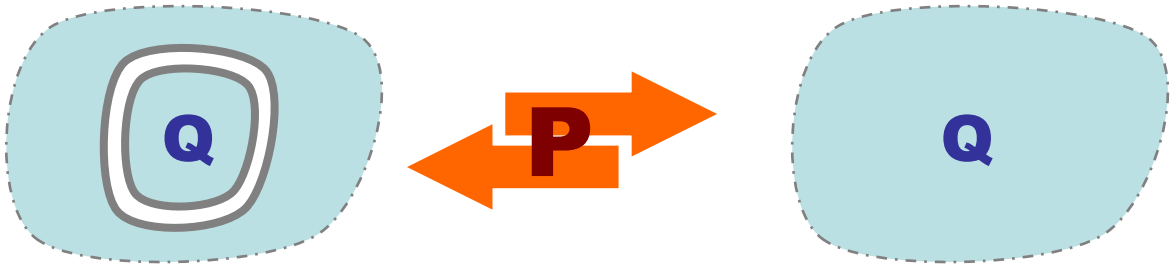


N.B. under both Endo/Exo and Mito/Mate, frothing/fizzing happens as soon as a single membrane exists. This is another reason why completely spontaneous frothing/fizzing seems natural.

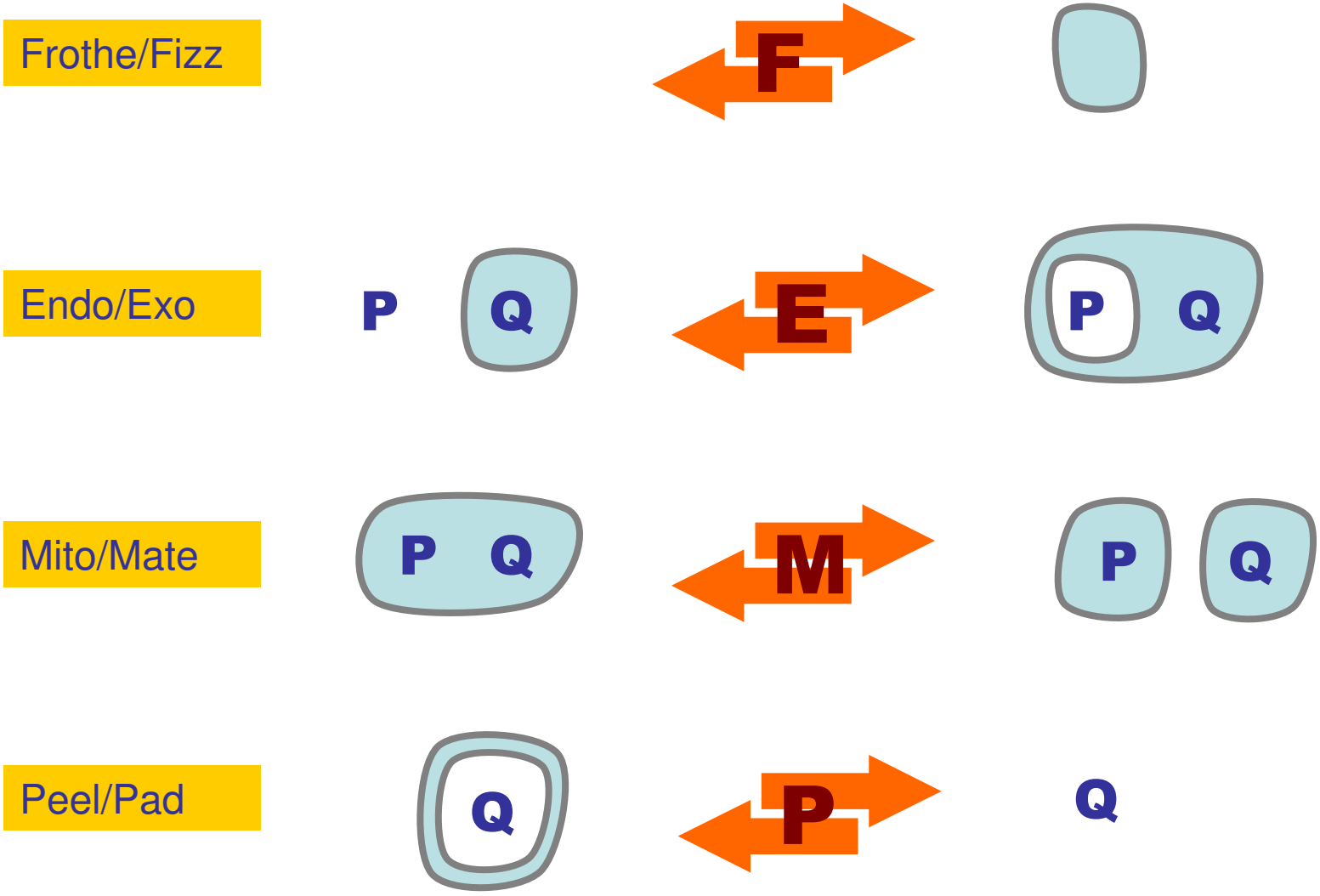
✓ Peel/Pad Reaction

Preserves color alternation and stability.

