Bitonal Membrane Systems

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Microsoft Research

MeCBIC 2006
Workshop on Membrane Computing and Biologically Inspired Process Calculi

Venice, 2006-07-09

Introduction

Related Work

- Membrane Computing
  - From computability theory
    (now being applied to biological modeling)

- BioAmbients
  - From distributed systems theory
    (then applied to biological modeling)

BioAmbients: An abstraction for biological compartments

Aviv Regev[a,*] Ekaterina M. Panina[b] William Silverman[c]
Luca Cardelli[d] Ehud Shapiro[c]

- Brane Calculi
  - Bio-inspired membrane operations

Brane Calculi
Interactions of Biological Membranes

Luca Cardelli

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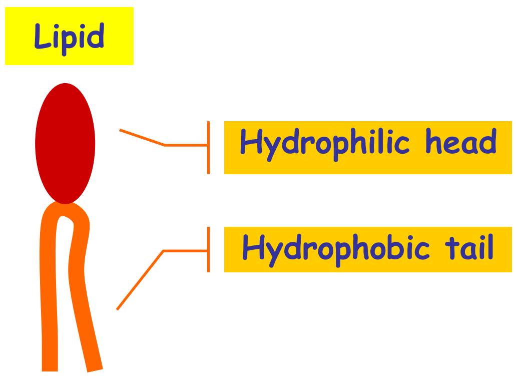
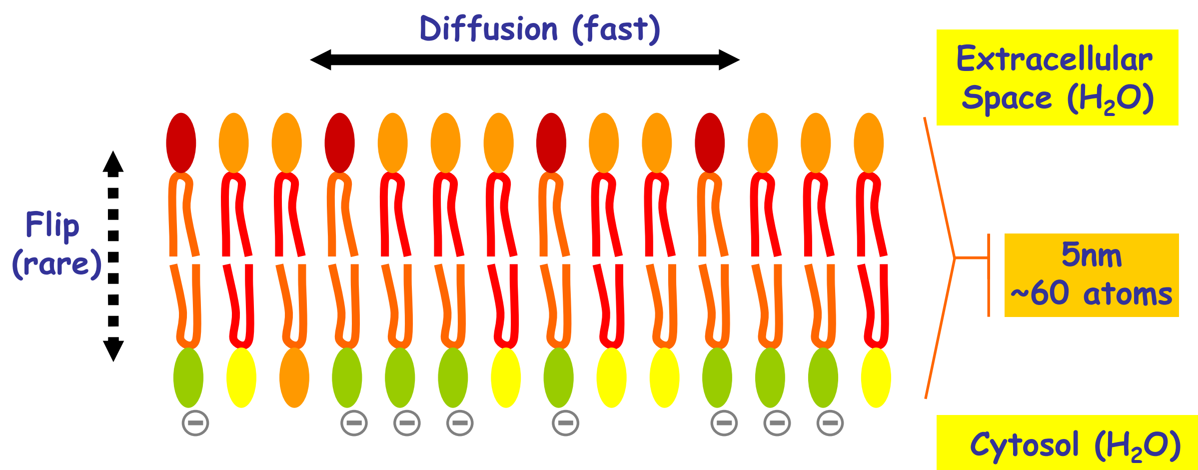
- Beta-Binders
  - Bio-inspired process interfaces

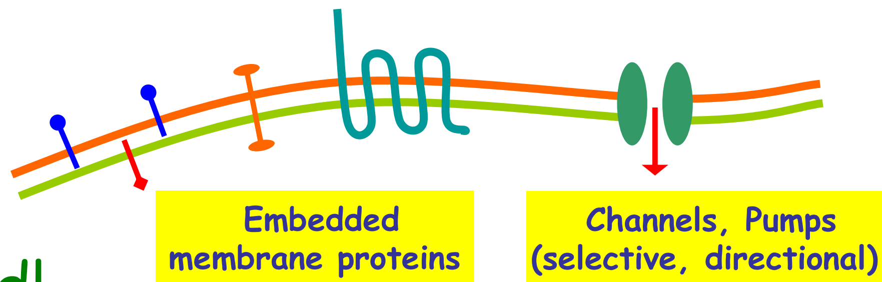
Beta Binders for Biological Interactions
AUTHORS Corrado Priami, Paola Quaglia
SOURCE In Proceedings of "Computational methods in system biology (CMSB04)", Parigi 2004 308221-34

