Membrane Interactions

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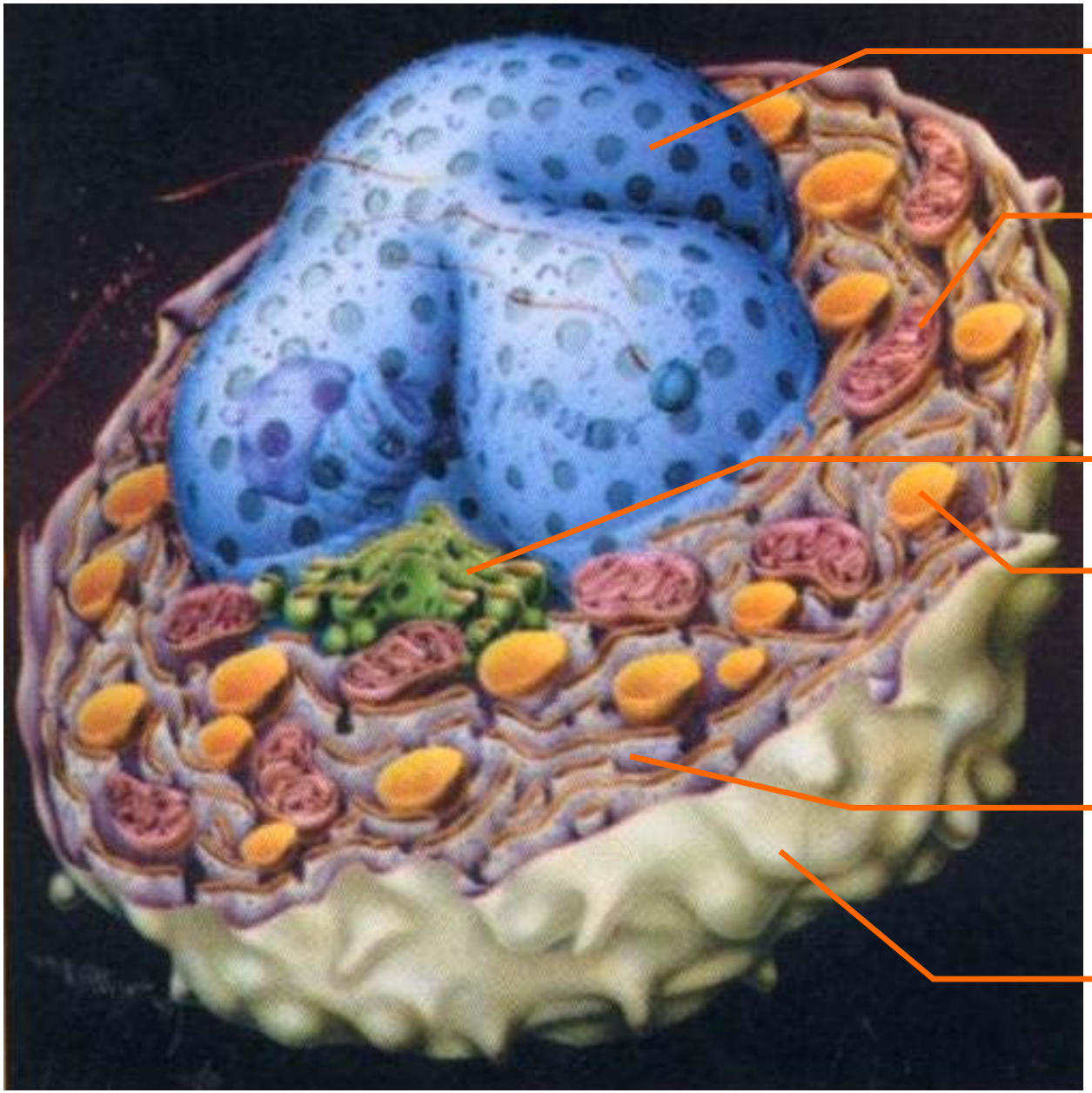
Eukaryotic Cell

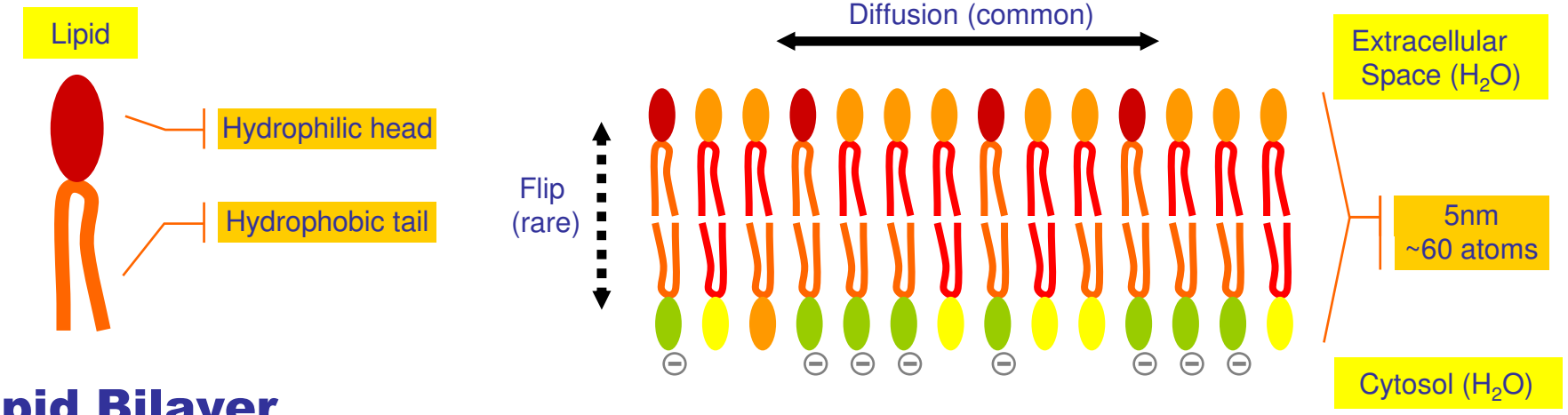
Membranes everywhere



Membrane-based Systems

- Many cellular processes involve membranes.
  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?
- In modeling it, we *must* use abstractions, to avoid combinatorial explosion: 1 membrane $\approx \infty$ molecules.
- Emerging area of *Systems Biology*
  (~ interdisciplinary study of relationships and interactions of biological components).

Membranes are Oriented 2D Surfaces



Lipid Bilayer

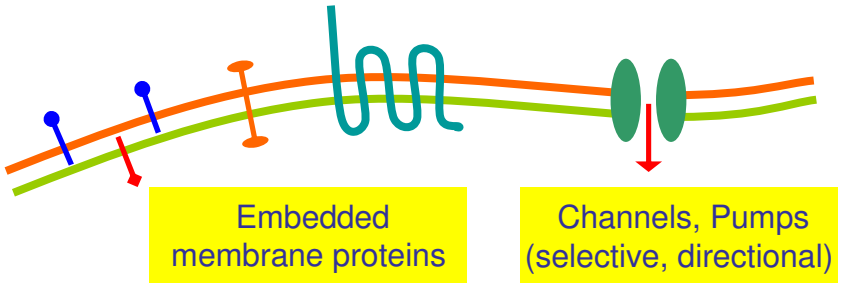
Self-assembling

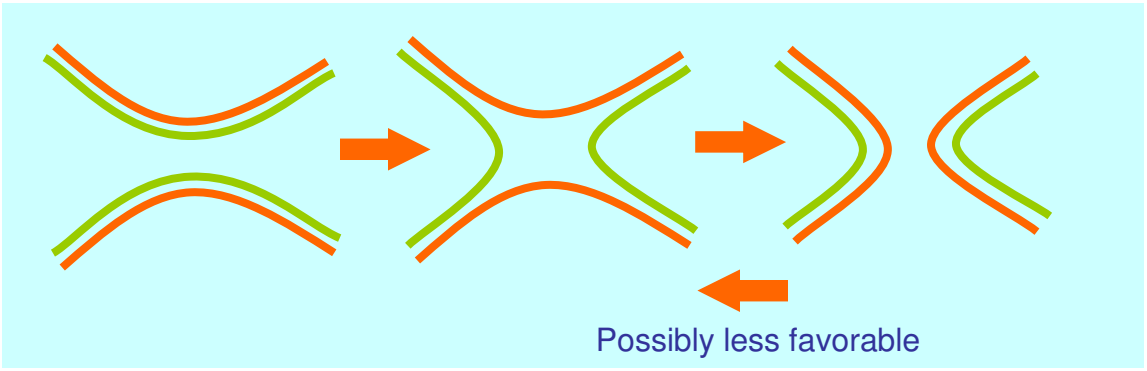
Largely impermeable

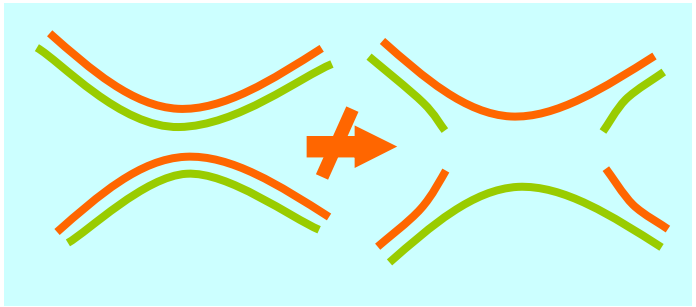
Asymmetrical (in real cells)

Embedded proteins

A 2D fluid inside a 3D fluid!

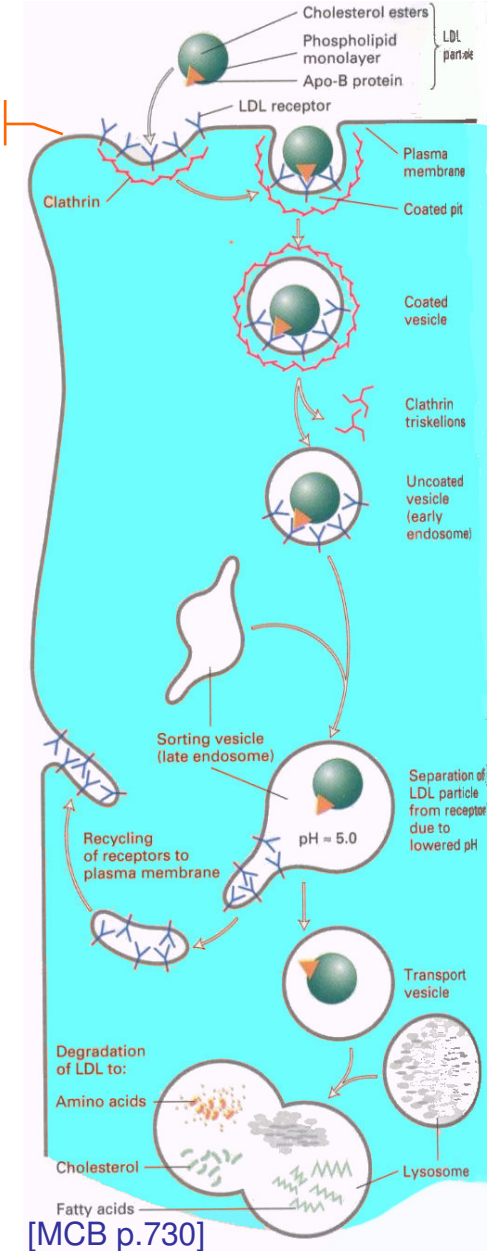






A Biological Algorithm

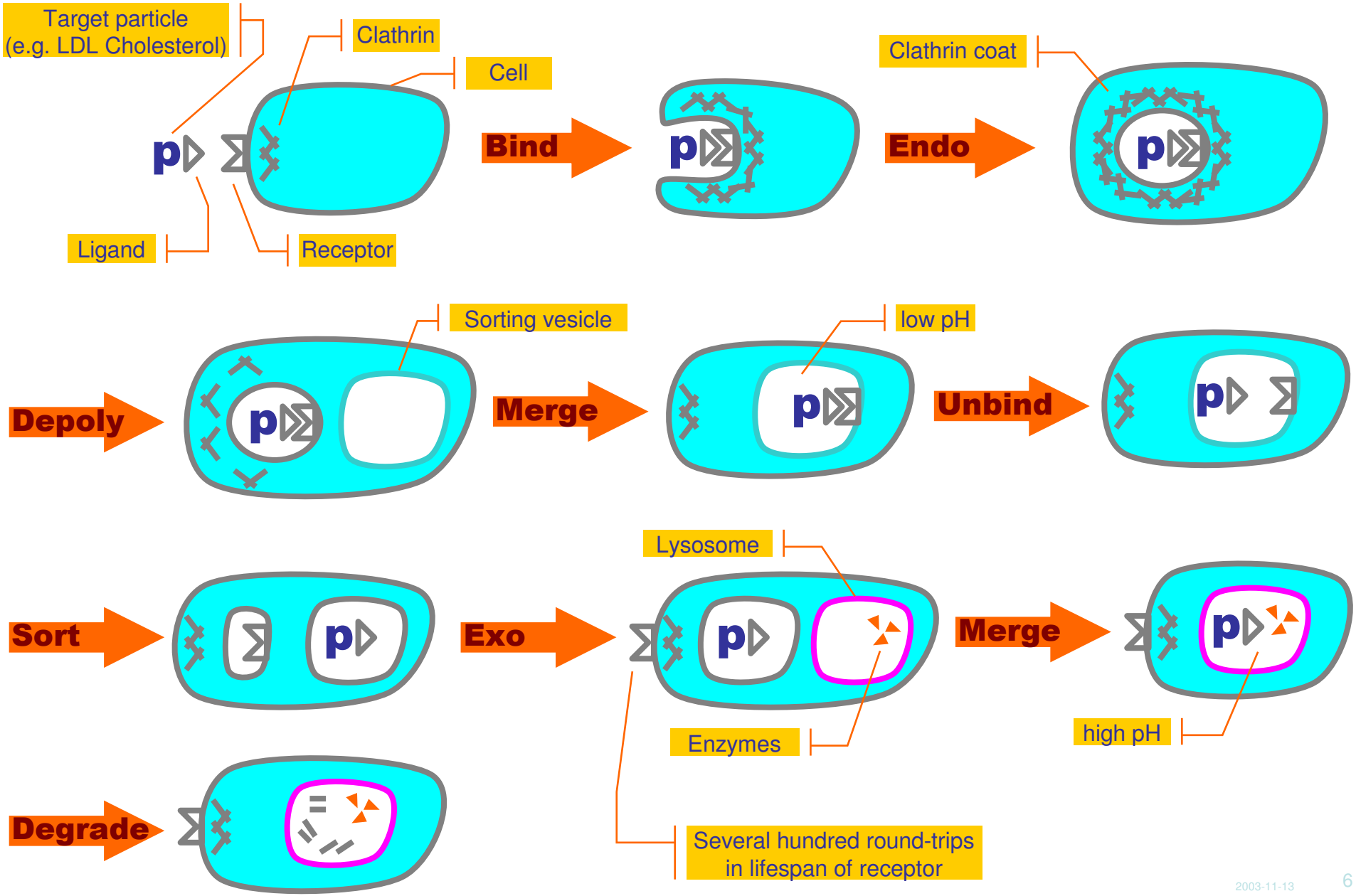
- LDL-Cholesterol Degradation
  - A cast of many thousands (molecules) just to get one molecule from A to B.
  - Membranes are key to the algorithm, we want to model *them*, not their individual molecules.
- How do people know all that?
  - They take pictures, see all stages of the algorithm in the same 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.