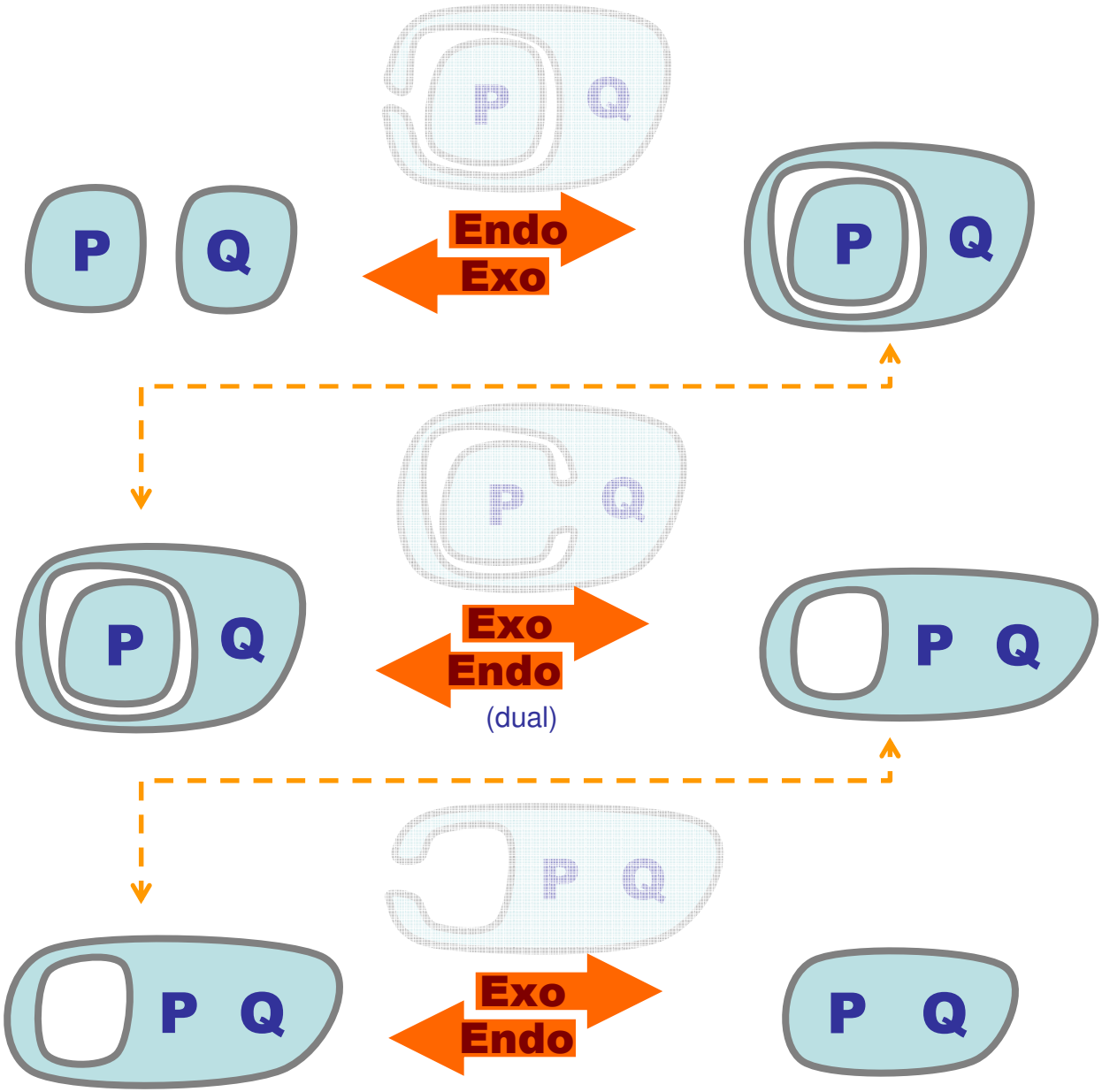
Dual:



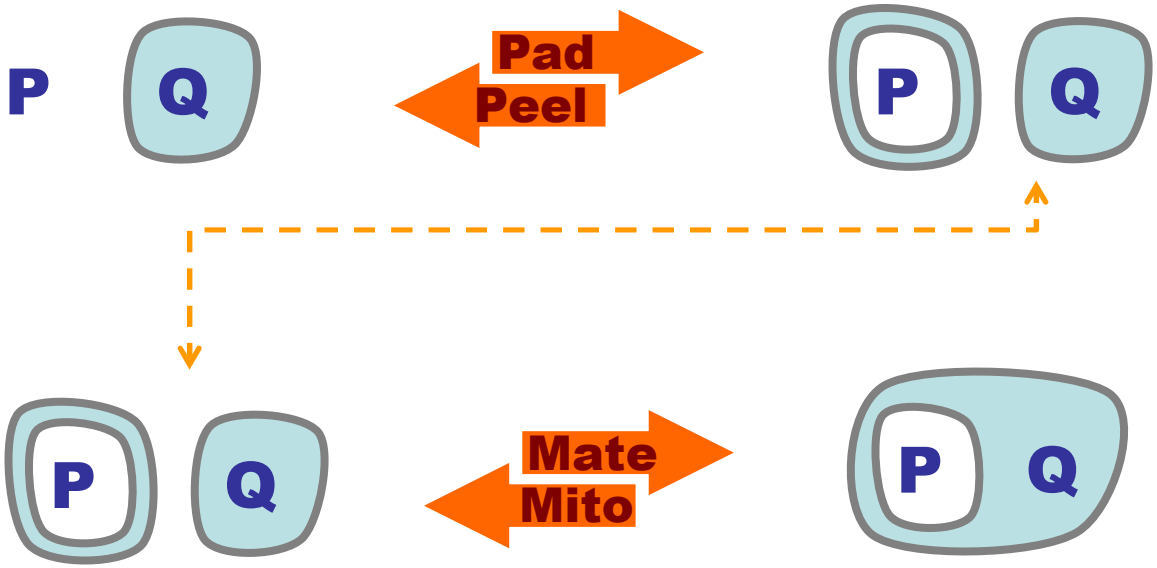
Summary: Four Good Reactions



Mito/Mate by 3 Endo/Exo

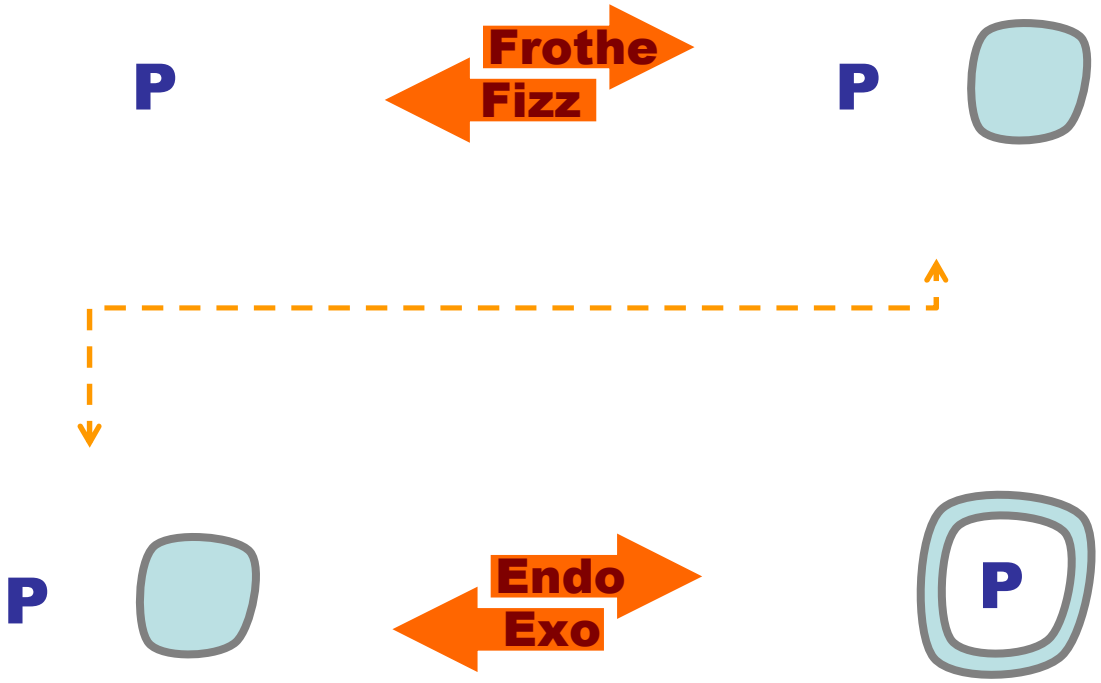


Endo/Exo by Mito/Mate and Peel/Pad

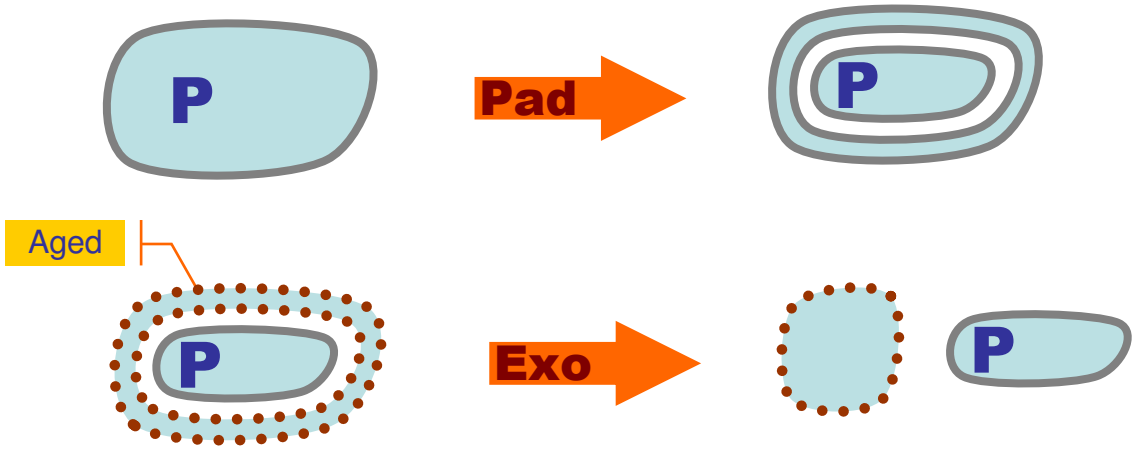


Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.