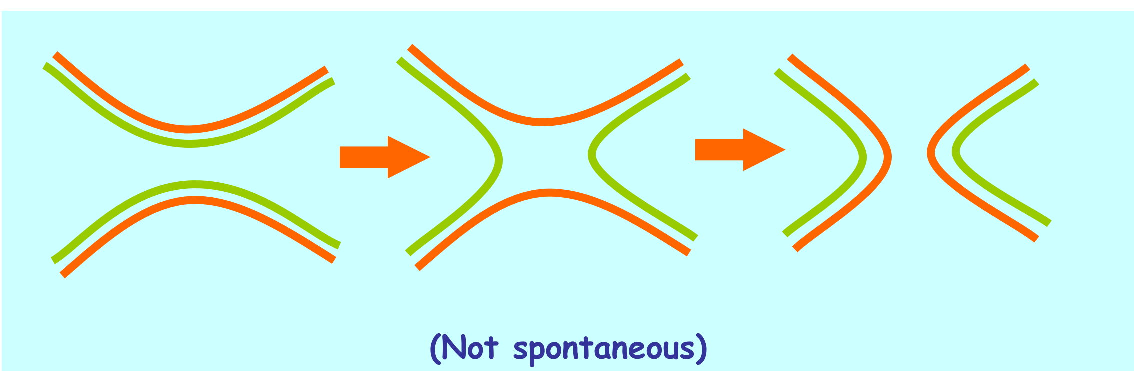
Membranes are Oriented 2D Surfaces

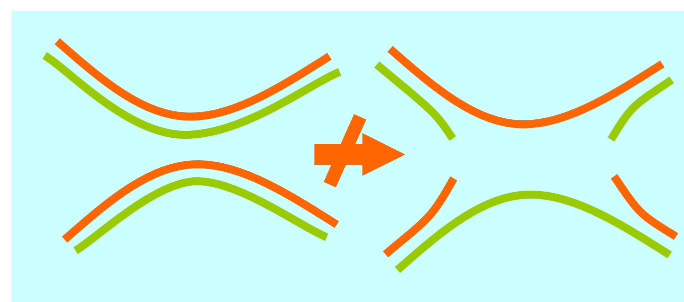




Lipid Bilayer
Self-assembling
Largely impermeable
Asymmetrical (in real cells)
With embedded proteins
A 2D fluid inside a 3D fluid!

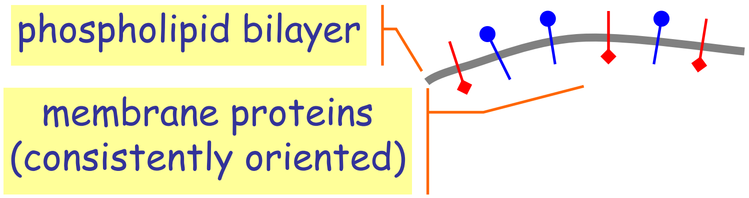




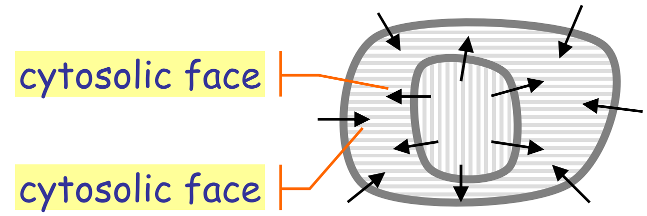


Systems of Oriented Membranes

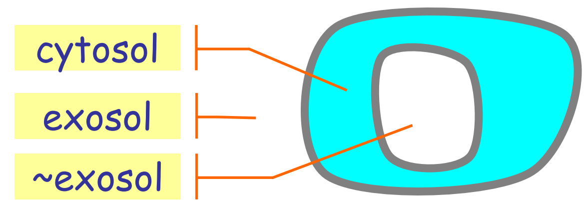
Membranes are closed non-intersecting curves, with an orientation[1].

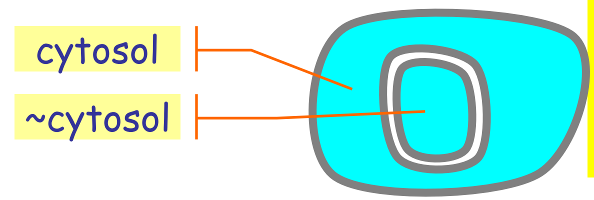


Each membrane has two faces. A cytosolic (~*inner*) face and an exoplasmic (~*outer*) face.
Nested membranes alternate orientation.
(E.g. cytosolic faces always face each other, by definition, or by fusion/fission dynamics)



This alternation is illustrated by using two tones: blue (cytosol[2]) and white (exosol[3]).
Bitonal diagrams.





Bitonal diagrams

Double membranes (e.g. the nuclear membrane) gives us 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 Structure

Bitonality

Blue and white areas alternate.

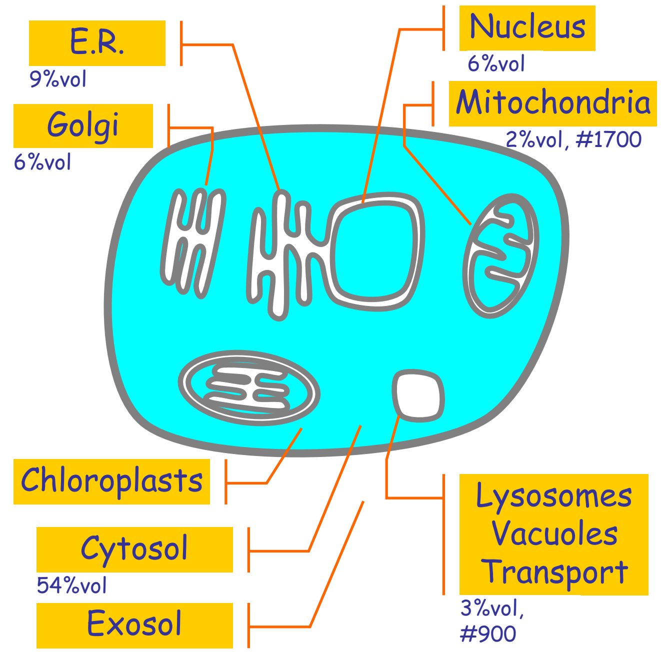
Bitonal Invariant

Bitonality and subsystem coloring is preserved by reactions. I.e., blue and white fluids *never mix and never flip color.*

Bitonal Duality

Reactions come in complementary-tone versions.

The cell maintains a strong compartment-based separation between *inside fluids* and *outside fluids* even when incorporating foreign material.