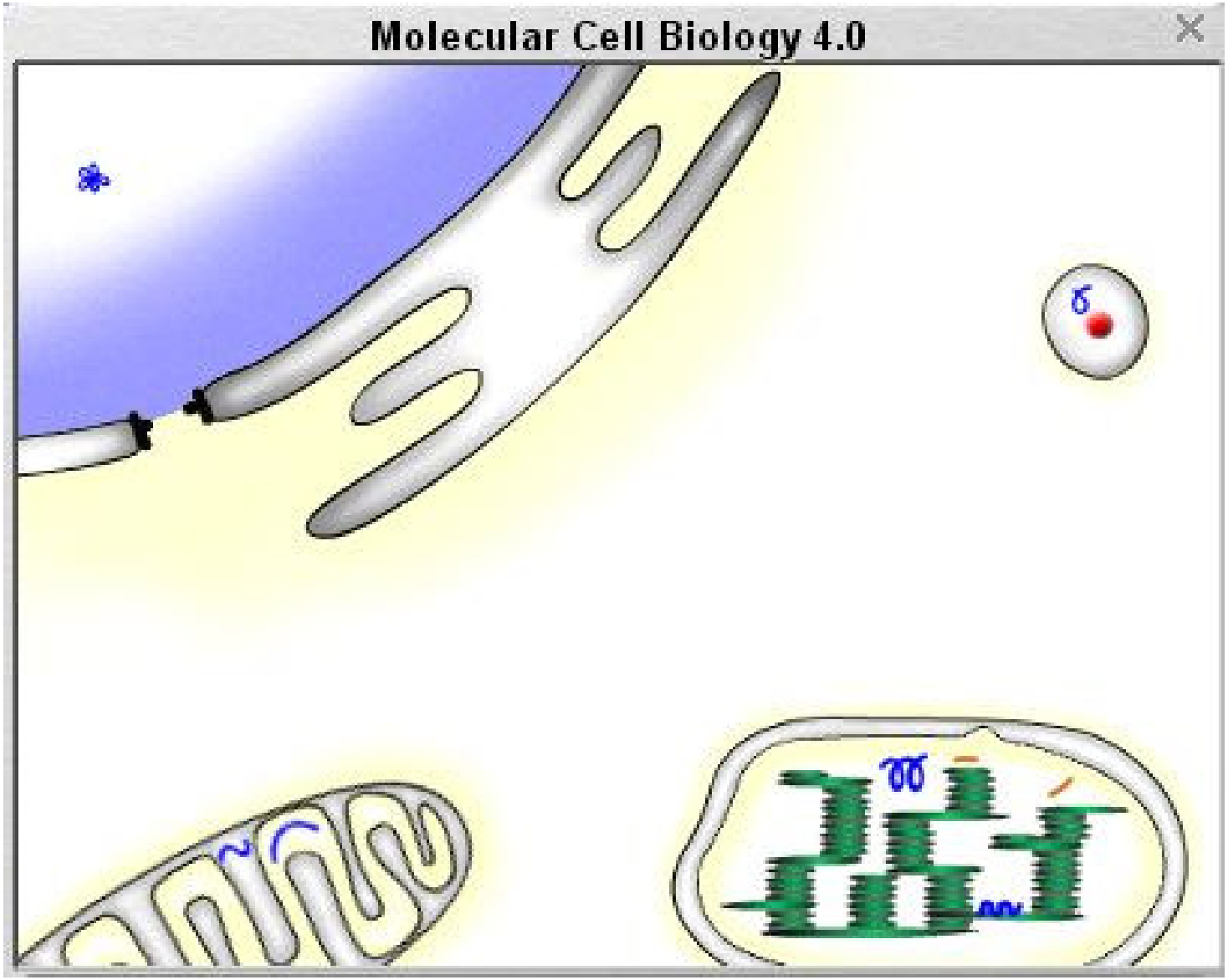
[MCB p.730]

Receptor-Mediated Degradation Pathway

(Abstract view)



Dynamic Compartments



Aims

- Describing biological processes
  - Avoid informal diagrams.
  - Write bioalgorithms in something close to a language.
- Abstraction options
  - 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 or two levels down.
- Approaches considered here
  - (Whole-)Membrane Reactions (*Bitonal Reactions*)
  - Rewriting systems (BiGraphs, Gamma, P-Systems, etc.)
  - Patch Reactions (BioSPi, BioAmbients, *Brane Calculi*)

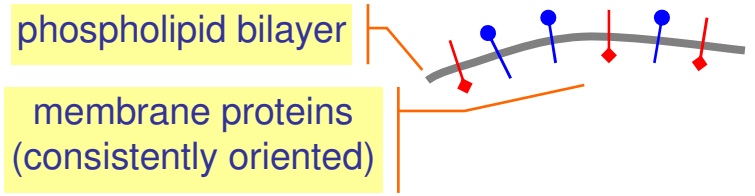
Stochastic Simulation

Part I

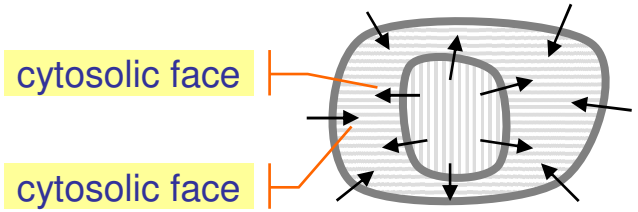
Bitonal Systems

Systems of Oriented Membranes

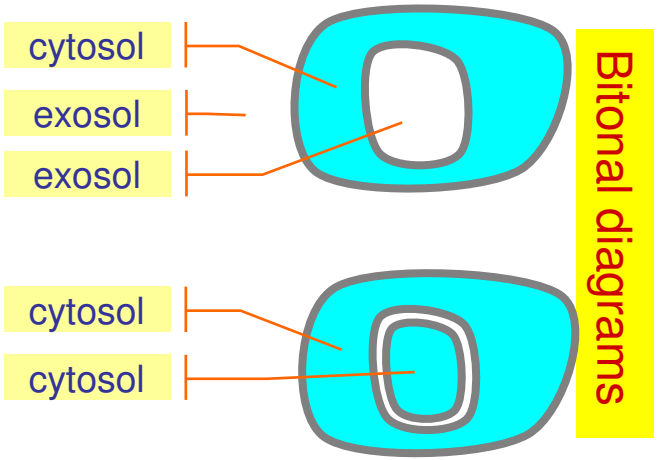
Membranes are closed non-intersecting curves, with an orientation[1].



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 tones: blue (cytosol[2]) and white (exosol[3]). Bitonal diagrams.



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).

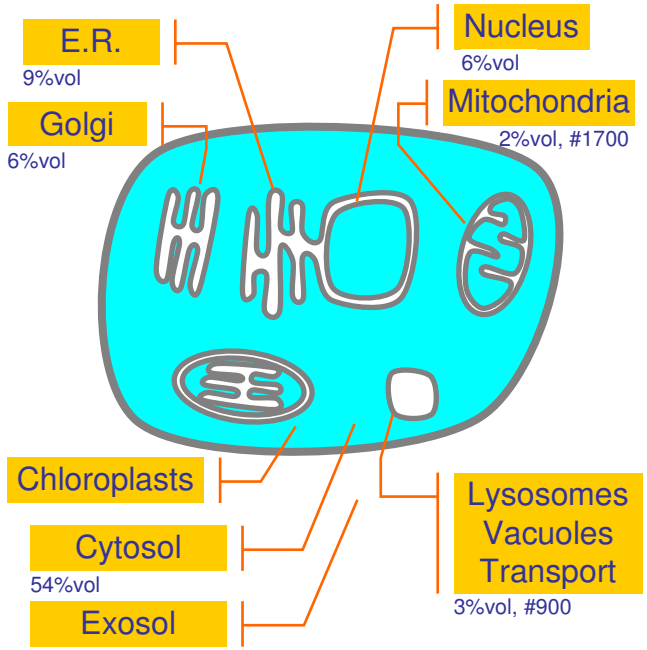
Bitonal Diagrams

Bitonal Postulate

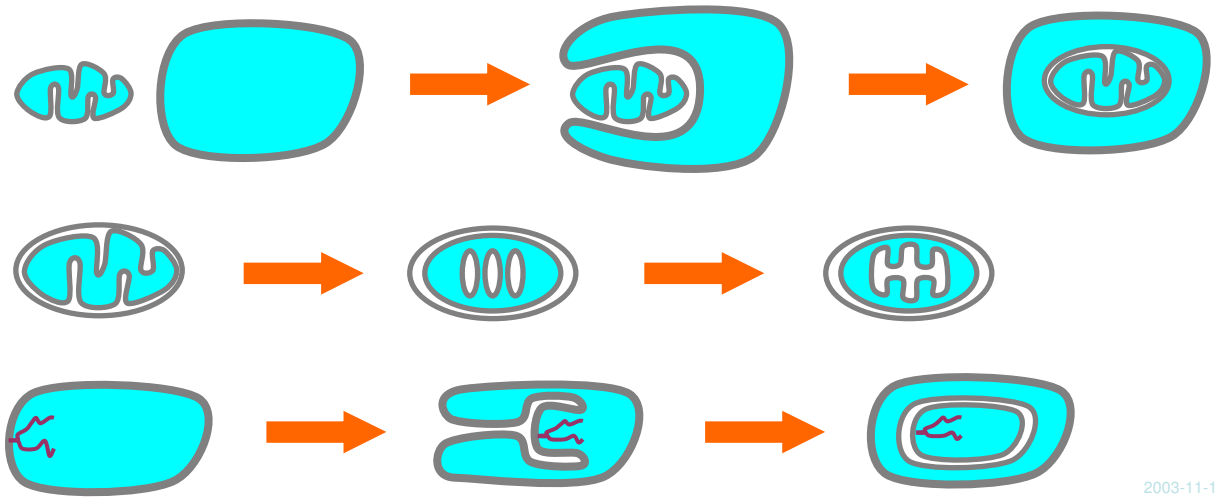
Blue and white areas alternate.

Bitonal Invariant

Bitonality is preserved by reactions (i.e. blue and white fluids never mix).

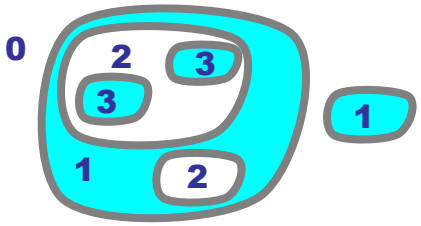


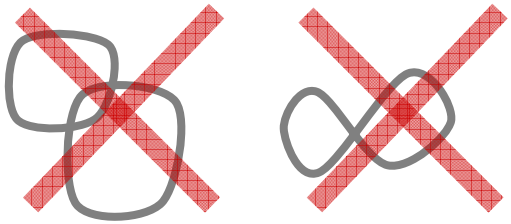
Evolutionary explanations of bitonality



Membrane Systems

Systems	**P,Q**
Empty	
Composition	**P Q**
Nesting	
Molecules	**m**





The *depth* of a point is the number of membranes that contain it.
The *tonality* of a point is white/blue iff its depth is even/odd.

Reactions

A *reaction* is a pair of membrane systems (before and after), but we are only interested in *gradual changes*; e.g.:

There are two ways to characterize gradual changes:

- Local interactions of membrane patches.
  (What really happens at the biochemical level.)
- Membrane reactions that preserve tonality “almost everywhere”.
  (Matching biological terminology, e.g. *mitosis*, *endocytosis*.)

These turn out to be equivalent!

Bitonal Reactions

Are “local”.

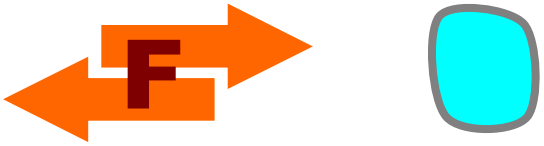
Do not mix “inside” and “outiside” fluids.

Preserve bitonal coloring.

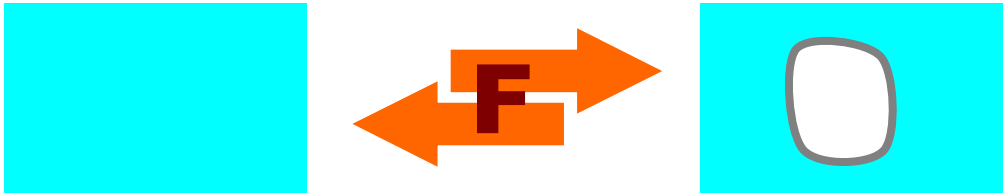
✓ Froth/Fizz Reaction

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

White expanse



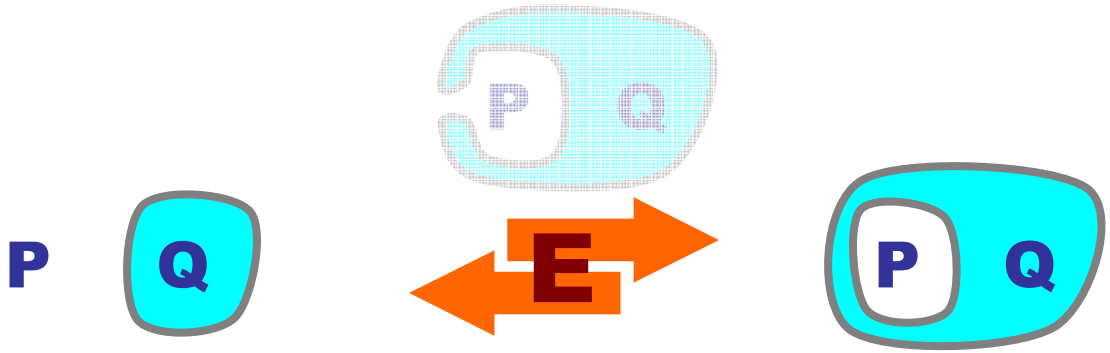
Blue expanse



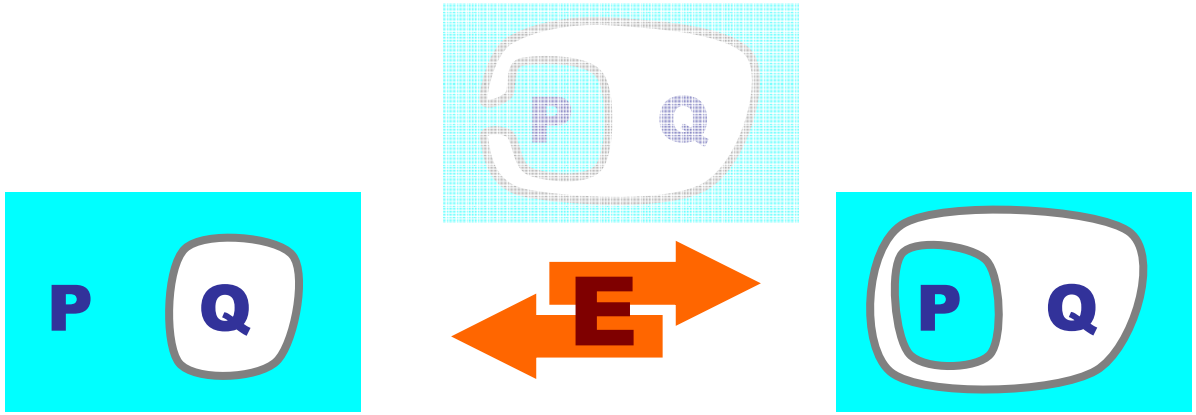
* Phospholipid molecules automatically assemble into closed membranes.

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

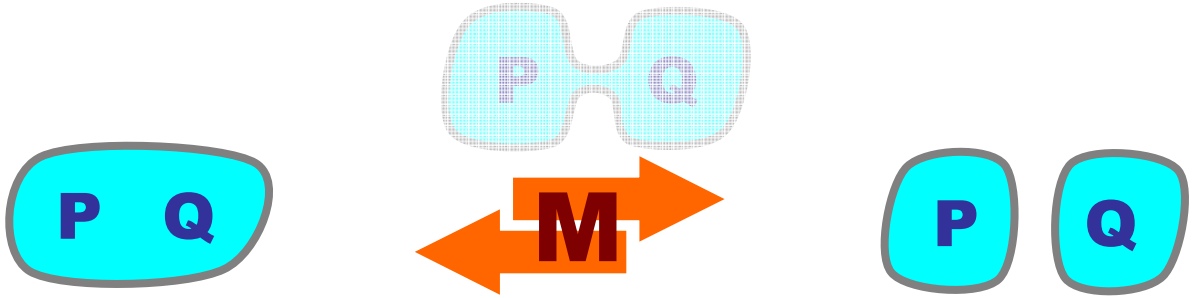
✓ Endo/Exo Reaction



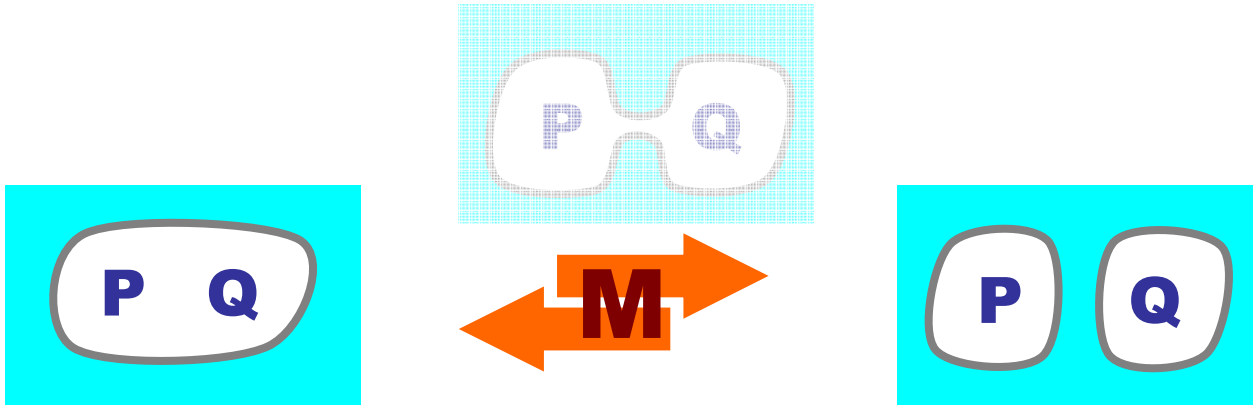
Dual:



✓ Mito/Mate Reaction

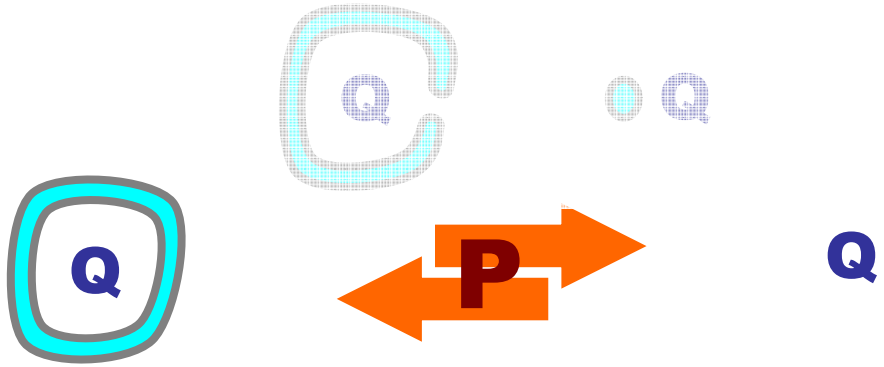


Dual:

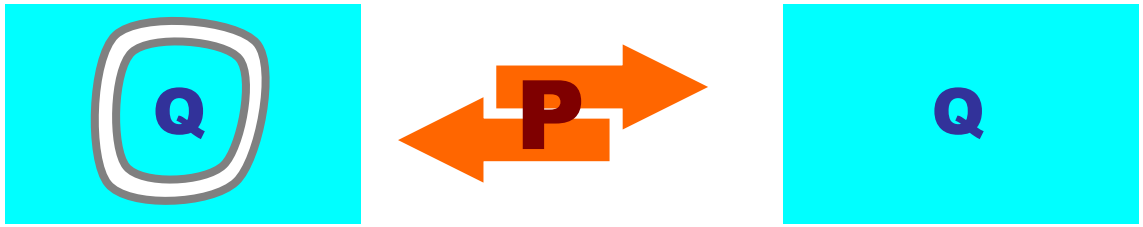


✓ Peel/Pad Transformation

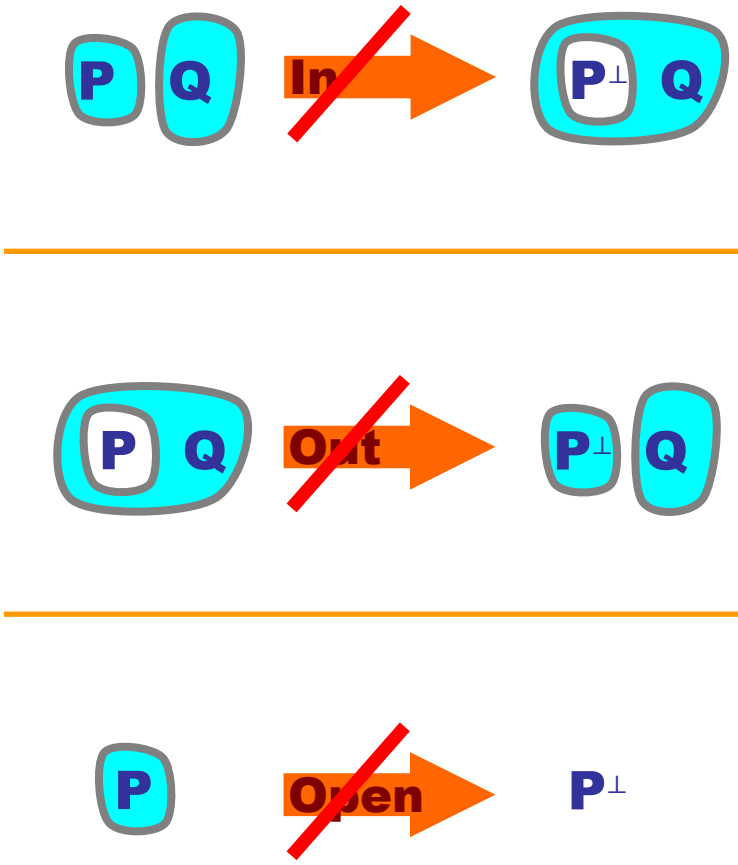
(Not local/bitonal, but composition of two such).