Peel/Pad by Frothe/Fizz and Endo/Exo

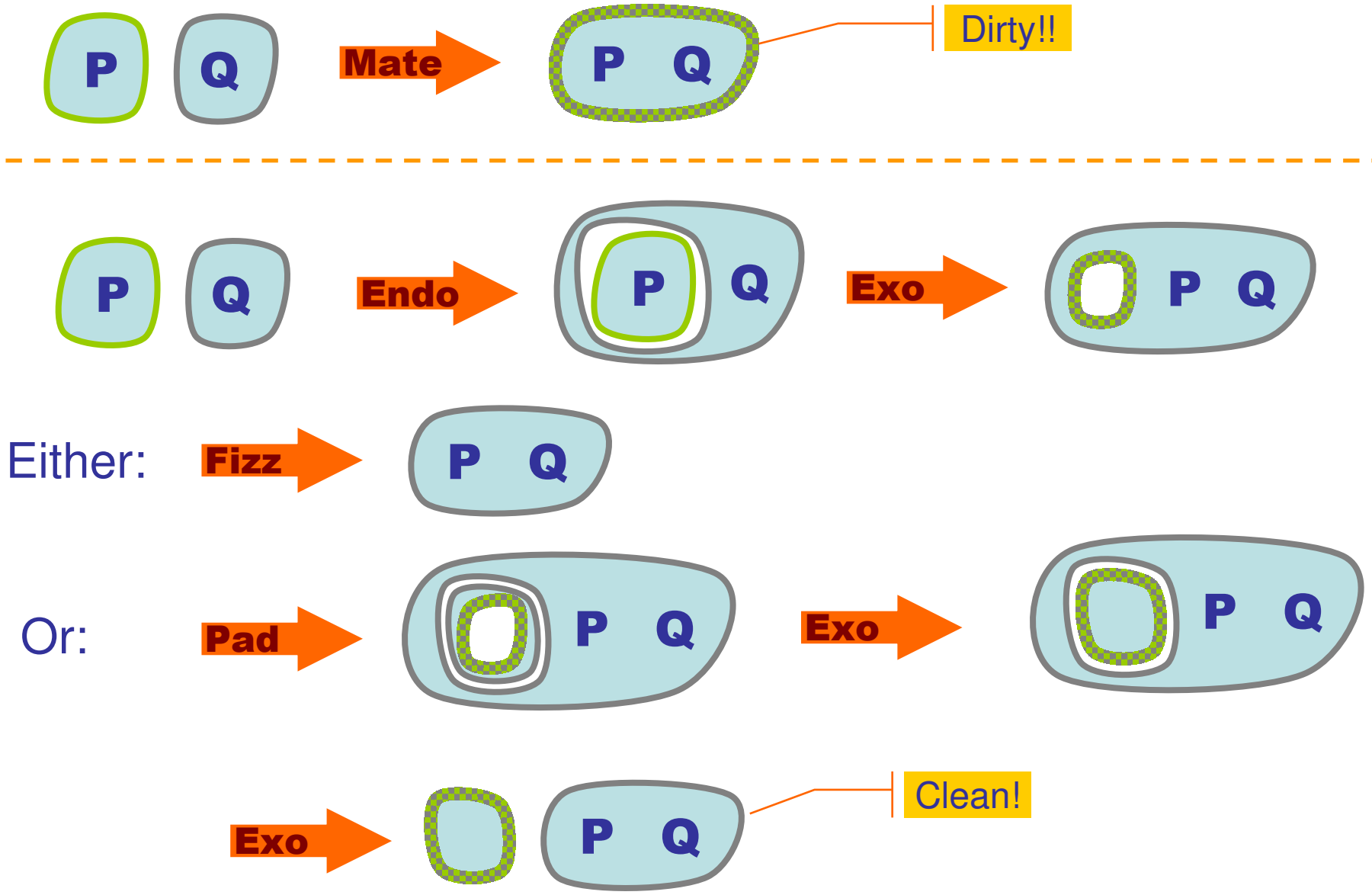


Ex: Molting



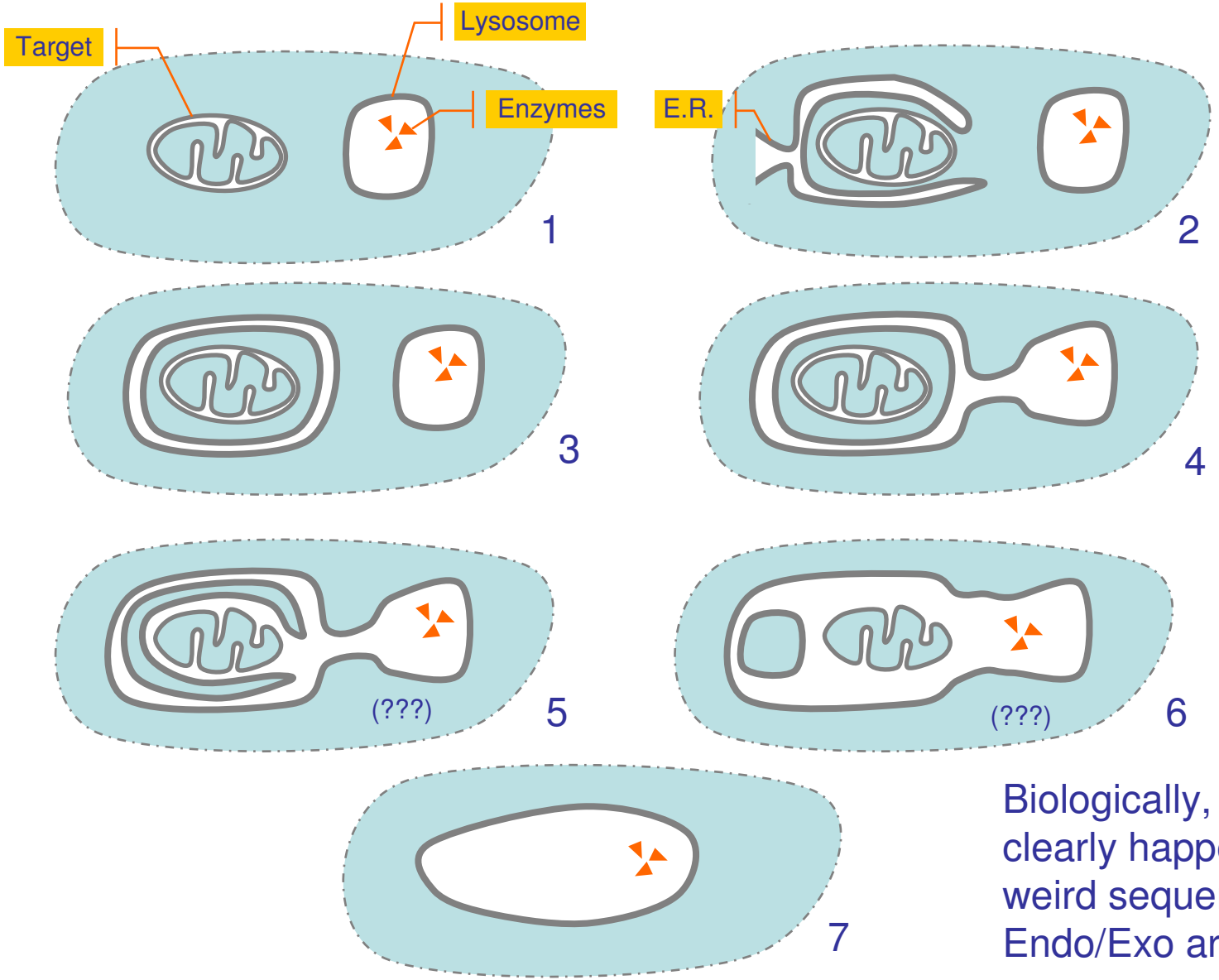
Ex: Clean Eating

(why Endo/Exo is "healthier" than Mito/Mate)



(Real) Ex: Autophagic Process

Lysosome and target don't just merge.



Biologically, Mito/Mate clearly happens. However, weird sequences of Endo/Exo are also common.

O'Brane Algebra

eXosol $X ::= \diamond \mid X \circ X \mid ⦇Y⦈$ — cyto brackets

cYtosol $Y ::= \blacklozenge \mid Y \bullet Y \mid ⦇X⦈$ — exo brackets

We look at this algebra as a preliminary abstraction of process calculi one may devise. Algebraic symmetries will soon be broken, but are still inspiring.

Axioms

$\diamond$ $\circ$ is a comm. monoid

$\blacklozenge$ $\bullet$ is a comm. monoid

F/F: $\diamond = ⦇\blacklozenge⦈$ $\quad \blacklozenge = ⦇\diamond⦈$

E/E: $X \circ ⦇Y⦈ = ⦇⦇X⦈ \bullet Y⦈$ $\quad ⦇X⦈ \bullet Y = ⦇X \circ ⦇Y⦈⦈$

Facts

(without using commutativity)

M/M:

$⦇Y⦈\ ⦇Y'⦈ = ⦇⦇⦇Y⦈⦈\ Y'⦈ = ⦇⦇\diamond\ ⦇Y⦈⦈\ Y'⦈$
$= ⦇⦇\diamond⦈\ Y\ Y'⦈ = \diamond\ ⦇Y\ Y'⦈ = ⦇Y\ Y'⦈$

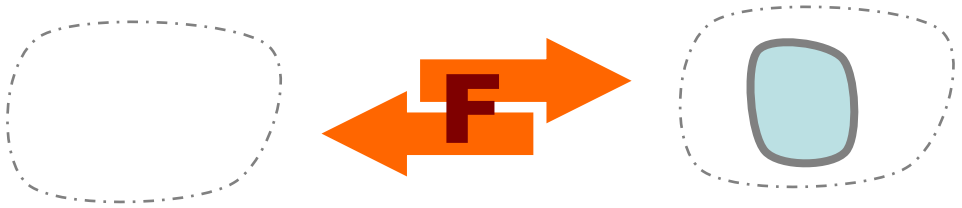
$⦇X⦈\ ⦇X'⦈ = ⦇X\ X'⦈$ symmetrically

P/P:

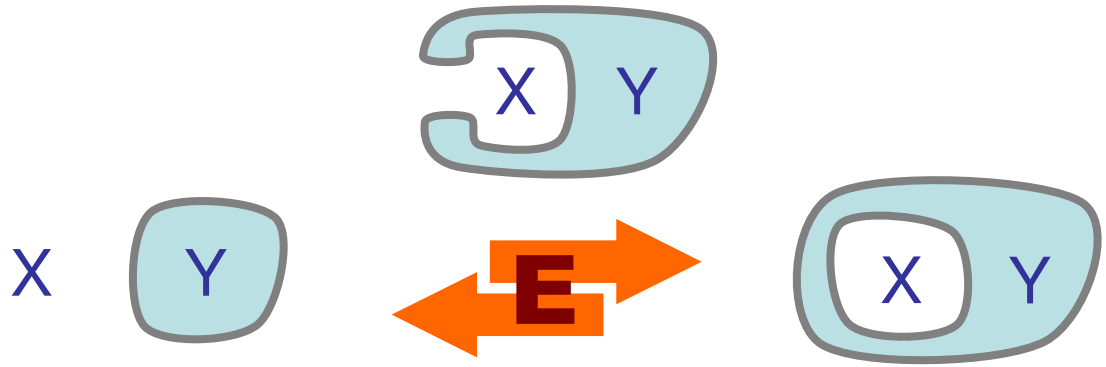
$X = X \diamond = X\ ⦇\blacklozenge⦈$
$= ⦇⦇X⦈\ \blacklozenge⦈ = ⦇⦇X⦈⦈$

$Y = ⦇⦇Y⦈⦈$ symmetrically

Axioms Illustrated



$$\diamond = (\blacklozenge)$$



$$X \circ (Y) = ((X) \bullet Y)$$

O'Brane Algebra v2

eXosol $X ::= \diamond \mid X \circ X \mid ⦇Y⦈$ — cyto brackets

cYtosol $Y ::= \blacklozenge \mid Y \bullet Y \mid ⦇X⦈$ — exo brackets

Axioms

$\diamond$ $\circ$ is a comm. monoid

$\blacklozenge$ $\bullet$ is a comm. monoid

M/M: $⦇Y \bullet Y'⦈ = ⦇Y'⦈ \circ ⦇Y⦈$ $⦇X \circ X'⦈ = ⦇X⦈ \bullet ⦇X'⦈$

P/P: $⦇⦇X⦈⦈ = X$ $⦇⦇Y⦈⦈ = Y$

Facts

E/E:

$X \circ ⦇Y⦈ = ⦇⦇X⦈⦈ \circ ⦇Y⦈ = ⦇⦇X⦈ \bullet Y⦈$

$⦇X⦈ \bullet Y = ⦇X \circ ⦇Y⦈⦈$ symmetrically

F/F:

$⦇\blacklozenge⦈ = \diamond \circ ⦇\blacklozenge⦈ = ⦇⦇\diamond⦈ \bullet \blacklozenge⦈ = ⦇⦇\diamond⦈⦈ = \diamond$

$⦇\diamond⦈ = \blacklozenge$ symmetrically

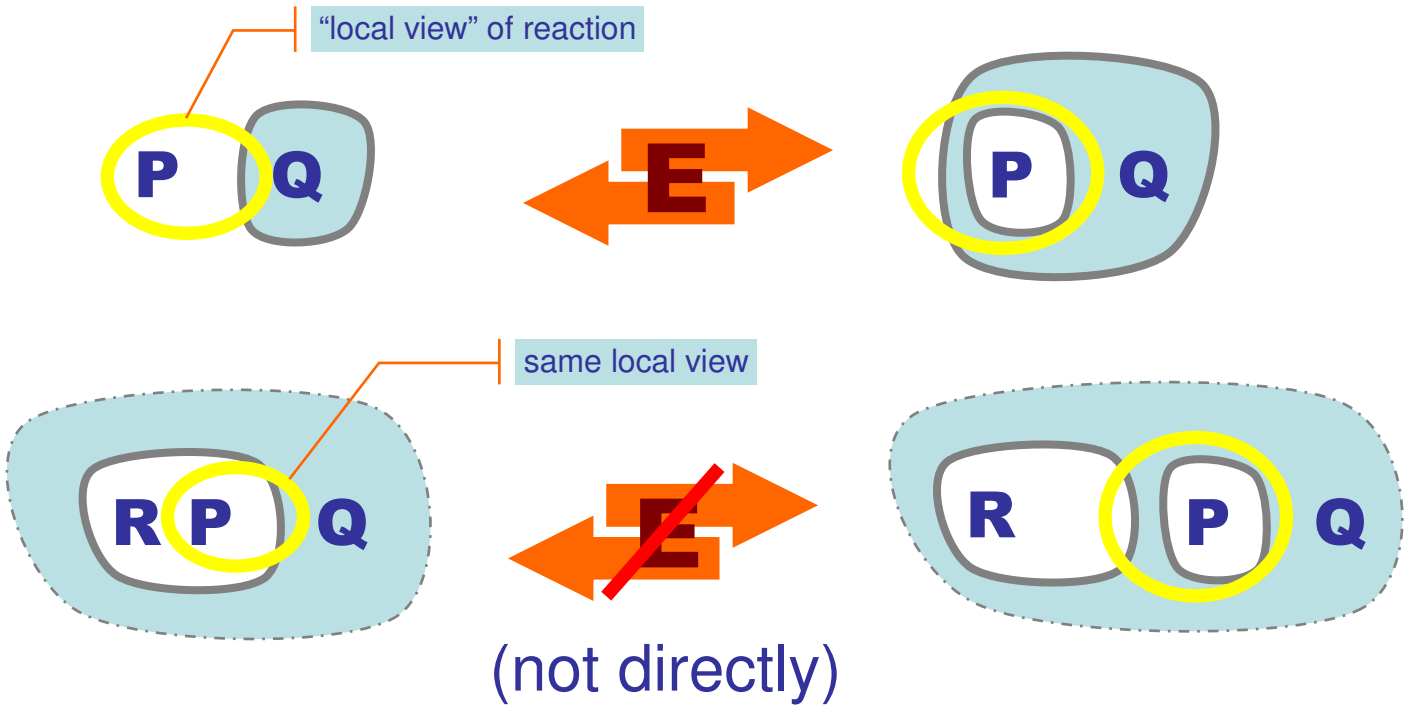
Back to: What Reactions to Allow

Locality Postulate

Interactions should be local to small membrane patches.

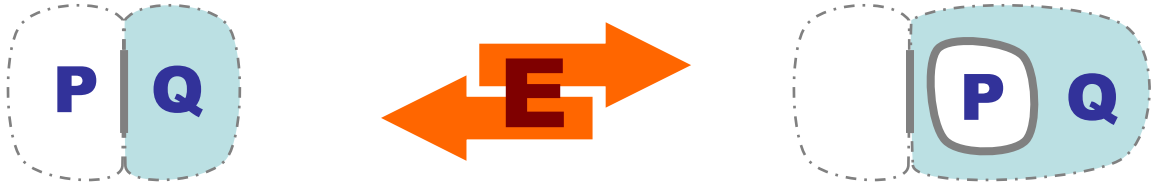
E.g., independent of global membrane properties such as overall curvature.

Endo/Exo Violates Locality

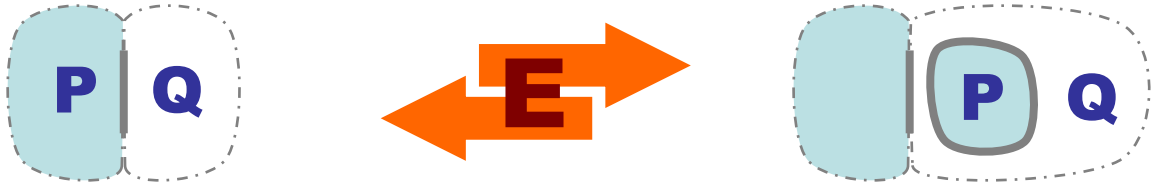


Oops…

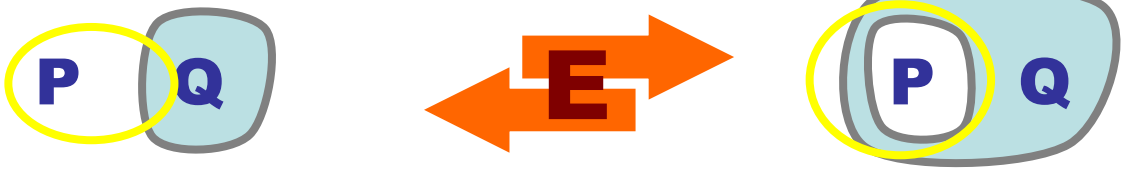
✓ Local Endo/Exo Reaction



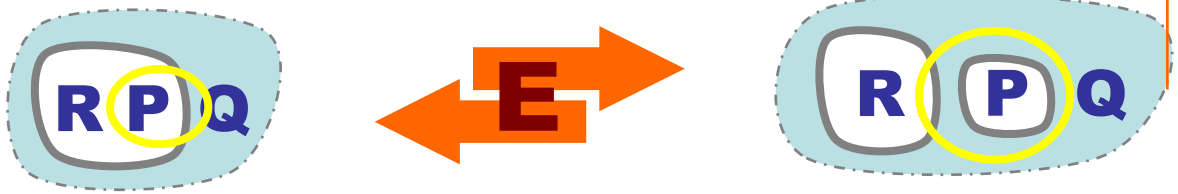
Dual:



Both:

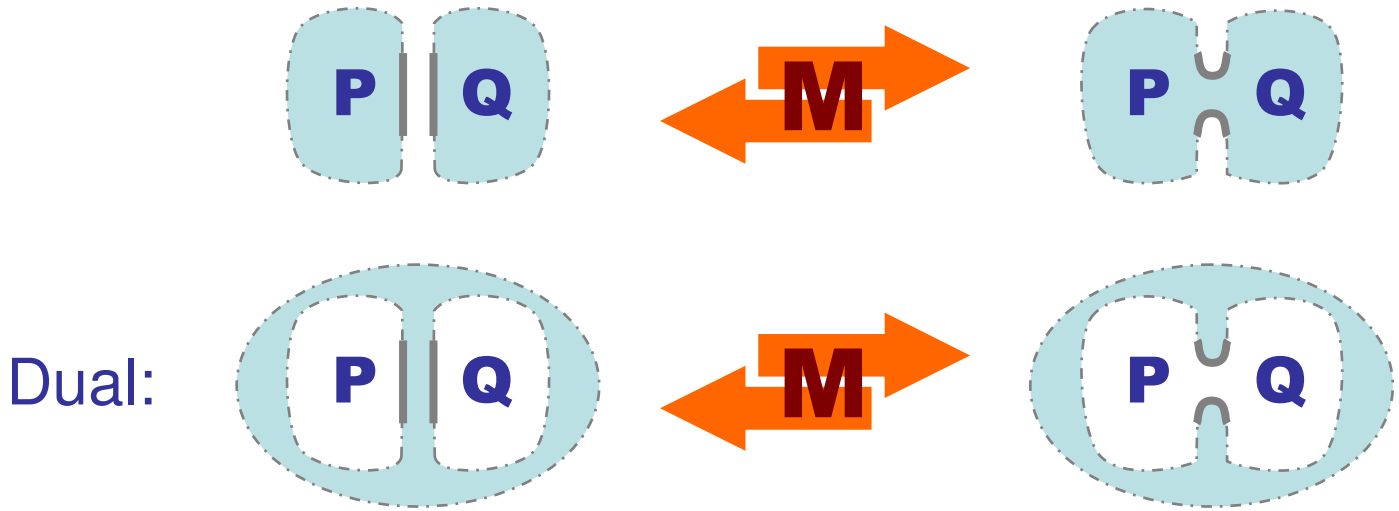


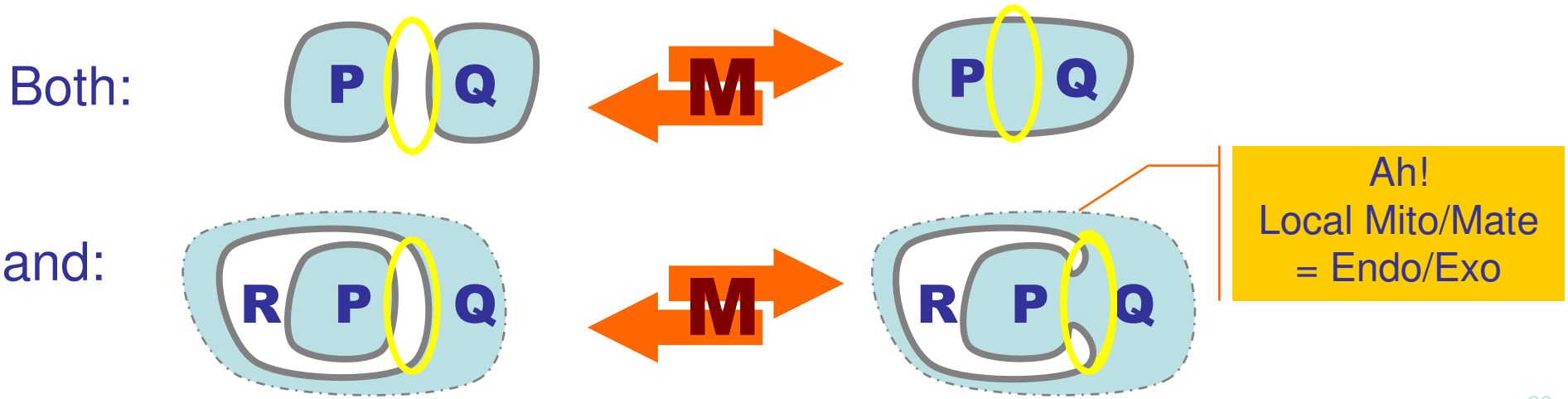
and:



Ah!
Local Endo/Exo
= Mito/Mate

✓ Local Mito/Mate Reaction





Locality is Not Violated

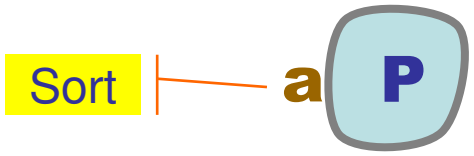
- Hence, even though Endo/Exo and Mito/Mate strictly violate locality, locality is preserved in a bigger system that can represent them both.
- (In any case, I am not sure how to express the local versions as an algebra.)

Assessment So Far

- Abstraction level still too high
  - We really want to talk at least about “different sorts” of membranes.
  - We need to be a bit more deterministic.
- Easy to slip too low
  - E.g. trying to emulate process calculi interactions: we cannot handle individual membrane proteins.
  - Difficult to handle even different kinds of membrane proteins and their groupings.
- Intermediate approach:
  - Abstractly talk about the “sort” of a membrane, and how it changes into other abstract sorts.

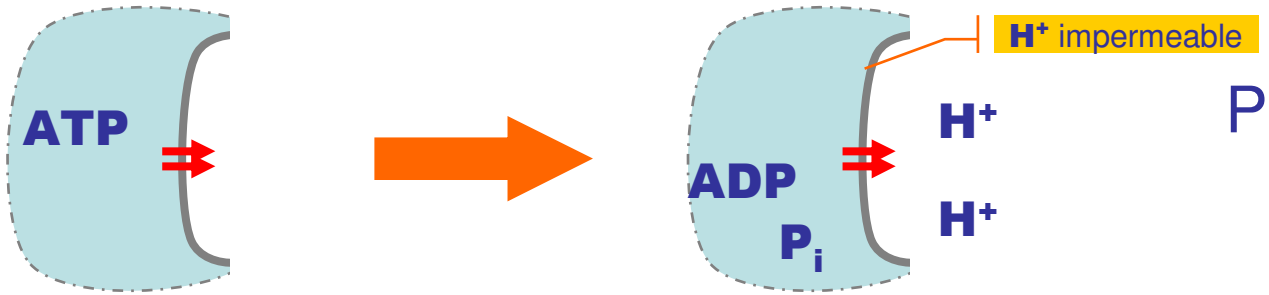
2: Sorted Membranes

- Different kinds of membranes.
  - Lipid bilayer is universal. All membranes can in principle merge, but the lipid compositions vary.
  - The set of proteins bound to a membrane confer unique characteristics to it and its contents.
- Each membrane is uniform.
  - Membrane proteins diffuse rapidly through the surface of a membrane; they are not localized (unless held together).
- Hence: sorts of membranes.
  - A single name will characterize the collection of features of a membrane; its *sort*.
  - Each sort is meant to be “implemented” by lower level mechanisms.