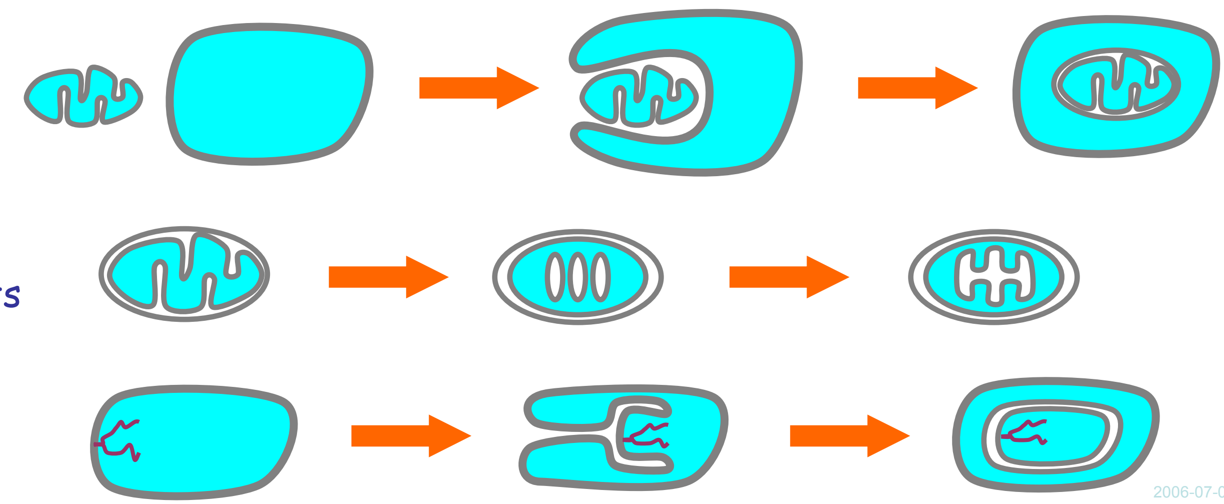


Evolutionary explanations of bitonal structure

Mitochondria acquisition

Mitochondria to Chloroplasts

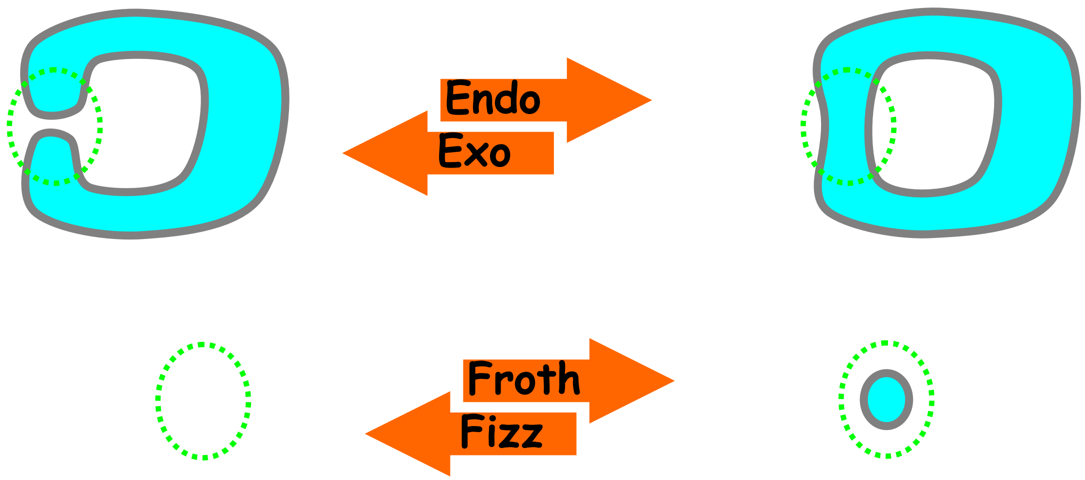
Pre-Eukarya to Eukarya



Before We Formalize Anything...

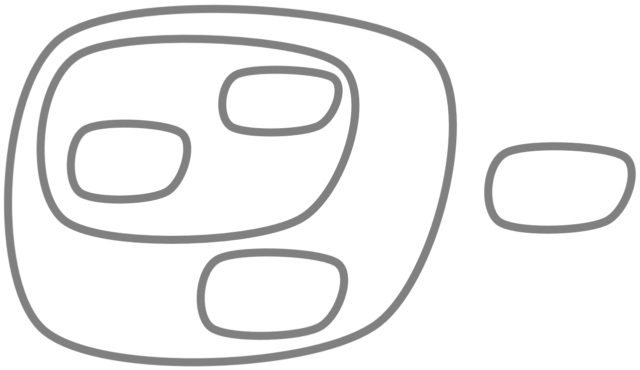
- What are the fundamental operations?
- What are the fundamental invariants?

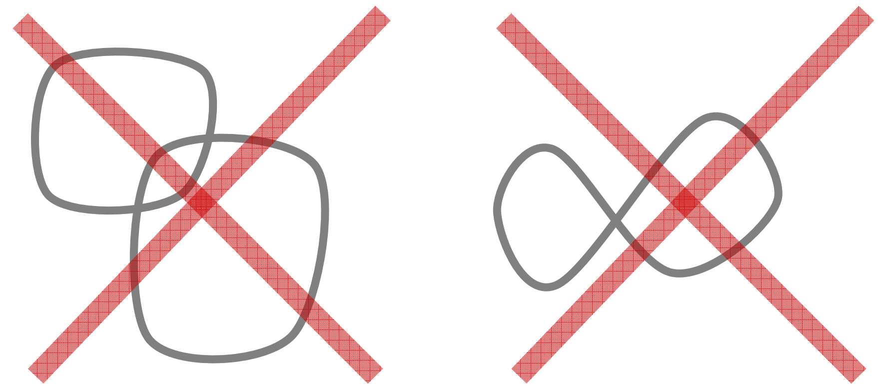
A complete set of bitonal reactions.