Dual:



Ambients

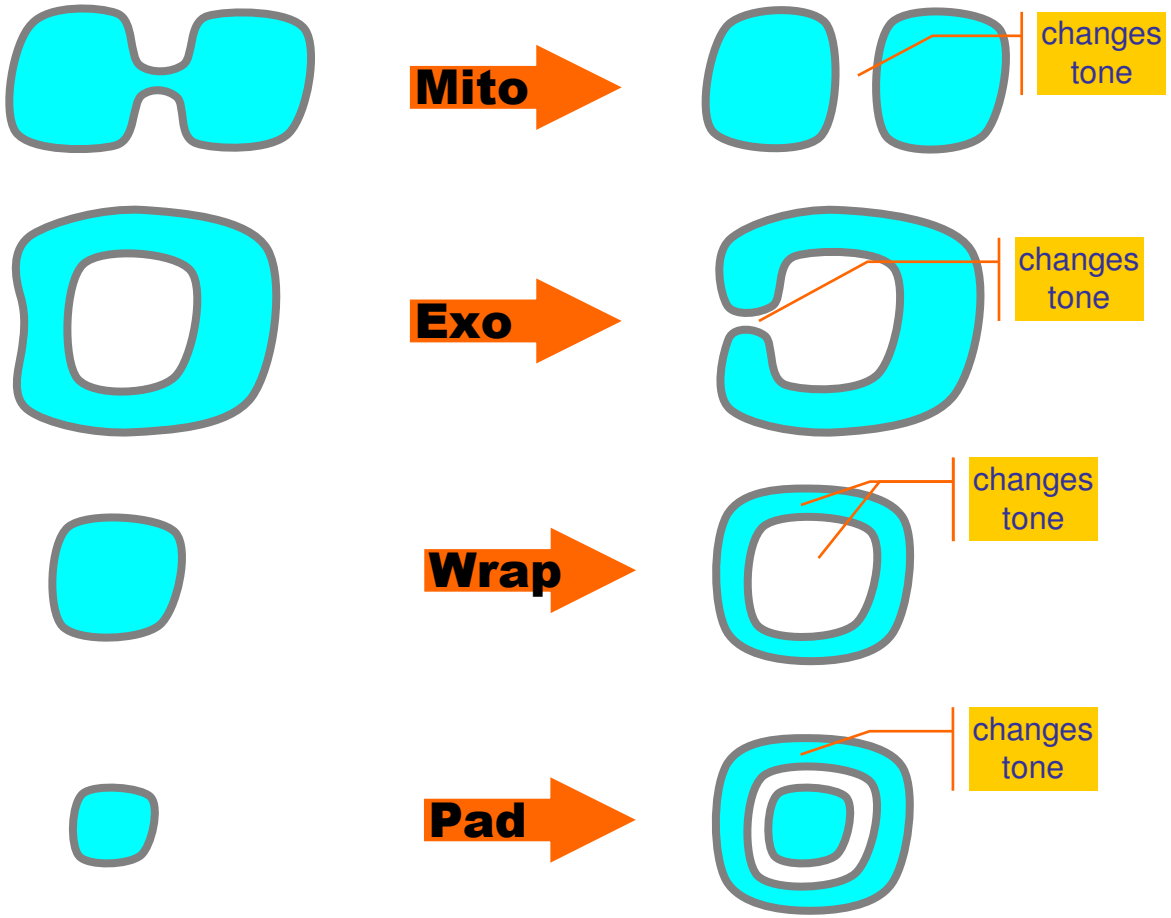


These abstract transformations are not bitonal (are not implementable by a finite and fixed sequence of abstract bitonal reactions); they invert the color of arbitrary subsystems which are in general not simply-connected.

Moreover, these transformations are not “implementable”: they imply either flipping orientation of membranes, or having membranes cross membranes, or destroying membranes (localized digestion excepted).

Bitonal Reactions

- A *bitonal (resp. layered) reaction* is such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes).



Layered Bitonal Reaction

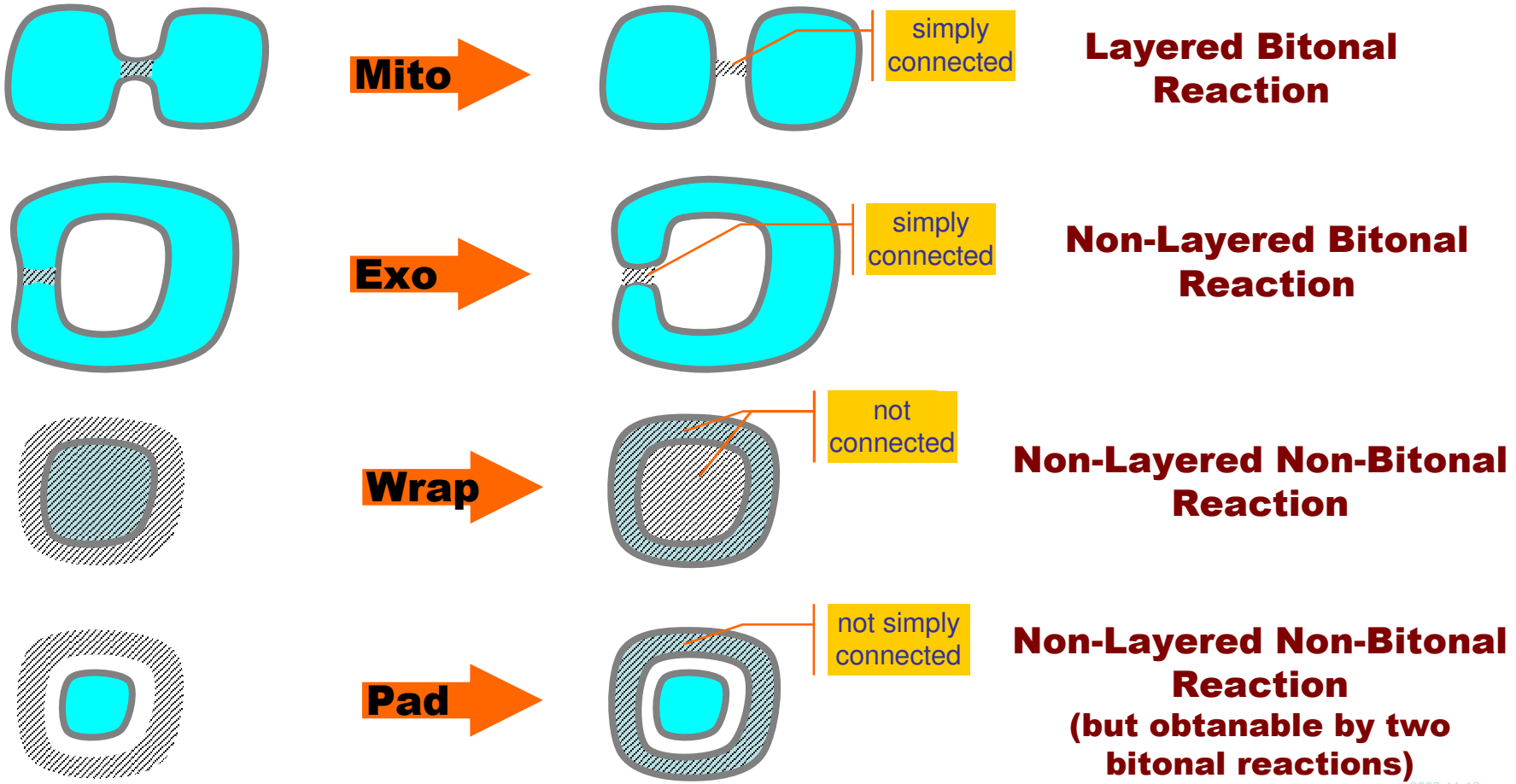
Non-Layered Bitonal Reaction

Non-Layered Non-Bitonal Reaction

Non-Layered Non-Bitonal Reaction (but obtainable by two bitonal reactions)

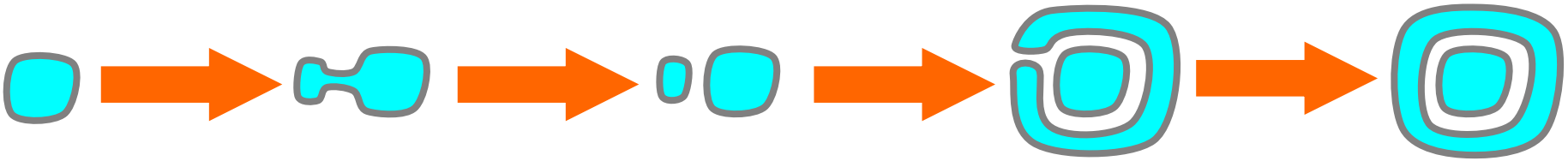
Bitonal Reactions

- A *bitonal (resp. layered) reaction* is a pair of membrane systems <M,M'> such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes).



Bitonal Transformations

- A *transformation* is a finite sequence of reactions. A *bitonal transformation* is a finite sequence of bitonal reactions.
- We want all “legal” transformations to be bitonal transformations (and hence “gradual” transformations). E.g.: padding:



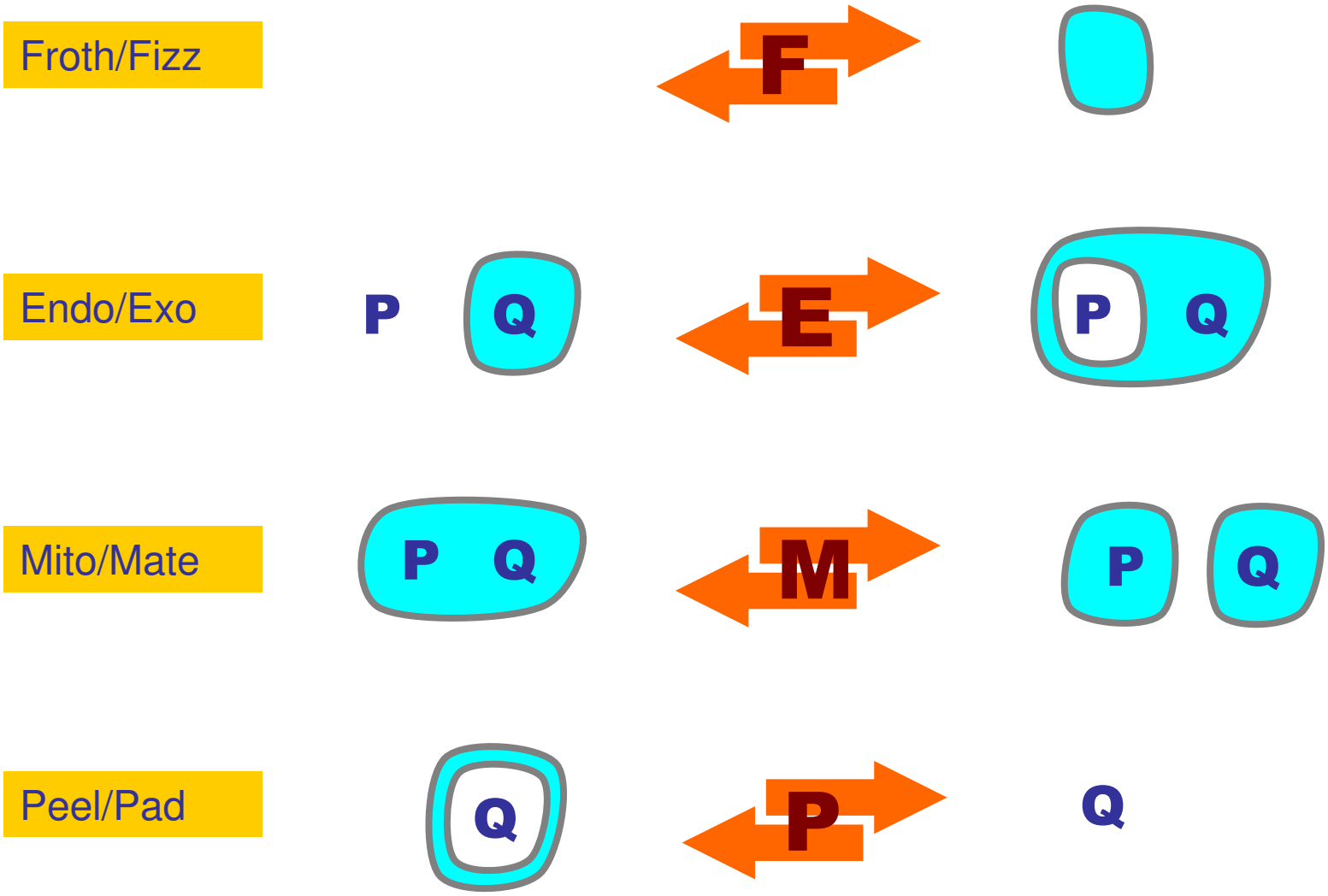
- Some transformations are inherently non-bitonal.

Abstract Transformations

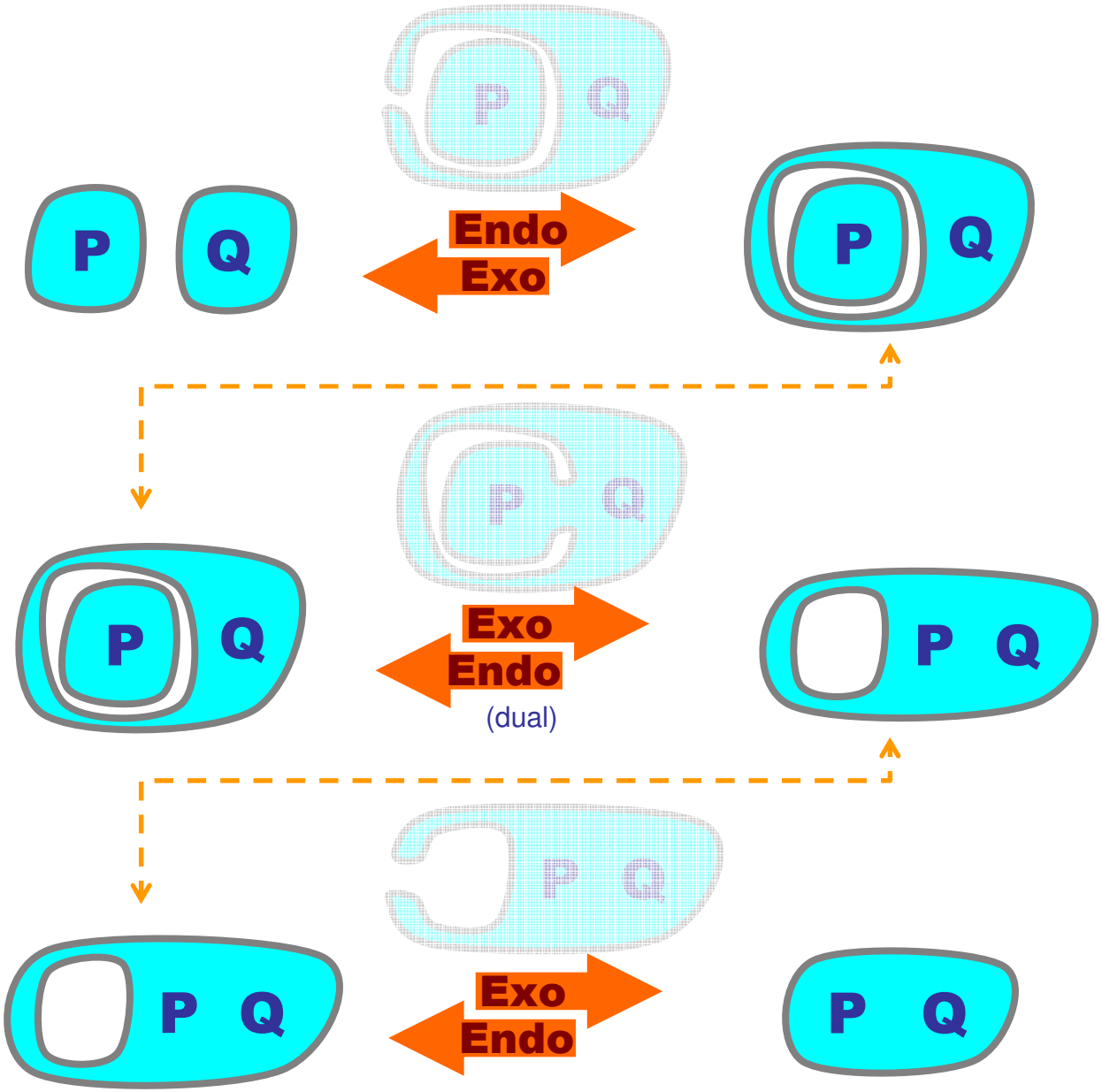
- An abstract reaction/transformation is a reaction/transformation where arbitrary subsystems (indicated by letters P,Q,…) are kept *fixed* on the plane, but other membranes can be changed.