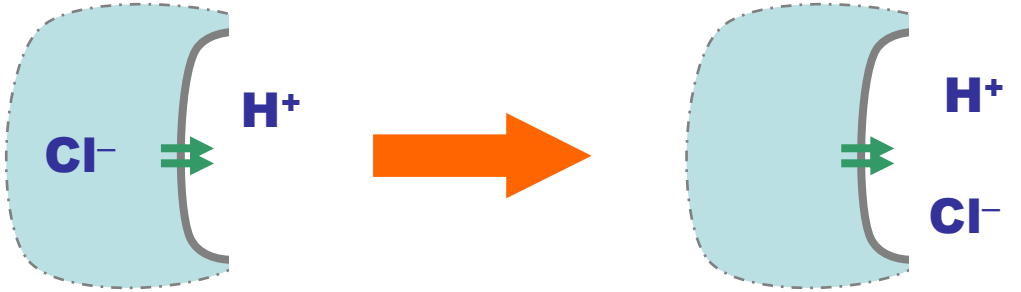
Ex: A Specialized Membrane

E.g. plant vacuole (white).

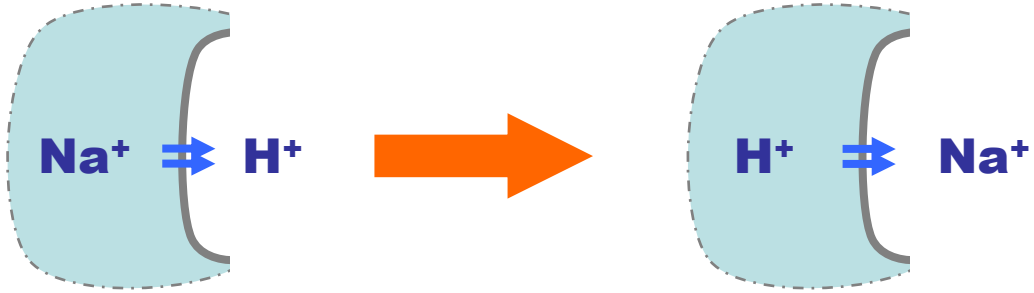


Proton Pump

ATP charges up the vacuole with H^+. Several other pumps work off that charge.



Ion Channel



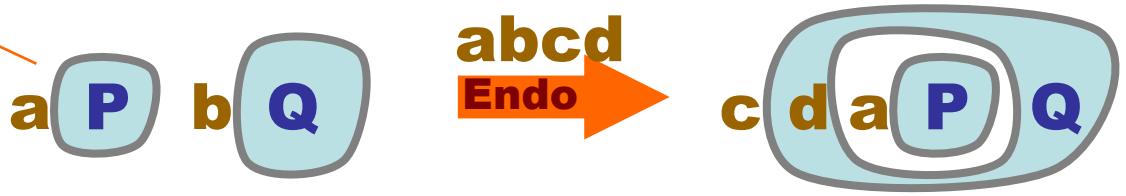
Proton Antiporter

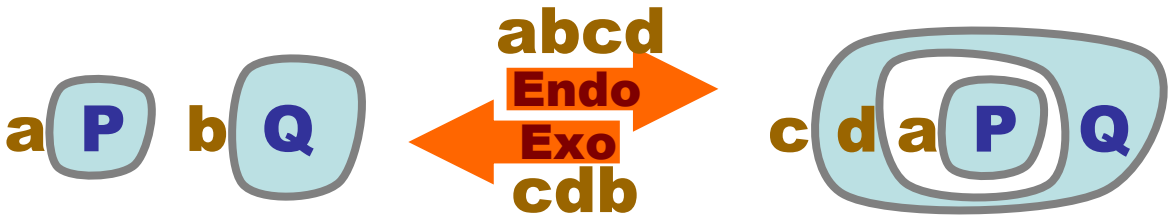
A membrane of sort “PlantVacuole” has all those things on it.