Gradual Transformations of Membrane Systems

Membrane Systems

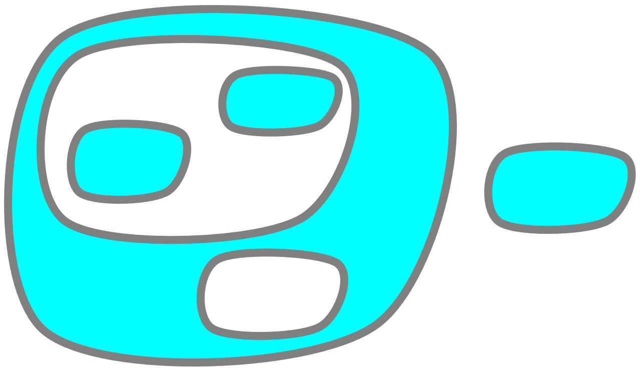


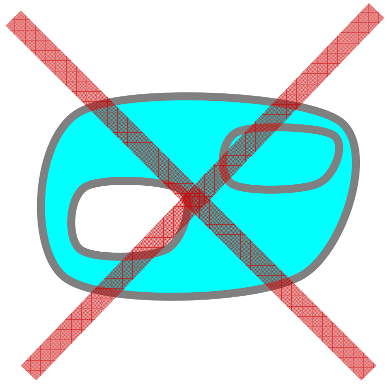


Good Systems
(Closed non-intersecting curves)

Bad Systems

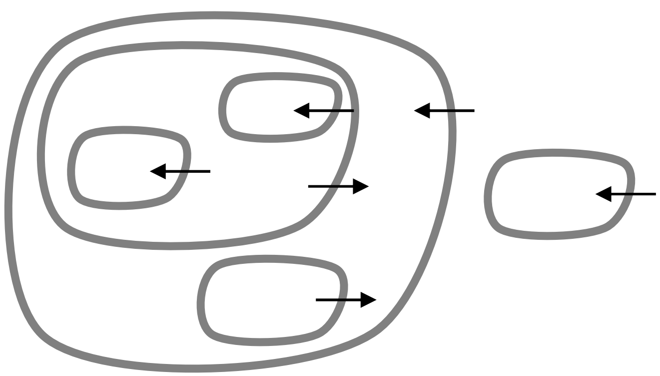
Bitonal Membrane Systems





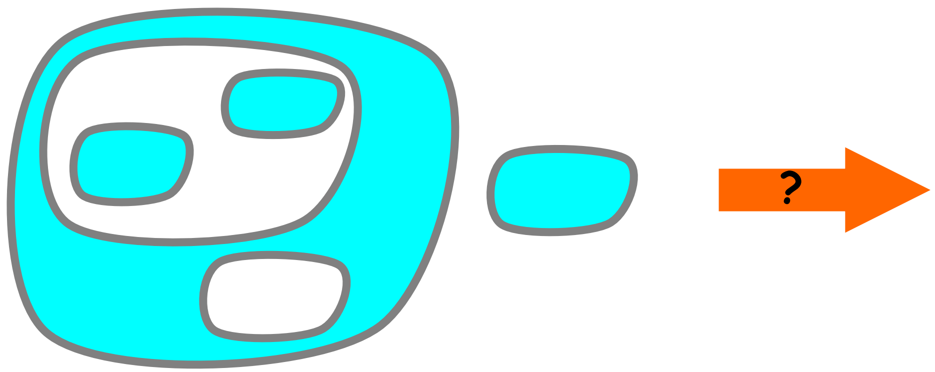
Good Bitonal Systems
(Alternating oriented curves)

Bad Bitonal Systems



Locally Realizable Reactions

Membrane System

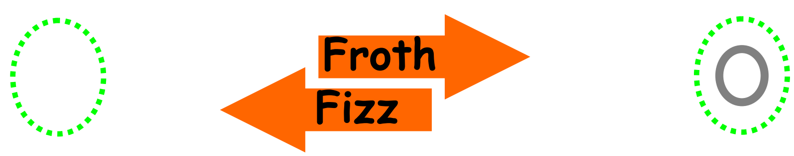


Q: What transformations "make sense"?

Local (Patch) Reactions

A: Transformations that obviously "make sense" from a local, molecular viewpoint

(Symmetric by 90° rotation.)



(Phospholipids thrown in water self-assemble into empty vesicles)

Gradual Change

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

There are three ways to characterize gradual changes:

- Local interactions of membrane patches.
  (What really happens at the biochemical level.)