- An abstract transformation is bitonal if it is bitonal for arbitrary subsystems (with the same number of steps).

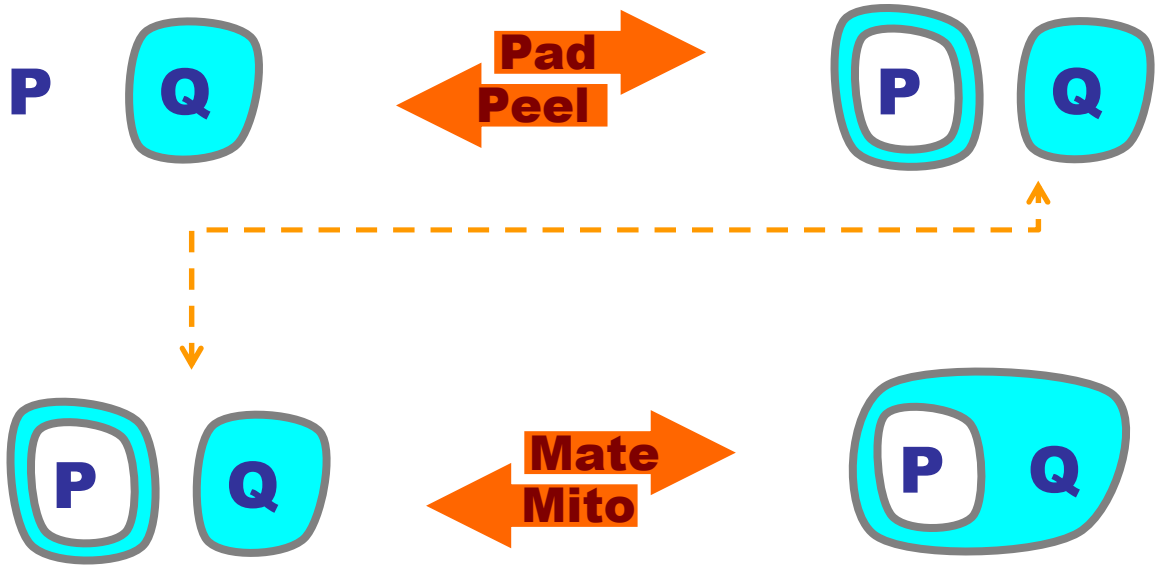
Summary: Four Good Transformations



Mito/Mate by 3 Endo/Exo

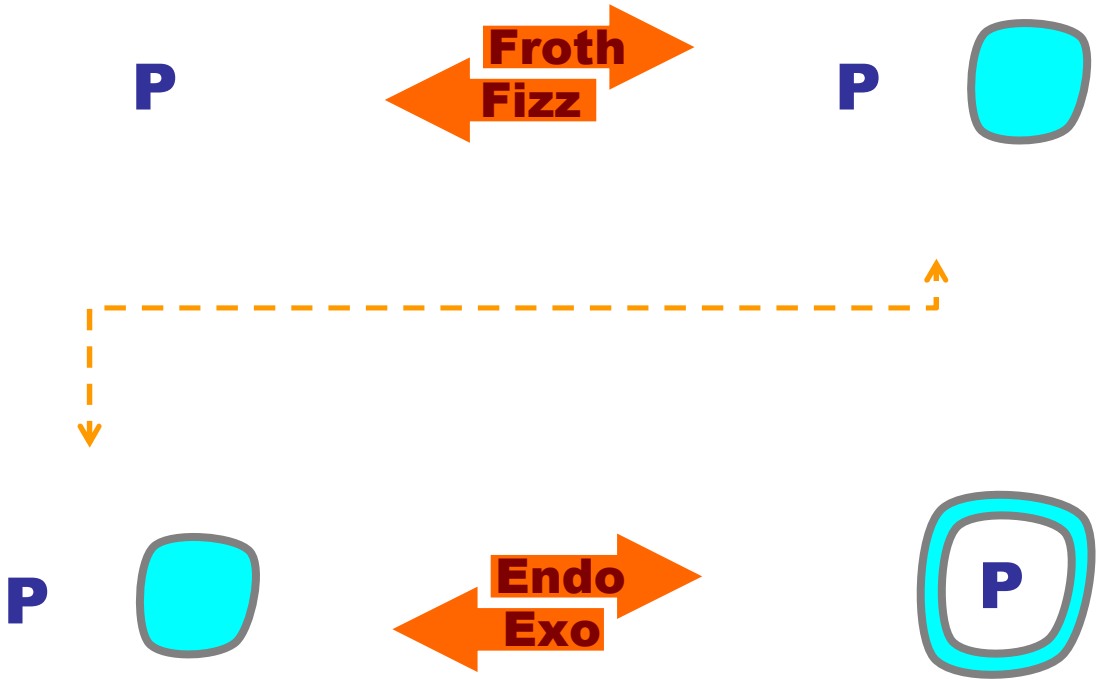


Endo/Exo by Mito/Mate and Peel/Pad



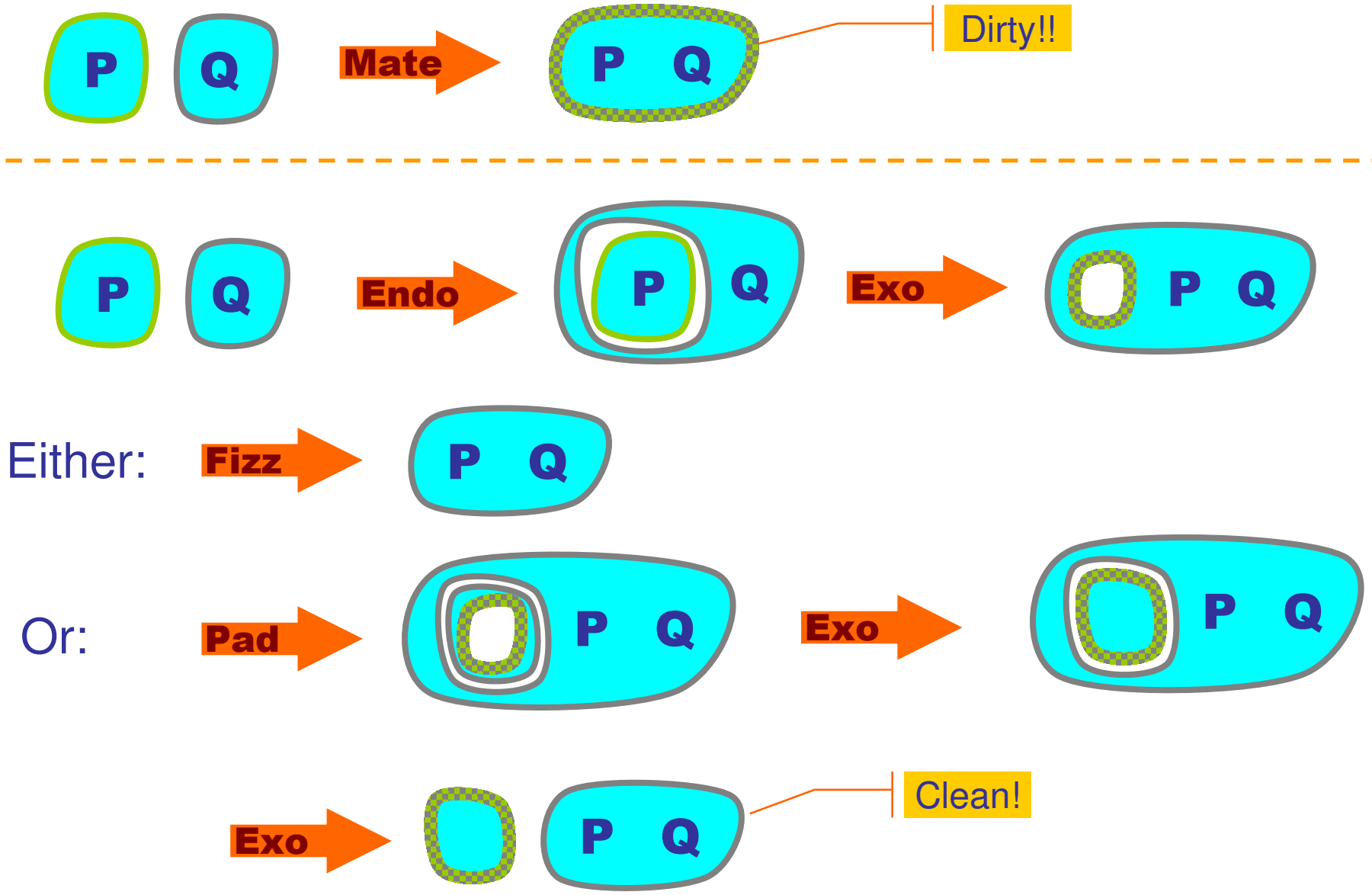
Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.

Peel/Pad by Froth/Fizz and Endo/Exo



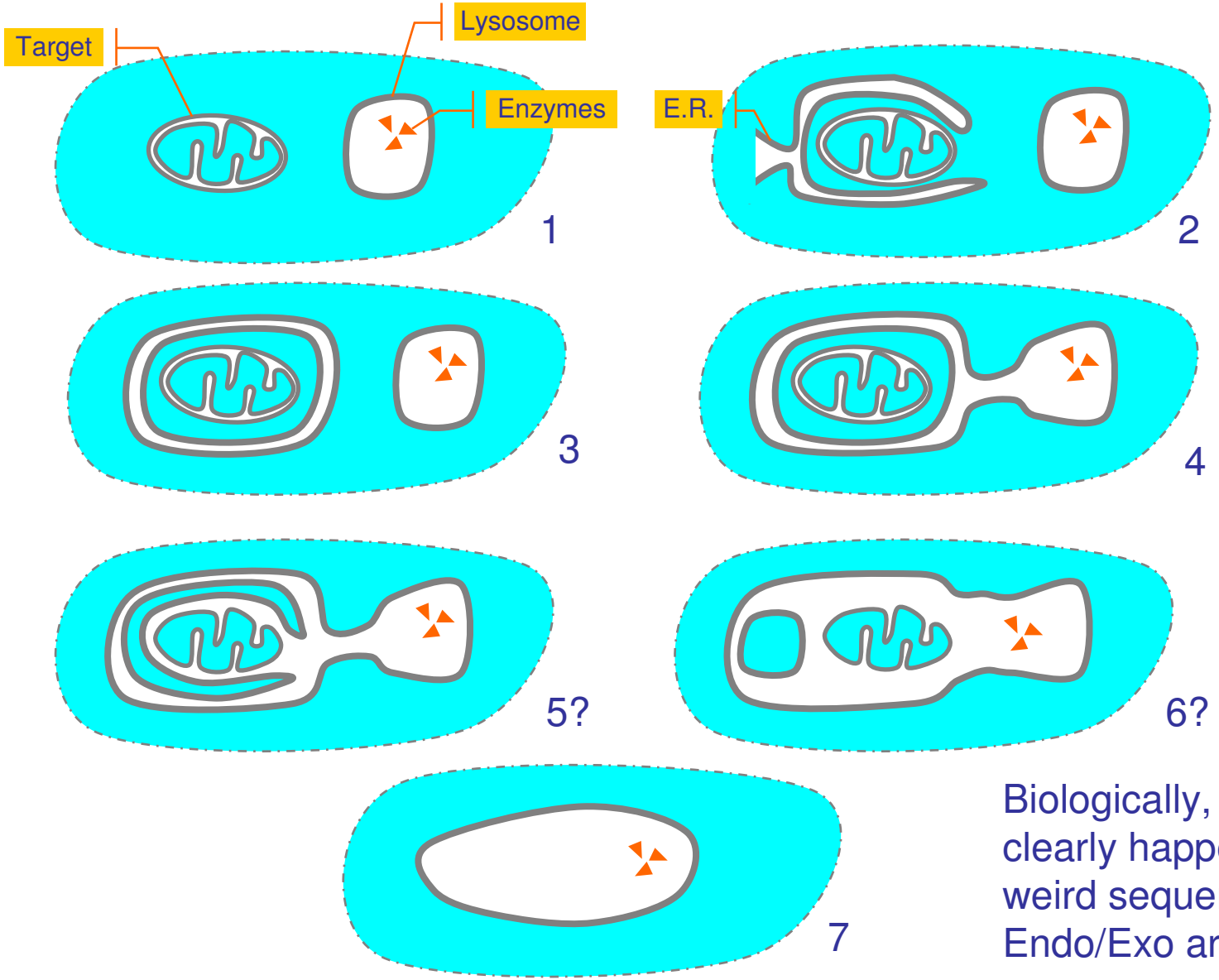
Ex: Clean Eating

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



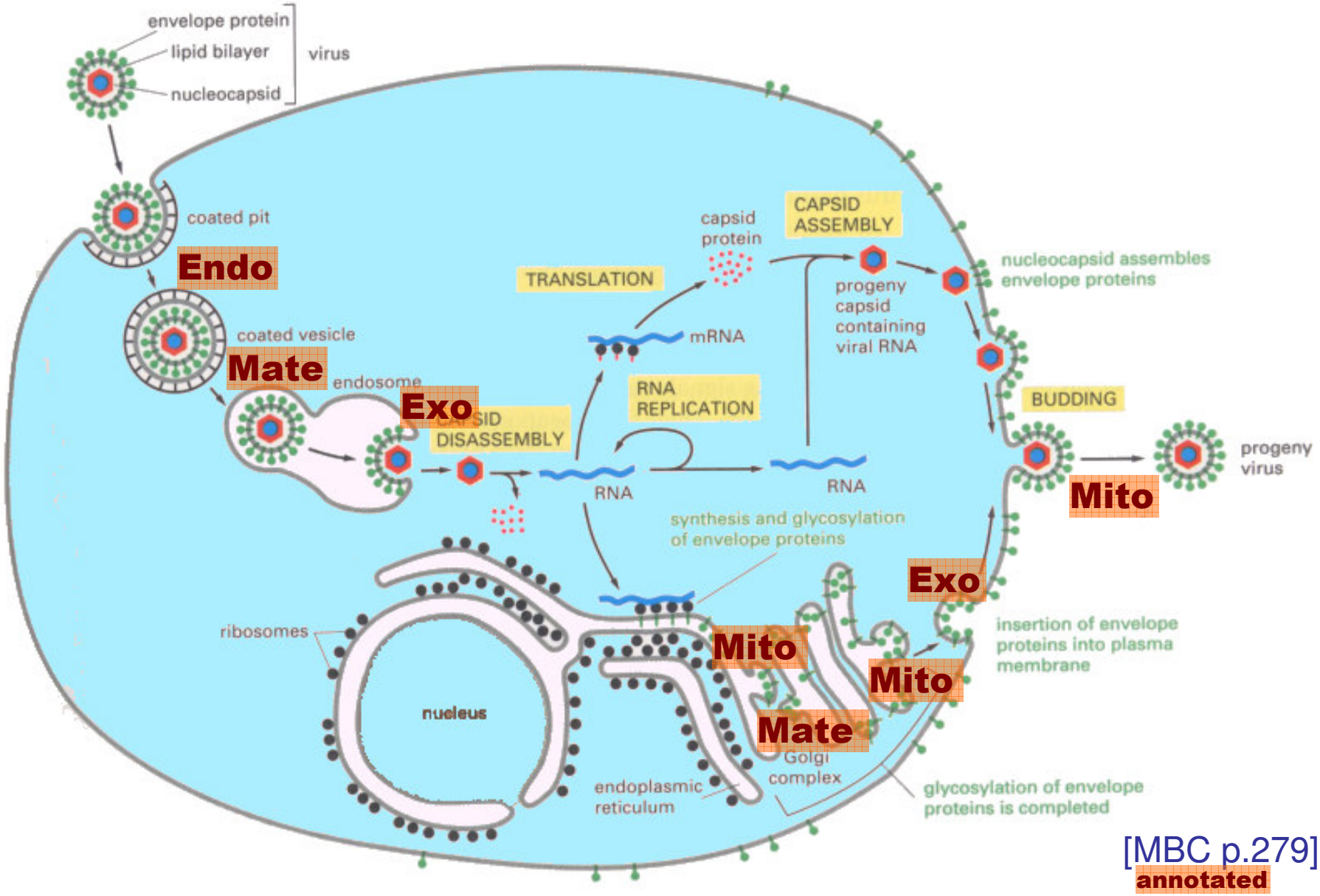
(Real) Ex: Autophagic Process

Lysosome and target don't just merge.



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

(Real) Ex: Viral Reproduction



[MBC p.279]
annotated

Bitonal Calculus

$X ::= \diamond \mid X \circ X \mid (X)$ — membrane

We look at this calculus as a preliminary abstraction of more detailed process calculi one may devise.