Sorted Frothe/Fizz Reactions

Sorted Endo/Exo Reactions

a identifies subsystem **P**

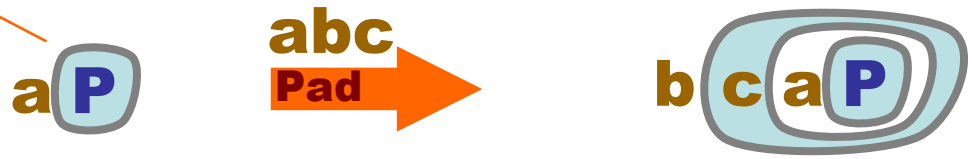




Reversible pair

Sorted Peel/Pad Reactions

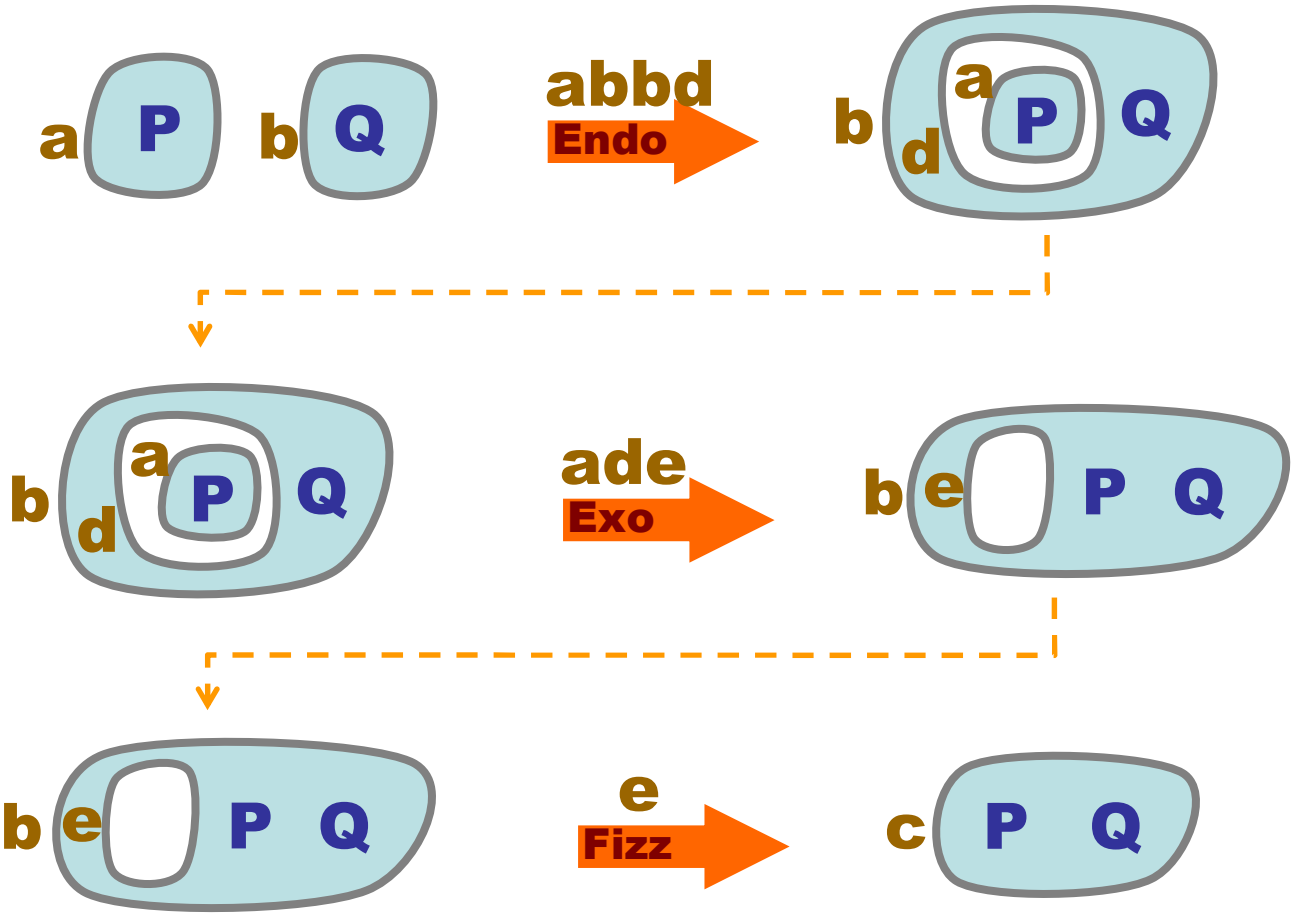
a identifies subsystem **P**



Emulation

Sorted Mate

Emulation



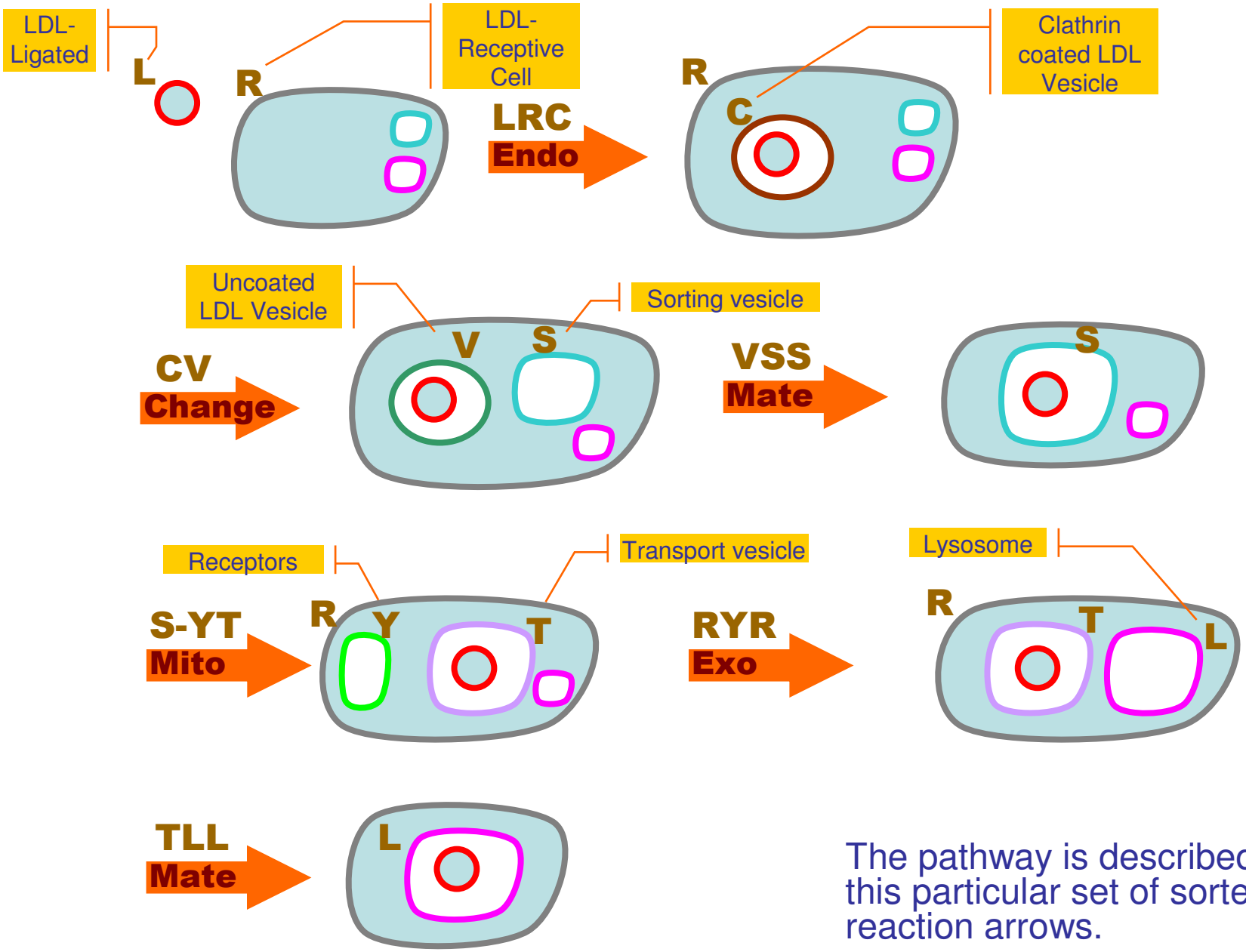
Sorted Mito

bc identifies subsystem **P**

Emulation

Sorted Change

Receptor-Mediated Degradation Pathway



The pathway is described by this particular set of sorted reaction arrows.

Conclusions

- Main insights:
  - Membranes are oriented. When nested, their orientations alternate.
  - Activities happen *on* membranes, not *inside* them.
- Looking for a language:
  - Preserving orientation invariants.
  - With sorted membranes.
  - With stochastic information on transitions.

General Aim: Direct Engineering

- Describe how systems work.
- Design systems to work as intended.
- As opposed to reverse engineering:

A biologist's approach to understanding jet engines

1) Use radioactive jet fuel.
2) Saw engine off airplane and kick-start it.
3) Freeze it very quickly in liquid nitrogen.
4) Cut it in very thin slices at odd angles.
5) Stain slices with various hair colors.
6) Take blurry pictures, send them to friends.
7) Start again; this time first throw a wrench in it.

References

- [MCB] Molecular Cell Biology, Fourth Edition. Freeman.
- [MBC] Molecular Biology of the Cell, Third Edition. Garland.