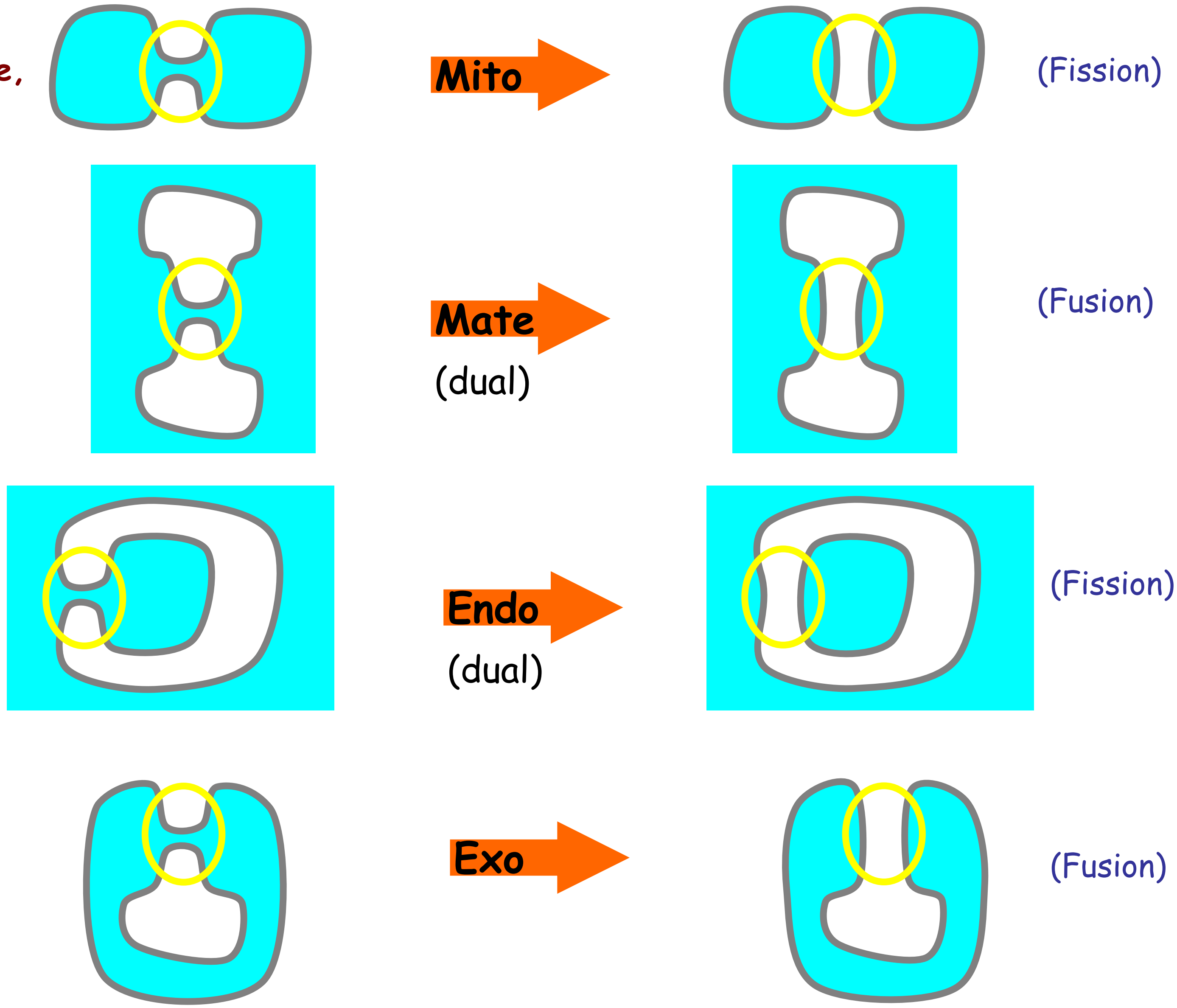
- A specific set of global reactions that are “biologically meaningful” (e.g. *mitosis*, *endocytosis*) and hence presumably gradually implemented.

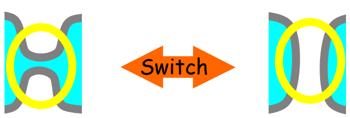
- The gradual transformation of “small areas” of a membrane system in ways that do not “mix fluids” on a large scale.

These turn out to be equivalent!

These Global Reactions are Local Reactions

Reactions that "make sense" from a descriptive, global viewpoint



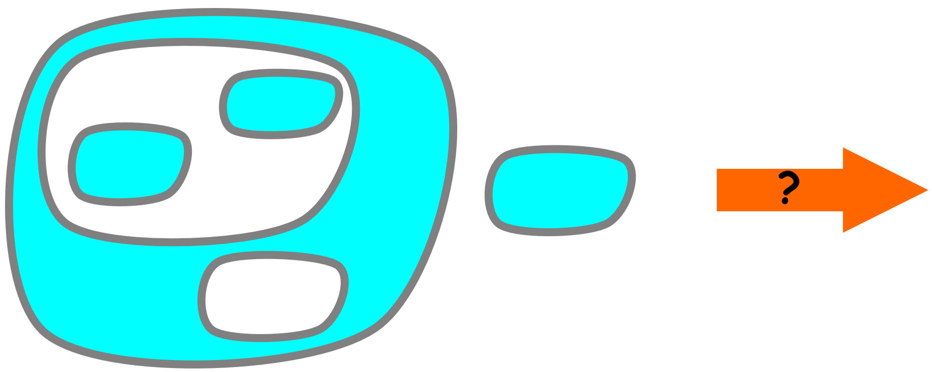


Same Local View!

Bitonal Transformations: Operational View

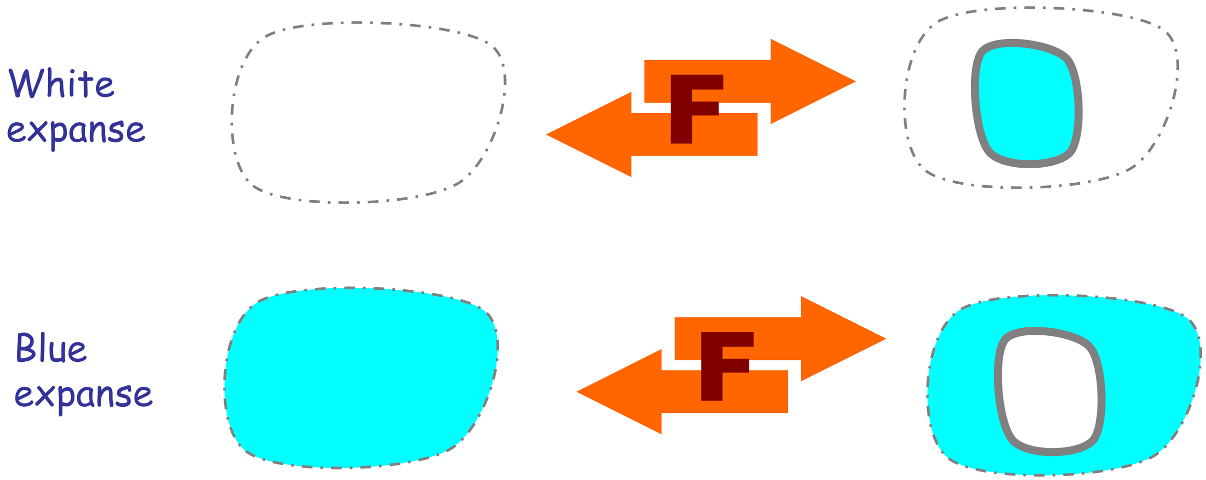
Bitonal Reactions

We look for reactions that "preserve" the bitonal coloring of a membrane system. (And hence preserve proper membrane orientation.)