Axioms

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

F/F: $\diamond \leftrightarrows (\diamond)$

E/E: $X \circ (Y) \leftrightarrows ((X) \circ Y)$

Facts

(without using commutativity)

M/M:

$(X) \circ (X') \leftrightarrows (((X)) \circ X') \leftrightarrows ((\diamond \circ (X)) \circ X')$
$\leftrightarrows ((\diamond) \circ X \circ X') \leftrightarrows \diamond \circ (X \circ X') \leftrightarrows (X \circ X')$

P/P:

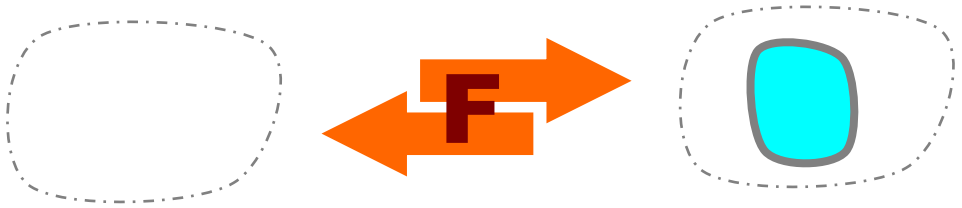
$X \leftrightarrows X \circ \diamond \leftrightarrows X \circ (\diamond)$
$\leftrightarrows ((X) \circ \diamond) \leftrightarrows ((X))$

It is possible to define a simple "type system" that consistently colors brackets and operators with appropriate tones:

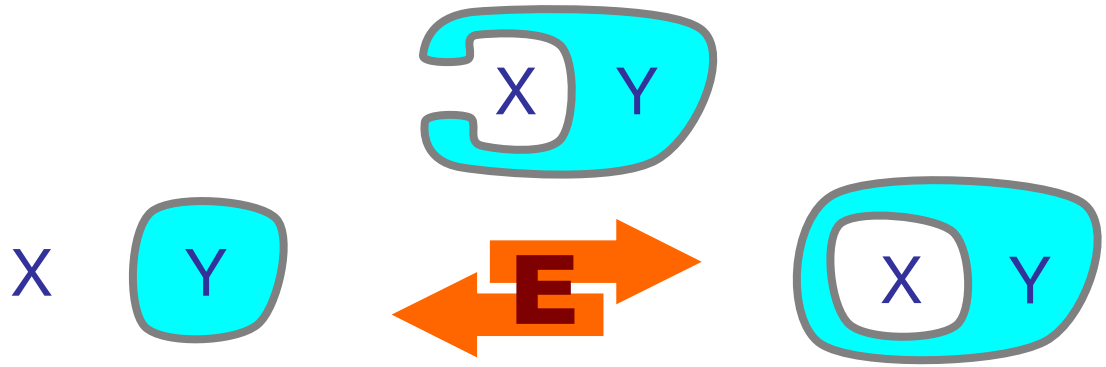
$\diamond \leftrightarrows (\bullet)$

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

Axioms Illustrated



$\diamond \quad \leftrightarrows \quad \Box\diamond$



$X \circ \Box Y \quad \leftrightarrows \quad \Box(\Box X \bullet Y)$

Bitonal Calculus v2

$X ::= \diamond \mid X \circ X \mid (X)$ — membrane

Axioms

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

M/M: $(X \circ X') \leftrightarrows (X') \circ (X)$

P/P: $((X)) \leftrightarrows X$

Facts

E/E:

$X \circ (Y) \leftrightarrows ((X)) \circ (Y) \leftrightarrows ((X) \circ Y)$

F/F:

$(\diamond) \leftrightarrows \diamond \circ (\diamond) \leftrightarrows ((\diamond) \circ \diamond) \leftrightarrows ((\diamond) \circ \diamond) \leftrightarrows ((\diamond)) \leftrightarrows \diamond$

Ex: Viral Infection

$(\text{capsid}) \circ ((\text{endosome}) \bullet \text{cytosol}) \rightarrow_{\text{Endo}}$

$((\text{capsid}) \bullet (\text{endosome}) \bullet \text{cytosol}) \rightarrow_{\text{Mate}}$

$((\text{capsid}) \circ \text{endosome}) \bullet \text{cytosol}) \rightarrow_{\text{Exo}}$

$((\text{endosome}) \bullet \text{capsid} \bullet \text{cytosol}) \rightarrow \ldots$

But what causes these reactions to happen (and in one direction only)?

To explain what "really happens" a bit better, we need to move to a lower level of abstraction.

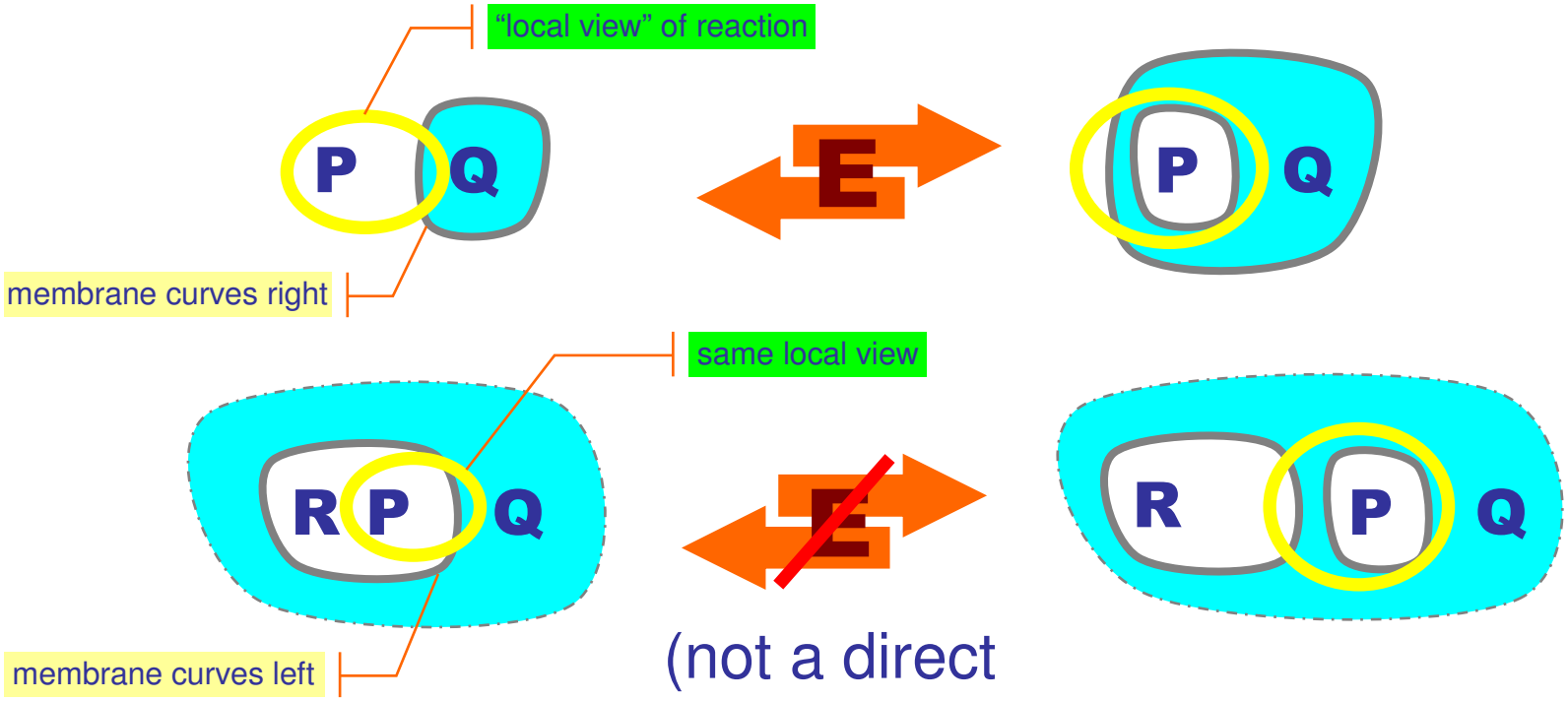
A Note About Locality

Locality Postulate

Interactions should be local to small membrane patches.

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

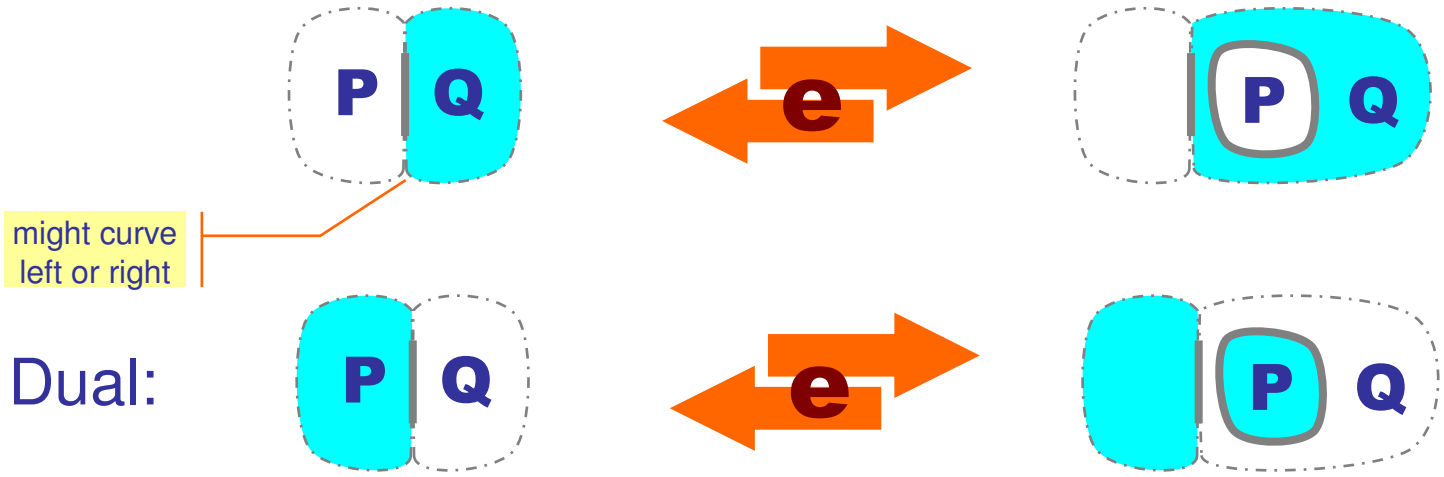
Endo/Exo Violates Locality



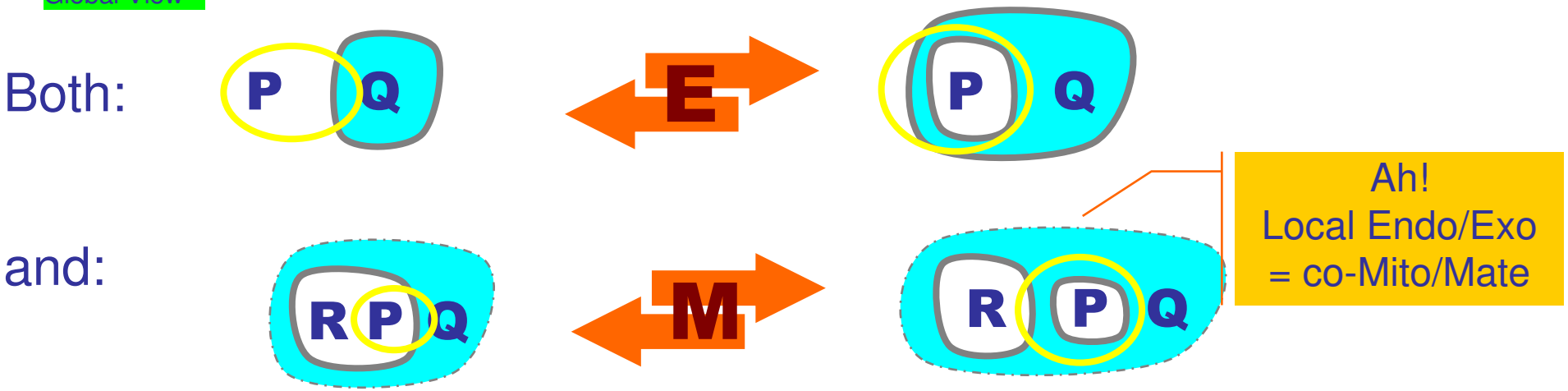
(not a direct instance of endo/exo)

Oops…

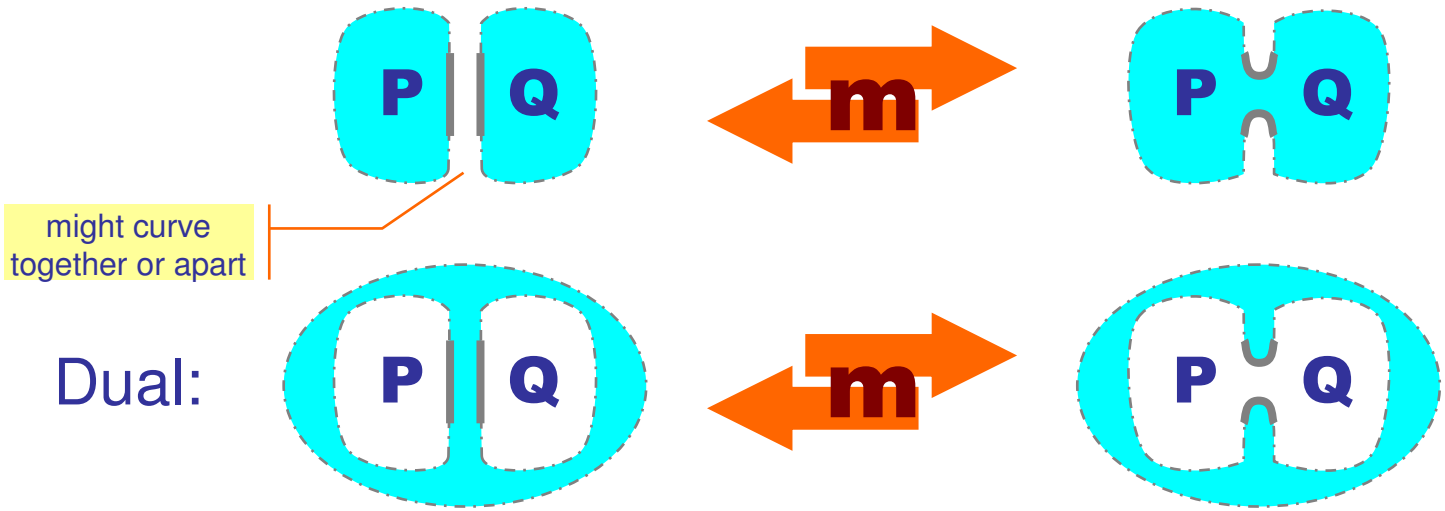
✓ Local-view Endo/Exo Reaction



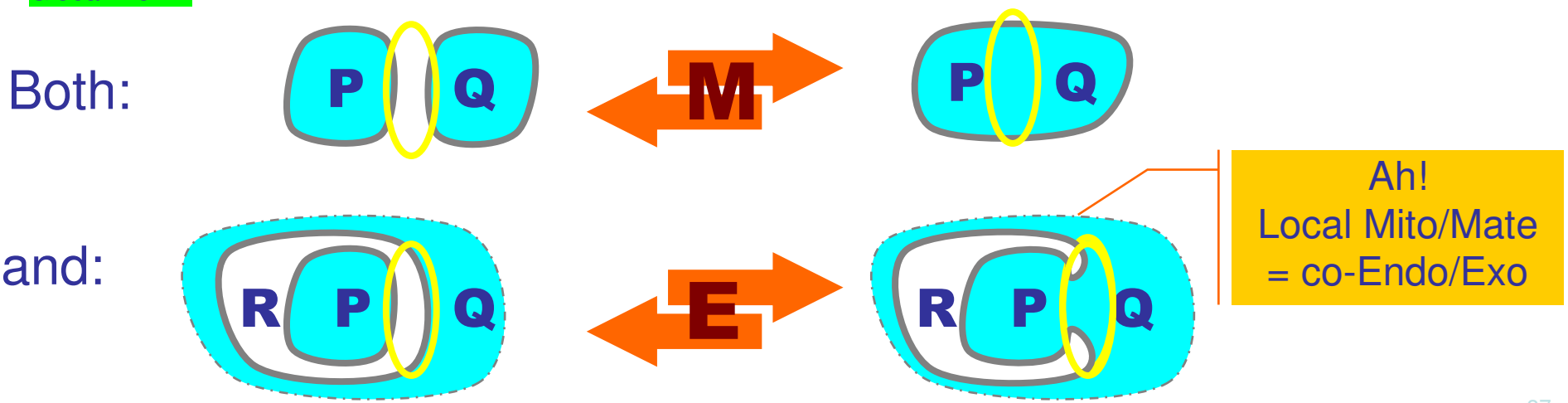
Global View



✓ Local-view Mito/Mate Reaction



Global View



Locality is Not Violated

- Hence, even though Endo/Exo and Mito/Mate strictly violate locality, locality is indirectly preserved in a bigger system that includes them both and their duals.
- This needs to be somewhat justified (L.Cardelli: “Bitonal Systems”) after which we can forget about local-view reactions.
- Problem: how to formally represent the local-view reactions?

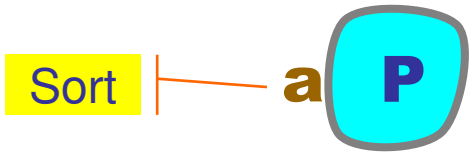
Assessment

- High-level: Membrane Interactions
  - Abstraction level still too high; we want to talk about “different sorts” of membranes.
  - We need to be a bit more deterministic.
- Mid-level: Graph Rewriting
  - Abstractly talk about the “sort” of a membrane, and how it changes into other abstract sorts.
- Lower-Level: Patch Interactions
  - Model individual membrane proteins.