✓ Froth/Fizz Reaction

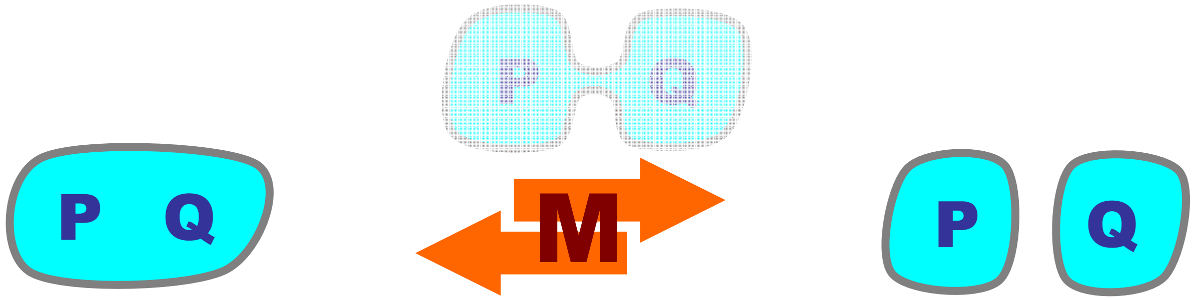
The spontaneous appearance/disappearance of empty bubbles (of the correct tonality).



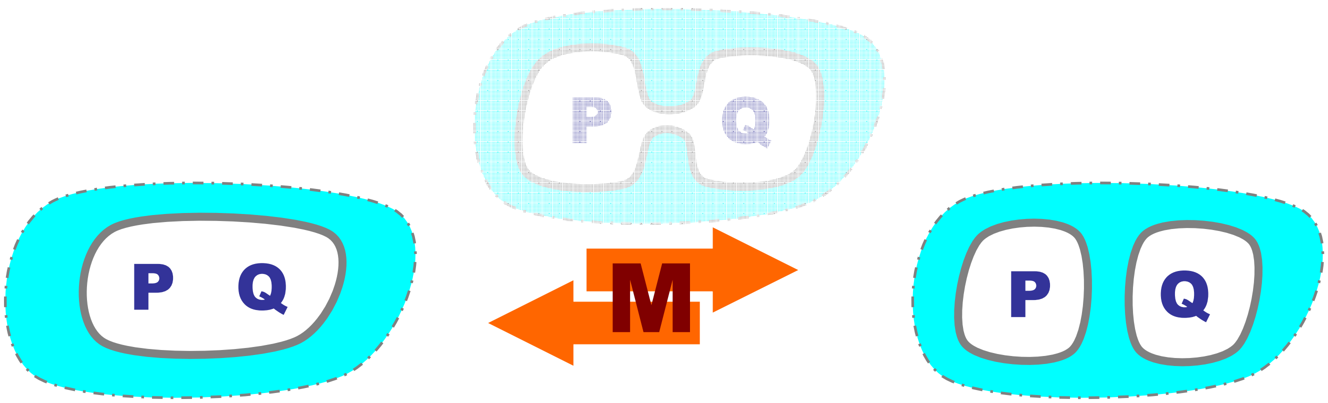
* Phospholipid molecules automatically assemble into closed membranes.

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.

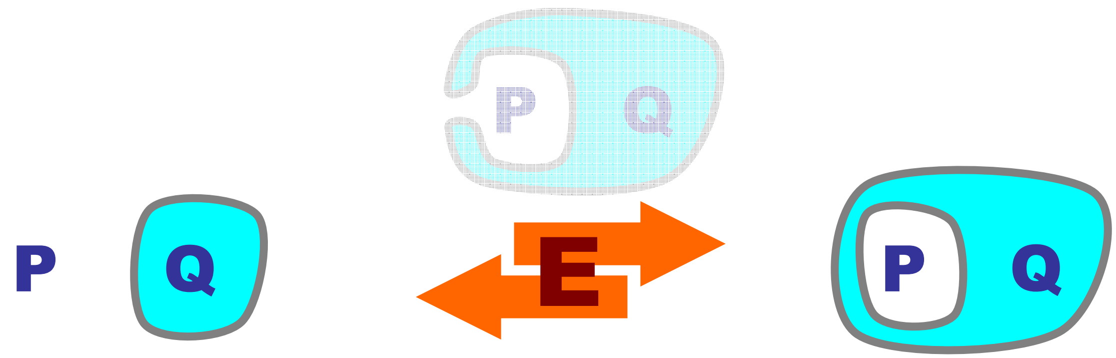
✓ Mito/Mate Reaction



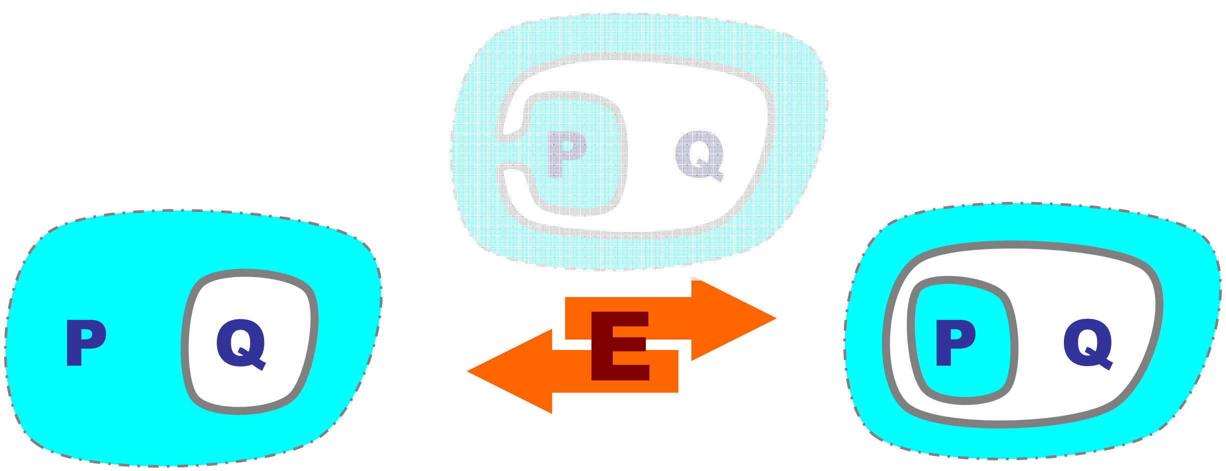
Dual:



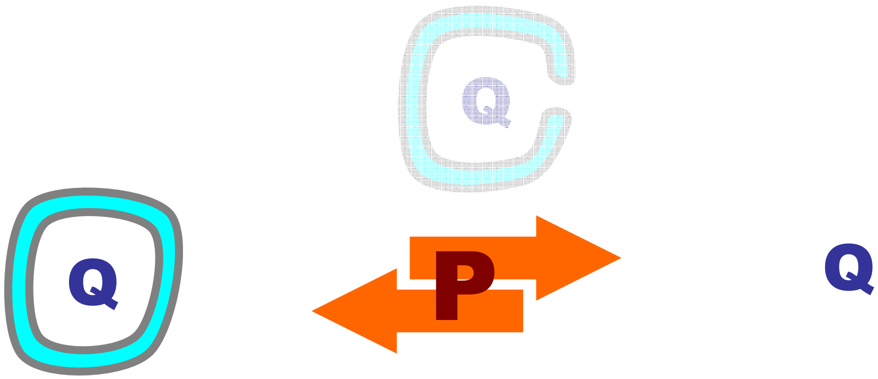
✓ Endo/Exo Reaction



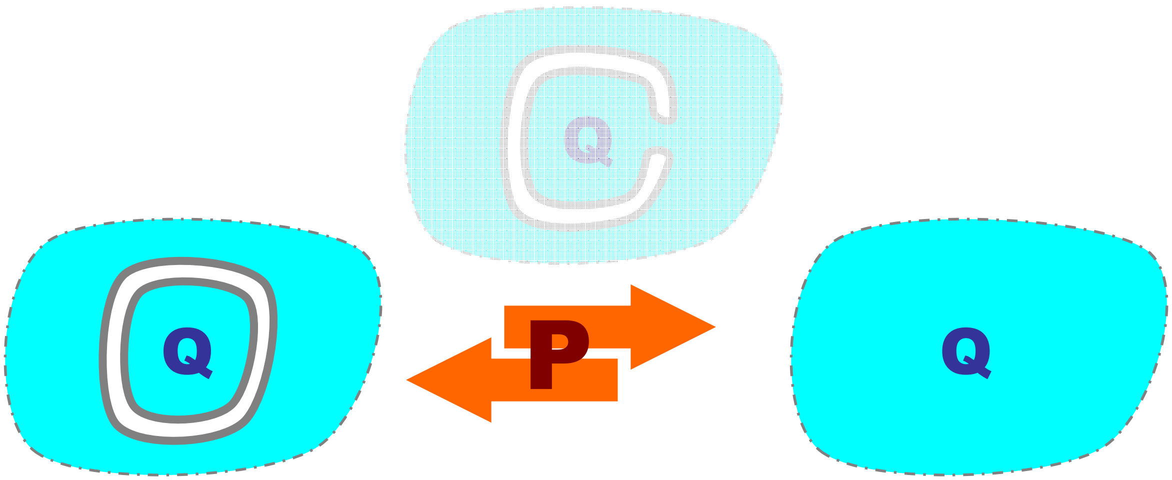
Dual:



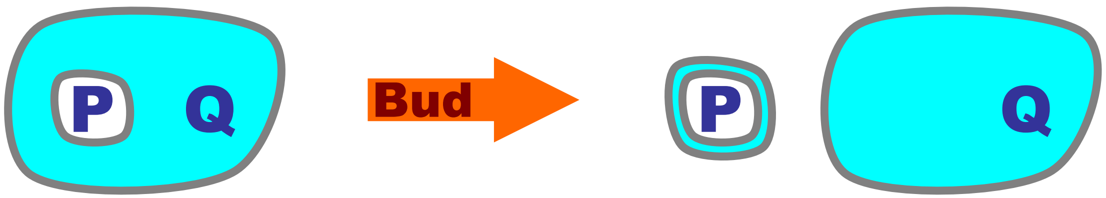
✓ Peel/Pad Reaction



Dual:

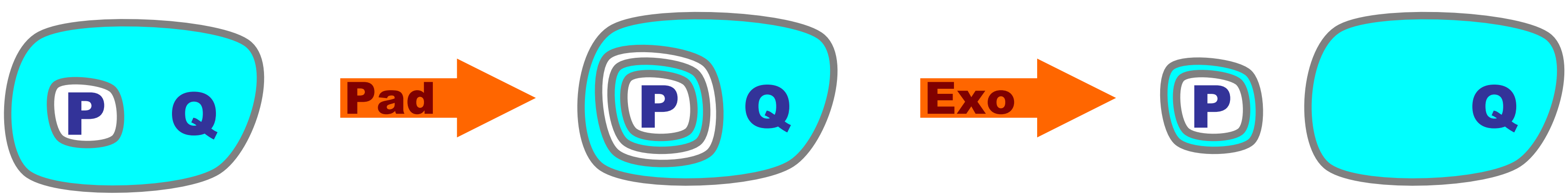


✓ Bud Reaction



Obviously a special case of Mito,
but it can be, both biologically and computationally,
considerably simpler (no arbitrary splitting).