Different Kinds of Membranes

Sorted Membranes

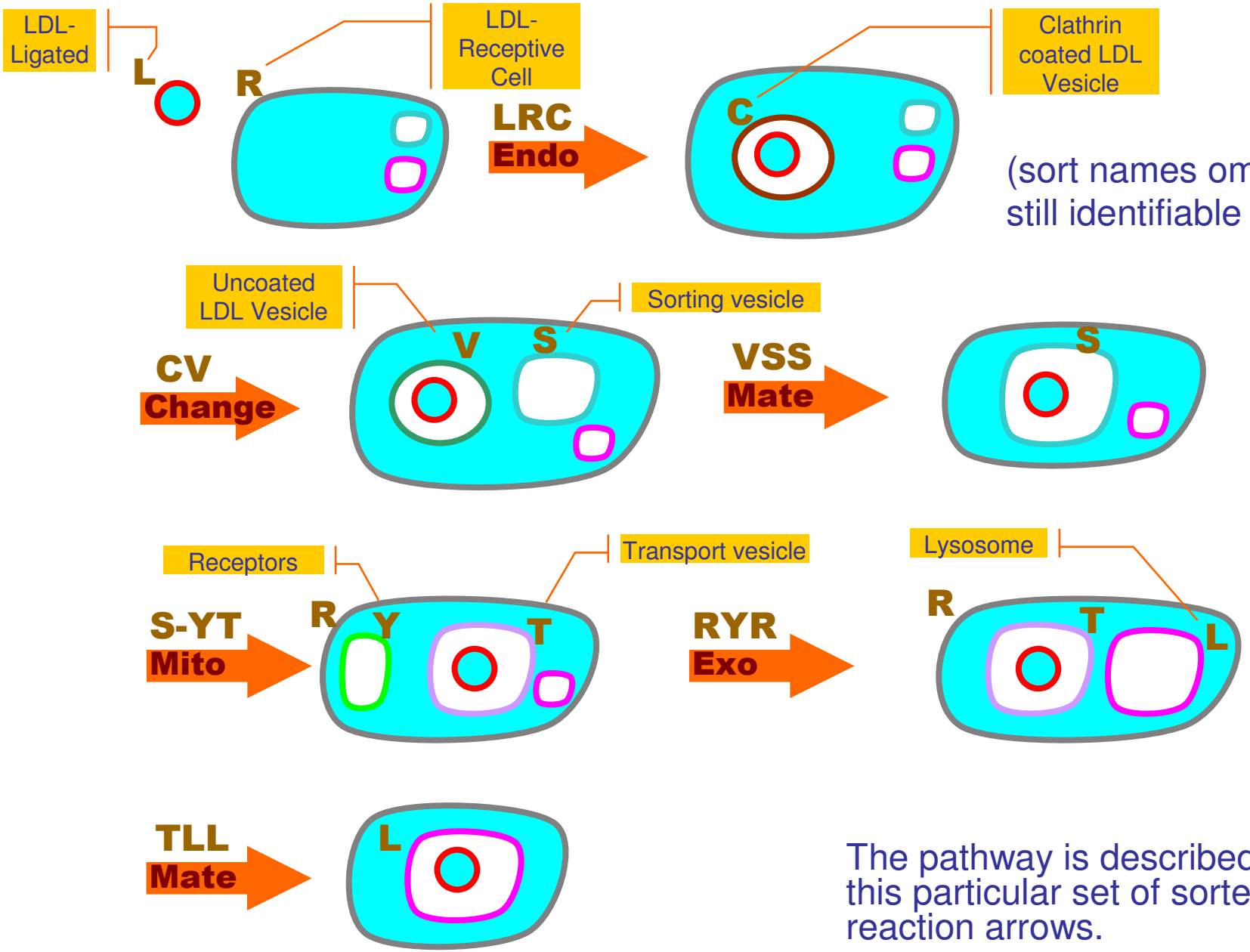
- Different kinds of membranes.
  - Lipid bilayer is universal. All membranes can in principle merge, but the lipid compositions vary.
  - The set of proteins bound to a membrane confer unique characteristics to it and its contents.
- Each membrane is uniform.
  - Membrane proteins diffuse rapidly through 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.



Sorted Membrane Rewrites

- Rewriting systems
  - We can describe sorted membrane reactions as labeled rewrites (such as labeled versions of endo/exo).
  - E.g. as a special case of Milner's BiGraphs, where the "sort" is the "control". This is possible because each node in a bigraph has a single control.

Receptor-Mediated Degradation Pathway



Part III

Brane Calculi

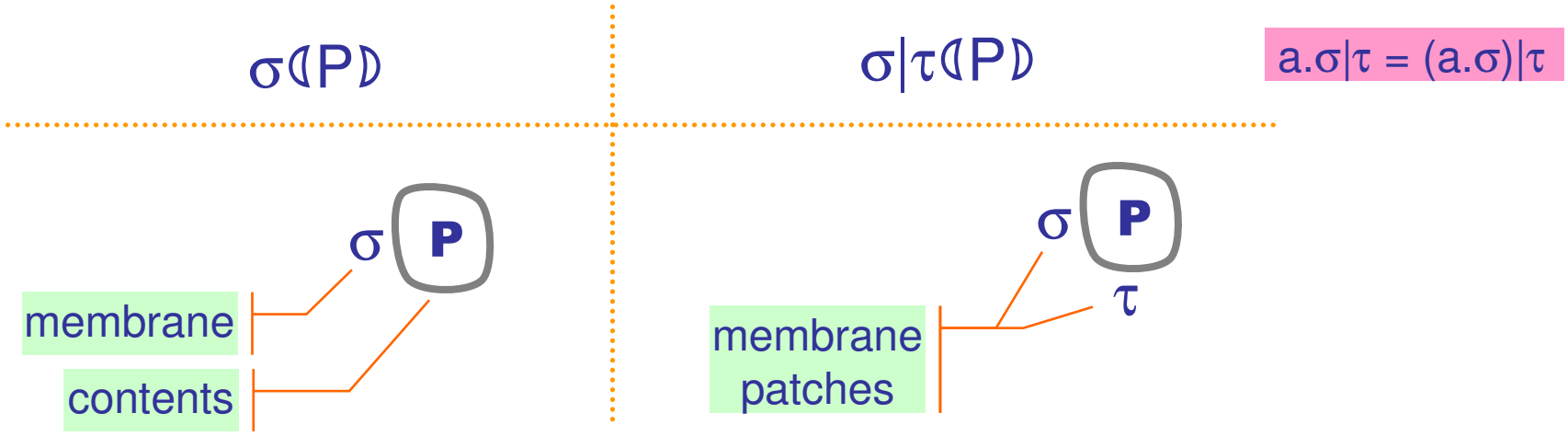
What makes Endo happen?

- Moving down a level, to explain “why” certain reactions like endo/exo happen: they do not happen magically.
- Describe membranes as composed of independently active “patches” or membrane proteins (not characterized by a single sort).
- Can be formalized pretty much as action/coaction interactions in process calculi.
- But with actions “on” the membranes, not “inside” them!

Brane Calculi

systems	$P,Q ::= \diamond \mid P \circ Q \mid !P \mid \sigma(\!|P|\!)$	nests of membranes
branes	$\sigma,\tau ::= 0 \mid \sigma|\tau \mid !\sigma \mid a.\sigma$	combinations of actions
actions	$a ::= 1 \mid \ldots$	(a great variety of possibilities)

1D fluids (σ) inside a 2D fluid (P)



N.B. Restriction (νn) could be added to both systems and branes. It usually originate in branes, but may extrude to whole systems.

Structural Congruences

$P \circ Q \equiv Q \circ P$

$P \circ (Q \circ R) \equiv (P \circ Q) \circ R$

$P \circ \diamond \equiv P$

$!P \equiv P \circ !P$ etc.

$\sigma | \tau \equiv \tau | \sigma$

$\sigma | (\tau | \rho) \equiv (\sigma | \tau) | \rho$

$\sigma | 0 \equiv \sigma$

$!\sigma \equiv \sigma | !\sigma$ etc.

$0(\!(\diamond)\!) \equiv \diamond$

$1.\sigma \equiv \sigma$

$P \equiv Q \Rightarrow P \circ R \equiv Q \circ R$

$P \equiv Q \Rightarrow !P \equiv !Q$

$P \equiv Q \wedge \sigma \equiv \tau \Rightarrow \sigma(\!(P)\!) \equiv \tau(\!(Q)\!)$

$\sigma \equiv \tau \Rightarrow \sigma | \rho \equiv \tau | \rho$

$\sigma \equiv \tau \Rightarrow !\sigma \equiv !\tau$

$\sigma \equiv \tau \Rightarrow a.\sigma \equiv a.\tau$

$P \equiv P' \wedge P' \rightarrow Q' \wedge Q' \equiv Q \Rightarrow P \rightarrow Q$

Bitonal Reactions

actions

a ::= … | $\circlearrowright_n$ | $\circlearrowright^{\perp}_n(\rho)$ | $\circlearrowleft_n$ | $\circlearrowleft^{\perp}_n$ | $\circledcirc(\rho)$

phago $\circlearrowright$, exo $\circlearrowleft$, pino $\circledcirc$

Old “spontaneous” endo splits into phagocytosis (phago, often still pronounced endo) and pinocytosis (pino).

Bitonal Reactions

actions

a ::= … | $\circlearrowright_n$ | $\circlearrowright^{\perp}_n(\rho)$ | $\circlearrowleft_n$ | $\circlearrowleft^{\perp}_n$ | $\circledcirc(\rho)$

phago $\circlearrowright$, exo $\circlearrowleft$, pino $\circledcirc$

,

Old “spontaneous” endo splits into phagocytosis (phago, often still pronounced endo) and pinocytosis (pino).

Bitonal Reactions

actions

a ::= … | $\circlearrowright_n$ | $\circlearrowright^{\perp}_n(\rho)$ | $\circlearrowleft_n$ | $\circlearrowleft^{\perp}_n$ | $\circledcirc(\rho)$

phago $\circlearrowright$, exo $\circlearrowleft$, pino $\circledcirc$

Old “spontaneous” endo splits into phagocytosis (phago, often still pronounced endo) and pinocytosis (pino).

Phago $\circlearrowright_n.\sigma|\sigma_0(\!|P|\!) \circ \circlearrowright^{\perp}_n(\rho).\tau|\tau_0(\!|Q|\!) \rightarrow \tau|\tau_0(\!|\rho(\!|\sigma|\sigma_0(\!|P|\!)|\!)\circ Q|\!)$

Exo $\circlearrowleft^{\perp}_n.\tau|\tau_0(\!|\circlearrowleft_n.\sigma|\sigma_0(\!|P|\!)\circ Q|\!) \rightarrow P \circ \sigma|\sigma_0|\tau|\tau_0(\!|Q|\!)$

Pino $\circledcirc(\rho).\sigma|\sigma_0(\!|P|\!) \rightarrow \sigma|\sigma_0(\!|\rho(\!|\diamond|\!)\circ P|\!)$

N.B.: the parity of nesting of P and Q is preserved;
this makes the reactions preserve bitonality.

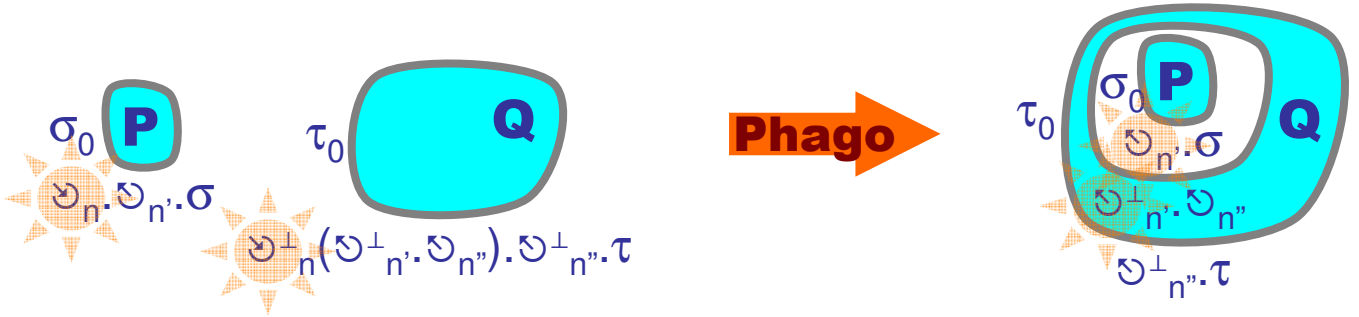
N.B.: in Phago (and Pino), one could perhaps require ρ to be, conservatively, a piece of τ, by a non-linear rewrite:

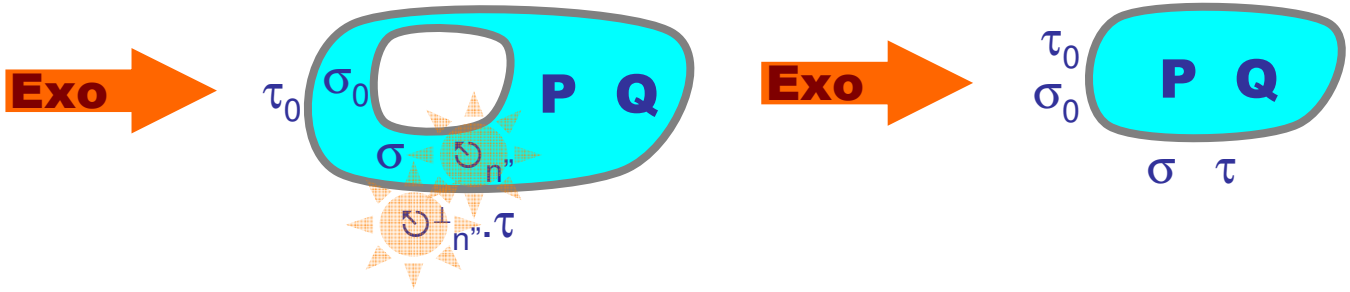
CPhago $\circlearrowright_n.\sigma|\sigma_0(\!|P|\!) \circ \circlearrowright^{\perp}_n(\rho).\tau|\tau_0|\rho(\!|Q|\!) \rightarrow \tau|\tau_0(\!|\rho(\!|\sigma|\sigma_0(\!|P|\!)|\!)\circ Q|\!)$

Abbreviations: Mate

Mate $\text{mate}_n.\sigma = \overleftarrow{\ }_n.\overleftarrow{\ }_{n'}.\sigma$

$\text{mate}^{\perp}_n.\tau = \overleftarrow{\ }^{\perp}_n(\overleftarrow{\ }^{\perp}_{n'}.\overleftarrow{\ }_{n''}).\overleftarrow{\ }^{\perp}_{n''}.\tau$



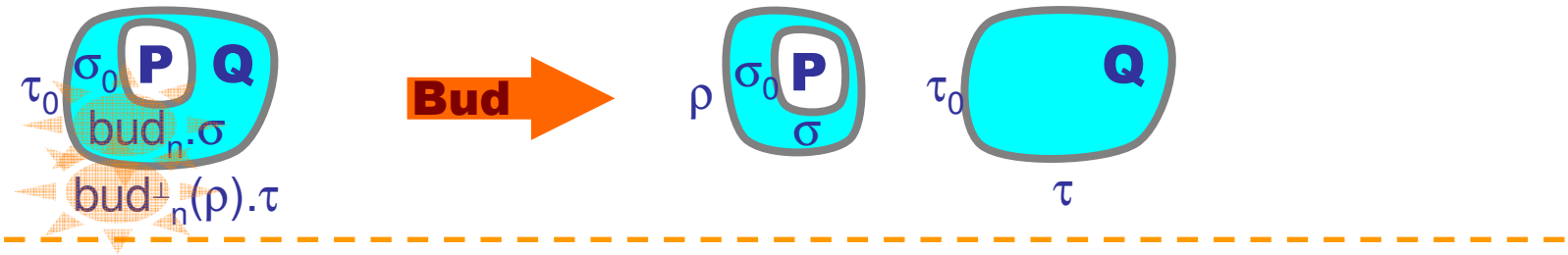


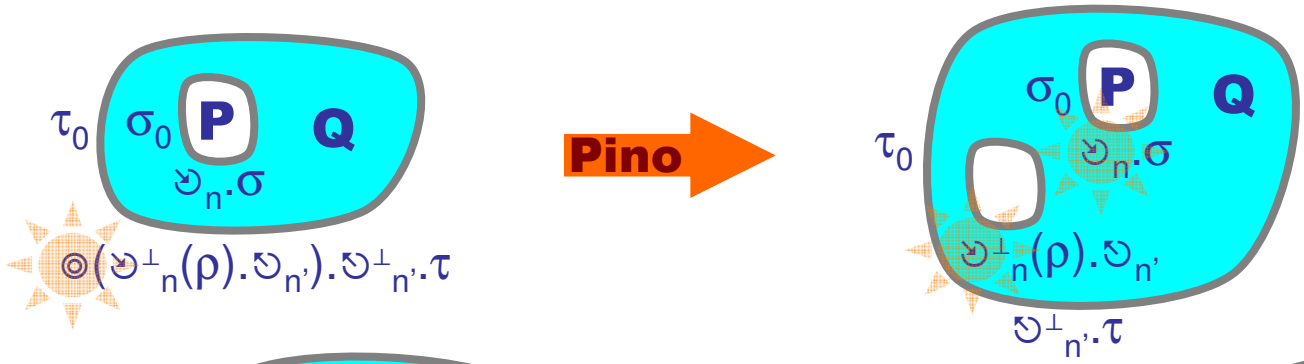
Abbreviations: Bud

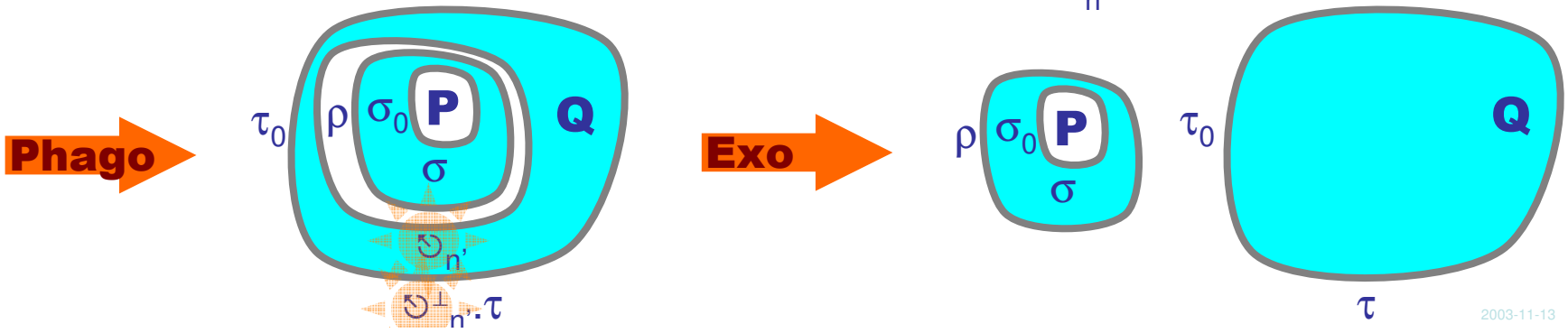
Bud $bud_n.\sigma = \circlearrowright_n.\sigma$

$bud^{\perp}_n(\rho).\tau = \circledcirc(\circlearrowright^{\perp}_n(\rho).\circlearrowright_{n'}).\circlearrowright^{\perp}_{n'}.\tau$

A budding version of old "spontaneous" mito, to avoid arbitrary splits. Follows the pattern of inverse-mate.



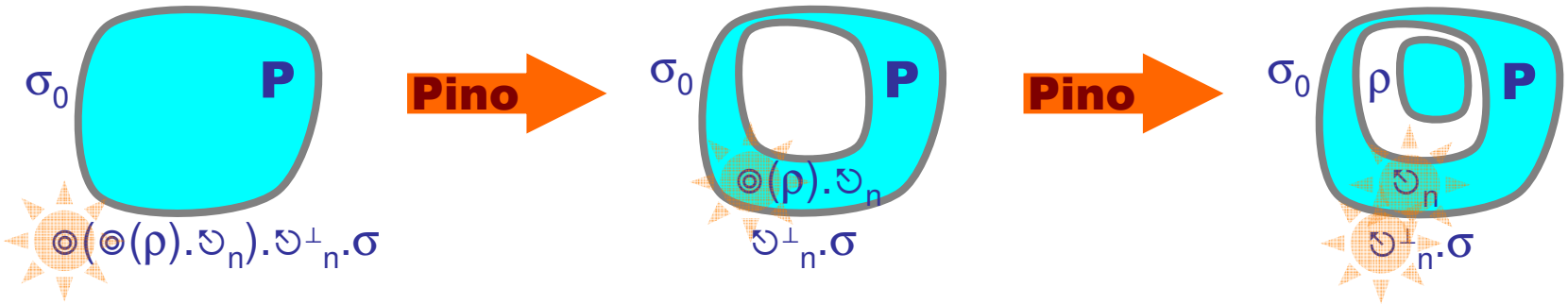


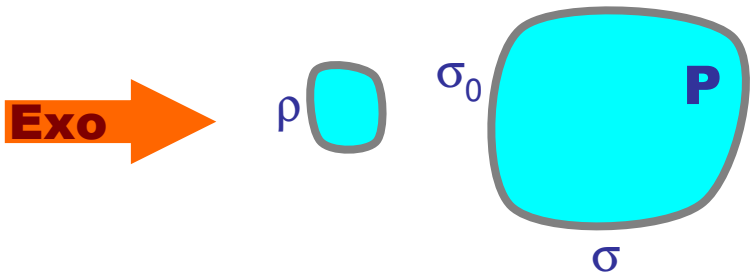


Abbreviations: Drip

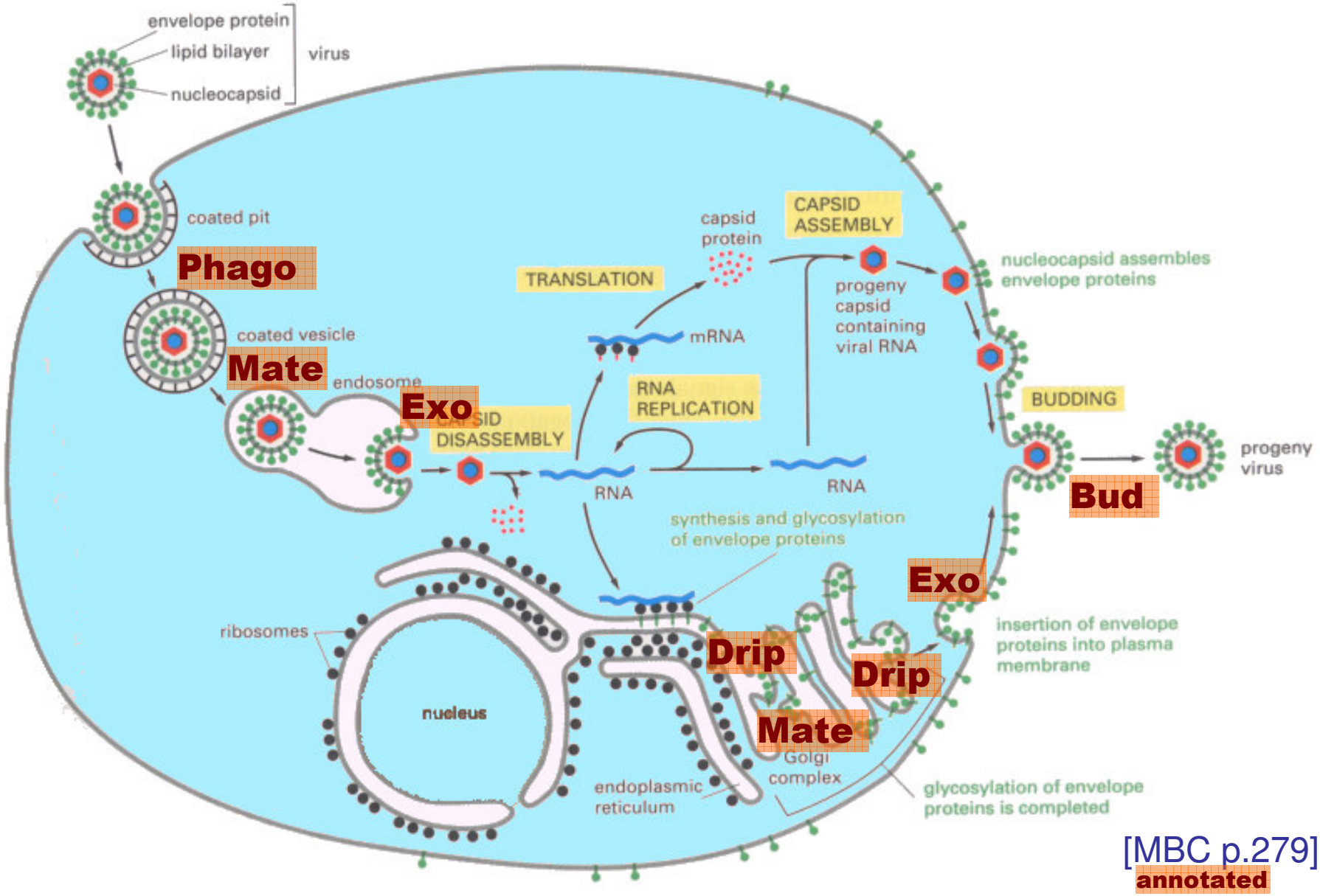
Drip $\text{drip}_n(\rho).\sigma = \circledcirc(\circledcirc(\rho).\circlearrowleft_n).\circlearrowleft^{\perp}_n.\sigma$

A zero-expelled-membranes version of old "spontaneous" mito, to avoid arbitrary splits. Follows the pattern of inverse-mate.



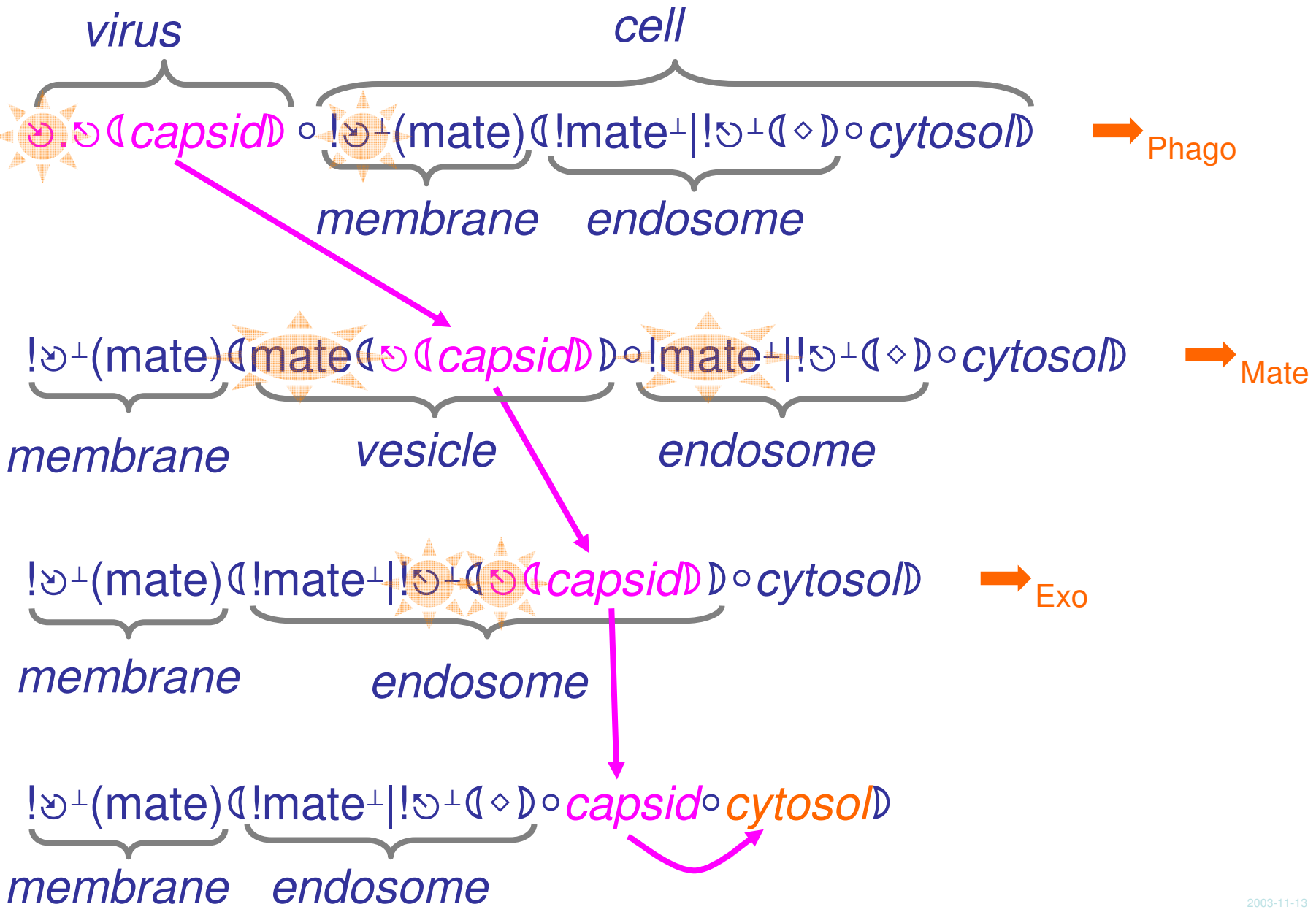


(Real) Ex: Viral Reproduction



[MBC p.279]
annotated

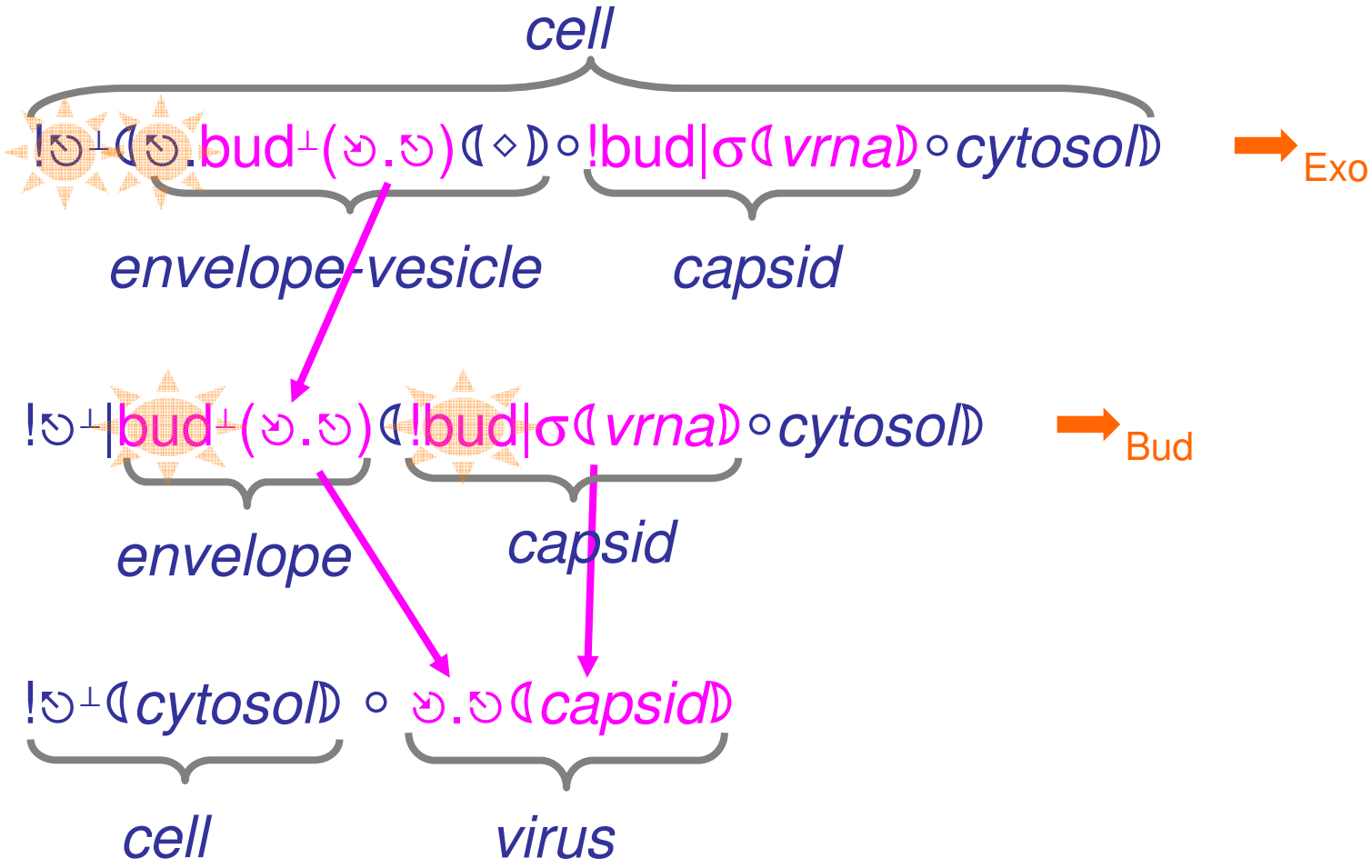
Ex: Viral Infection



Ex: Viral Progeny

capsid ∘ *cytosol* ➡➡ !*envelope-vesicle* ∘ !*capsid* ∘ *cytosol*

by available cellular machinery



Ex: LDL Degradation Pathway

Compartments
Membranes

LigatedLdl = LdlLigand◖LDL◗
Cell = CellBrane◖!Lysosome ∘ !SortingVesicle◗
Lysosome = LysoBrane ◖LysoBody◗
SortingVesicle = SortingBrane◖⋄◗

LdlLigand = $\curvearrowright_{ldlReceptor}.bud_{xferVesicle}$

CellBrane = $!\curvearrowright^{\perp}_{ldlReceptor}(VesicleBrane) \mid !\circlearrowleft^{\perp}_{recycle}$

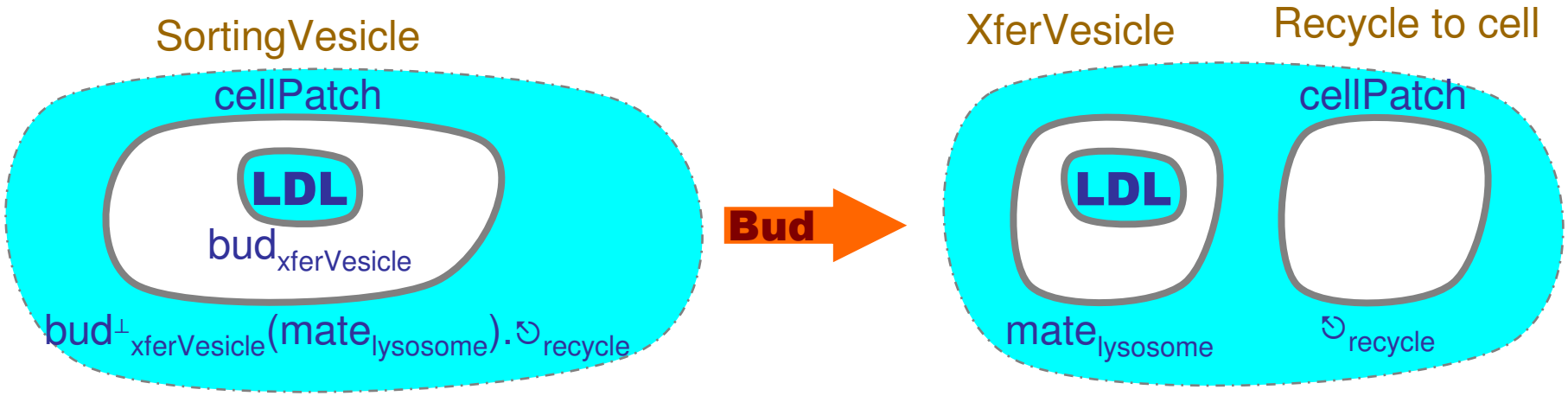
VesicleBrane = $mate_{sortingVesicle} \mid cellPatch^{(1)}$

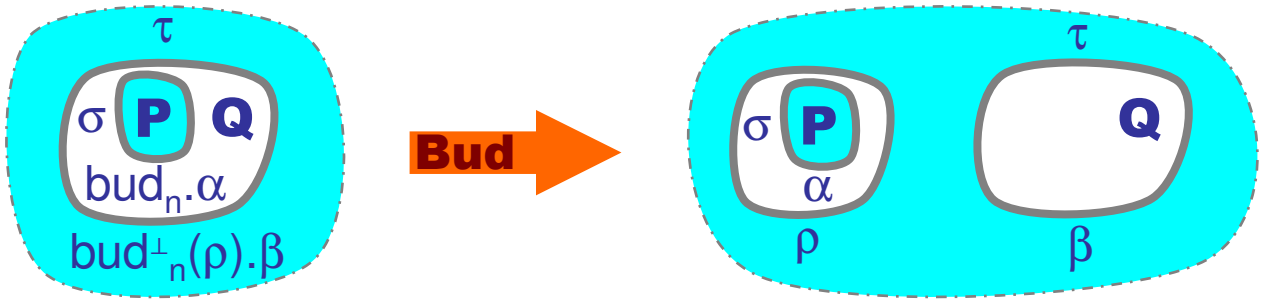
SortingBrane = $mate^{\perp}_{sortingVesicle}.\ bud^{\perp}_{xferVesicle}(XferBrane).\ \circlearrowleft_{recycle}$

XferBrane = $mate_{lysosome}$
LysoBrane = $!mate^{\perp}_{lysosome}$

(1) whatever gets dragged by phago from the cell membrane, e.g. more LDL receptors.

... the critical Bud step





Ex: LDL Degradation Pathway in BioAmbients

Compartments
Processes

$LigatedLdl = [LdlLigand \mid LDL]$
$Cell = [CellBrane \circ !Lysosome \circ !SortingVesicle]$
$Vesicle(n) = [VesicleBrane(n)]$
$SortingVesicle = [SortingBrane \mid XferVesicle]$
$XferVesicle = [XferBrane]$
$Lysosome = [LysoBrane \mid LysoBody]$

$LdlLigand = s2s_{ldlBind}{}^{\perp}(n).in_n.in_n.merge_{xferVesicle}$
$LdlReceptor = (\nu n)\ s2s_{ldlBind}(n).in^{\perp}{}_n \mid Vesicle(n)$
$CellBrane = !LdlReceptor \mid !pop^{\perp}{}_{recycle}{}^{(1)}$
$VesicleBrane(n) = in^{\perp}{}_n.\ merge_{sortingVesicle} \mid cellPatch^{(2)}$
$SortingBrane = merge^{\perp}{}_{sortingVesicle}.out^{\perp}{}_{bud}.pop_{recycle}$
$XferBrane = merge^{\perp}{}_{xferVesicle}.out_{bud}.merge_{lysosome}$
$LysoBrane = !merge^{\perp}{}_{lysosome}$

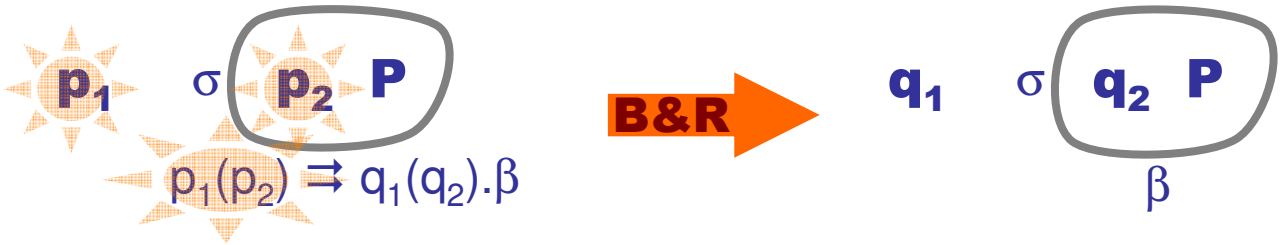
(1)pop is out + merge. (2)cellPatch is cell membrane to be recycled

Molecular Actions

systems $P,Q ::= \ldots \mid m$ $\quad m \in M$ molecules

$p,q ::= m_1 \circ \ldots \circ m_k$ molecule multisets

actions $a ::= \ldots \mid p_1(p_2) \rightrightarrows q_1(q_2)$ bind&release



B&R $p_1 \circ p_1(p_2) \rightrightarrows q_1(q_2).\alpha|\sigma(p_2 \circ P)$ ➡ $q_1 \circ \alpha|\sigma(q_2 \circ P)$

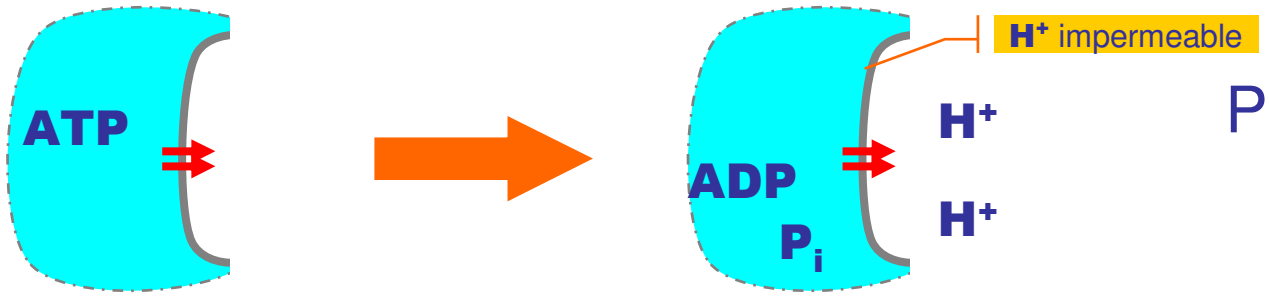
(multiset rewriting, inside and outside membranes)

Special cases: "$\diamond(\diamond)$" is omitted

$m(\diamond)\rightrightarrows$	bind out	$\rightrightarrows m(\diamond)$	release out
$\diamond(m)\rightrightarrows$	bind in	$\rightrightarrows \diamond(m)$	release in

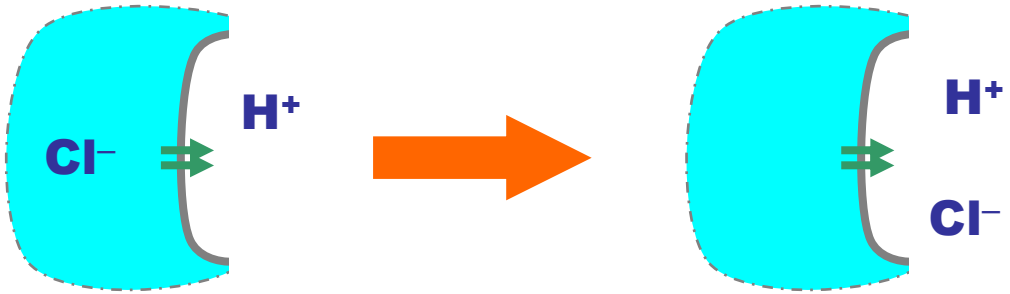
Ex: A Specialized Membrane

E.g. plant vacuole (white).

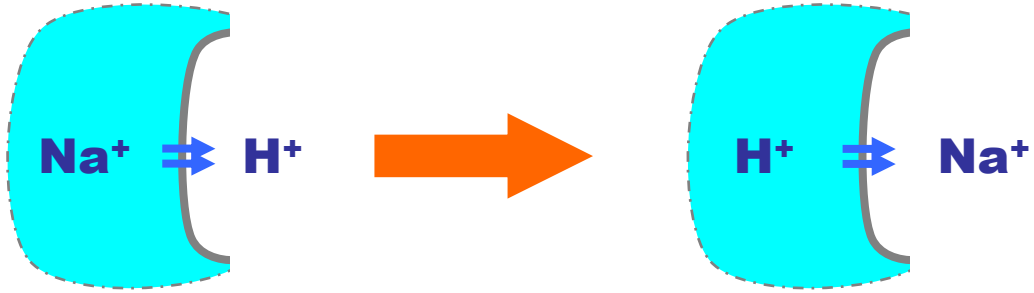


Proton Pump

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.

$$\mathrm{ProtonPump} = !\ \mathrm{ATP}(\diamond) \rightrightarrows \mathrm{ADP} \circ \mathrm{P_i}(\mathrm{H^+} \circ \mathrm{H^+})$$

$$\mathrm{IonChannel} = !\ \mathrm{Cl^-}(\mathrm{H^+}) \rightrightarrows \diamond(\mathrm{H^+} \circ \mathrm{Cl^-})$$

$$\mathrm{ProtonAntiporter} = !\ \mathrm{Na^+}(\mathrm{H^+}) \rightrightarrows \mathrm{H^+}(\mathrm{Na^+})$$

$$\mathrm{PlantVacuole} = \mathrm{ProtonPump} \mid \mathrm{IonChannel} \mid \mathrm{ProtonAntiporter}\ (\!|\diamond|\!)$$

Encoding Brane Calculi?

$$\sigma(\!|P|\!)^\dagger \triangleq s[\sigma^\dagger \mid P^\dagger] \quad ?$$

This encoding confuses membrane with contents, so that the exo encoding is problematic:

Exo $\circlearrowleft^\perp_n.\beta|\tau(\!|\circlearrowleft_n.\alpha|\sigma(\!|P|\!)\circ Q|\!) \rightarrow P \circ \alpha|\sigma|\beta|\tau(\!|Q|\!)$

That is, find $\circlearrowleft^\dagger$ encodings such that:

$s[\circlearrowleft^{\perp\dagger}_n.\beta \mid s[\circlearrowleft^\dagger_n.\alpha \mid \sigma \mid P] \mid \tau \mid Q] \rightarrow P \mid s[\alpha \mid \sigma \mid \beta \mid \tau \mid Q]$

but the split $\sigma \mid P$ is *arbitrary* here: some reactions could not be reflected back to legal brane calculus reactions ($P^\dagger \rightarrow Q \Rightarrow \exists R.\ P \rightarrow R \wedge Q \rightarrow^* R^\dagger$), and it would be in any case difficult to define $\circlearrowleft^\dagger$ so that it splits σ from P.

One cannot easily represent the Exo reaction in (Bio)Ambients, nor can one easily add it as a new primitive!

For exo at least, we need to explicitly identify the membrane.

either $\sigma(\!|P|\!)^\dagger \triangleq s[m[\sigma^\dagger] \mid P^\dagger]$

or $\sigma(\!|P|\!)^\dagger \triangleq s[\sigma^\dagger \mid c[P^\dagger]]$

The second option should be chosen to avoid crossing 4 brackets in s2s reactions, so:

Exo $\circlearrowleft^{\perp}_{n}.\beta|\tau(\!|\circlearrowleft_{n}.\alpha|\sigma(\!|P|\!)\circ Q|\!) \rightarrow P \circ \alpha|\sigma|\beta|\tau(\!|Q|\!)$

$s[\circlearrowleft^{\perp}_{n}.\beta \mid \tau \mid s[\circlearrowleft_{n}.\alpha \mid \sigma \mid c[P]] \mid c[Q]] \rightarrow P \mid s[\alpha \mid \sigma \mid \beta \mid \tau \mid c[Q]]$

But this emulation interferes badly with concurrent Phago's (emulated by at least two "in" steps because of the double bracketing): neither emulations is atomic.

One cannot easily emulate atomic Phago/Exo in (Bio)Ambients.

Conversely, in (Bio)Ambients one can use an action to create a whole new filled-in membrane:

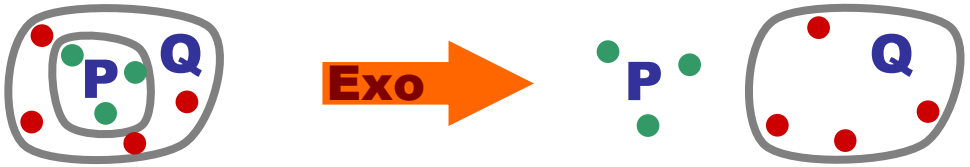
$$a.s[\sigma \mid P] \;=\; a.(\sigma(\!|P|\!))$$

this is not allowed, nor easily representable, in brane calculi.

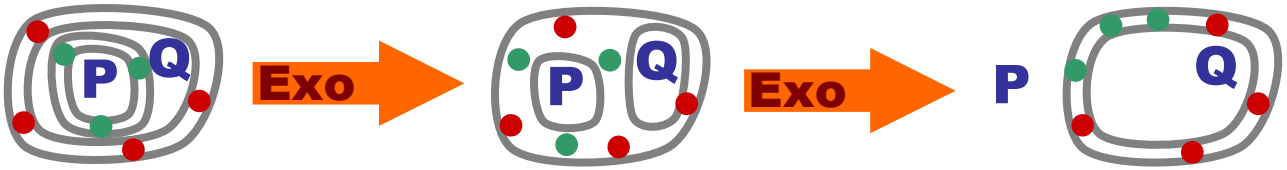
This is a power that real membranes do not seem to have.

Exo Encodings

Original "on brane" actions



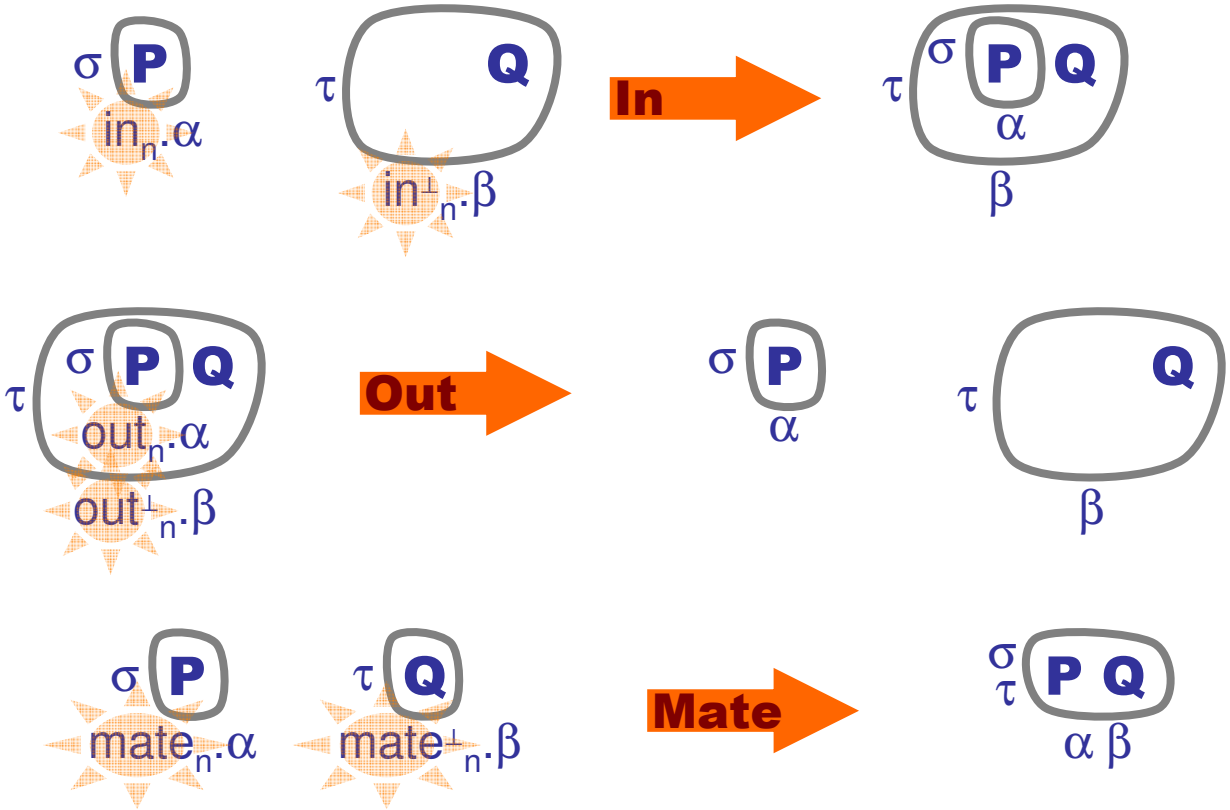
"In brane" encoding attempt



"Ball bearing" encoding

BioAmbients-like Mobility Actions

actions $a ::= \ldots \mid in_n \mid in^{\perp}_n \mid out_n \mid out^{\perp}_n \mid mate_n \mid mate^{\perp}_n$



In $in_n.\alpha|\sigma(\!|P|\!)\circ in^{\perp}_n.\beta|\tau(\!|Q|\!) \rightarrow \beta|\tau(\!|\alpha|\sigma(\!|P|\!)\circ Q|\!)$

Out $out^{\perp}_n.\beta|\tau(\!|out_n.\alpha|\sigma(\!|P|\!)\circ Q|\!) \rightarrow \alpha|\sigma(\!|P|\!)\circ\beta|\tau(\!|Q|\!)$

Mate $mate_n.\alpha|\sigma(\!|P|\!)\circ mate^{\perp}_n.\beta|\tau(\!|Q|\!) \rightarrow \alpha|\sigma|\beta|\tau(\!|P\circ Q|\!)$

N.B.: out + mate gives a “melt” primitive that is a good membrane-preserving approximation of “open”:

$melt^{\perp}_n.\beta|\tau(\!|melt_n.\alpha|\sigma(\!|P|\!)\circ Q|\!) \rightarrow \alpha|\sigma|\beta|\tau(\!|P\circ Q|\!)$

Diffusion (CCS-like channels)

actions $a ::= \ldots \mid df_n(m) \mid df^{\perp}_n(m)$ diffusion (within membrane)

BioAmbients-like Channels

actions $a ::= \ldots \mid s2s_n(m) \mid s2s^{\perp}_n(m)$ sibling to sibling

$\mid p2c_n(m) \mid p2c^{\perp}_n(m)$ parent to child

$\mid c2p_n(m) \mid c2p^{\perp}_n(m)$ child to parent

$s2s_n(m).\alpha|\sigma\langle P\rangle \circ s2s^{\perp}_n(p).\beta|\tau\langle Q\rangle$

$\rightarrow \alpha|\sigma\langle P\rangle \circ \beta\{p \leftarrow m\}|\tau\langle Q\rangle$

$p2c_n(m).\alpha|\sigma\langle p2c^{\perp}_n(p).\beta|\tau\langle Q\rangle \circ P\rangle$

$\rightarrow \alpha|\sigma\langle \beta\{p \leftarrow m\}|\tau\langle Q\rangle \circ P\rangle$

$c2p^{\perp}_n(p).\beta|\tau\langle c2p_n(m).\alpha|\sigma\langle Q\rangle \circ P\rangle$

$\rightarrow \beta\{p \leftarrow m\}|\tau\langle \alpha|\sigma\langle Q\rangle \circ P\rangle$

Implementabilty?

- An implementable “instruction set” could consist of:
  - Bitonal mobility operators, including bud/mate (possibly restricting the ρ in $\circlearrowleft^{\perp}_{n}(\rho)$ and ⊚(ρ)).
  - Selected bind&release pumps.
  - Selected s2s/p2c/c2p operators.
- N.B. BioAmbients in/out do not seem as likely to be directly implementable.

Conclusions

- What's different about "bio"-calculi?
  - Orientability and bitonality invariants inspire new, and possibly more bio-realistic, operators.
  - Low-dimensional fluids inside high-dimensional fluids: two commutative monoids.
  - Computing *on* the membrane, not *inside* of it.

- Papers
  - ***Bitonal Systems***: membrane reactions and their connections to "local" patch reactions.
  - ***Brane Calculi***: a class of process calculi with computation "on" the membranes, not inside them.

http://www.luca.demon.co.uk

References

[MCB] Molecular Cell Biology, Freeman.

[MBC] Molecular Biology of the Cell, Garland.