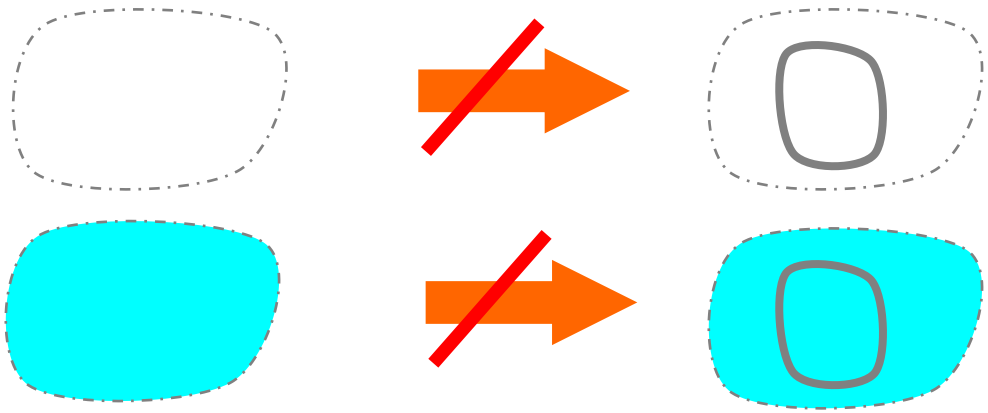
Can also be seen as Pad + Exo:



✘ Bad Bubbles

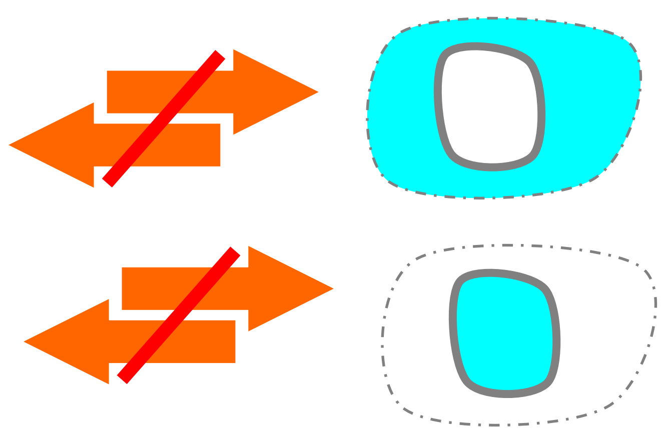
Wrong bubbles:

Violates bitonality.



Bubble catastrophe:

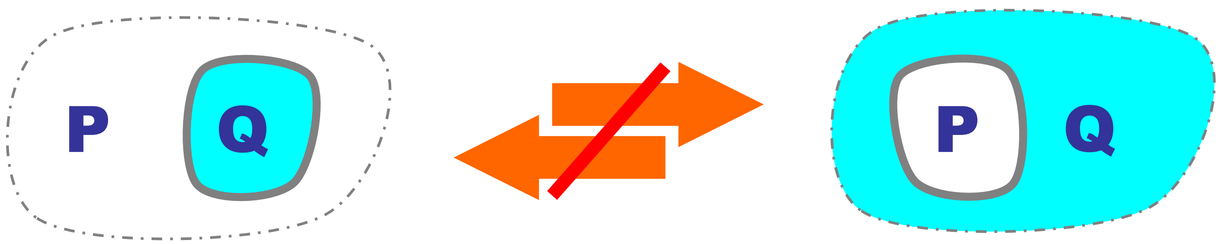
Violates bitonality in context.
Also, ill-toned reaction arrow.



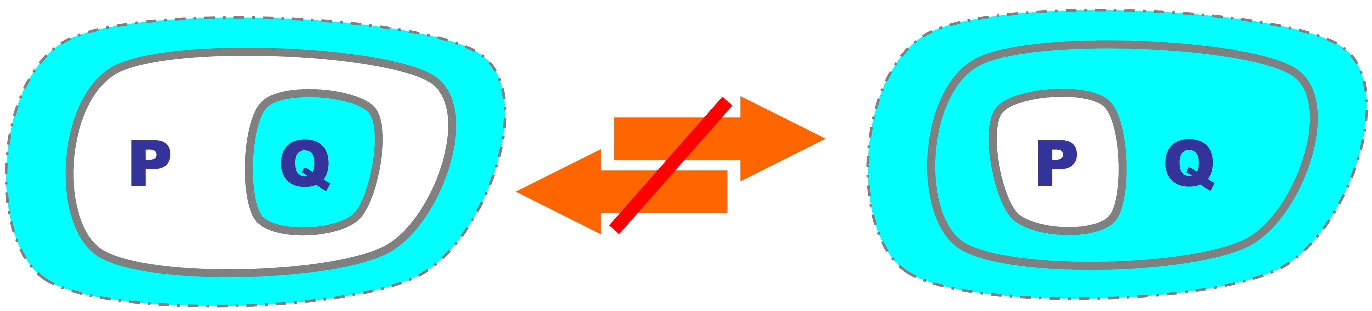
✘ Flooding

Flooding

Violates bitonality in context.
Also, ill-toned reaction arrow.

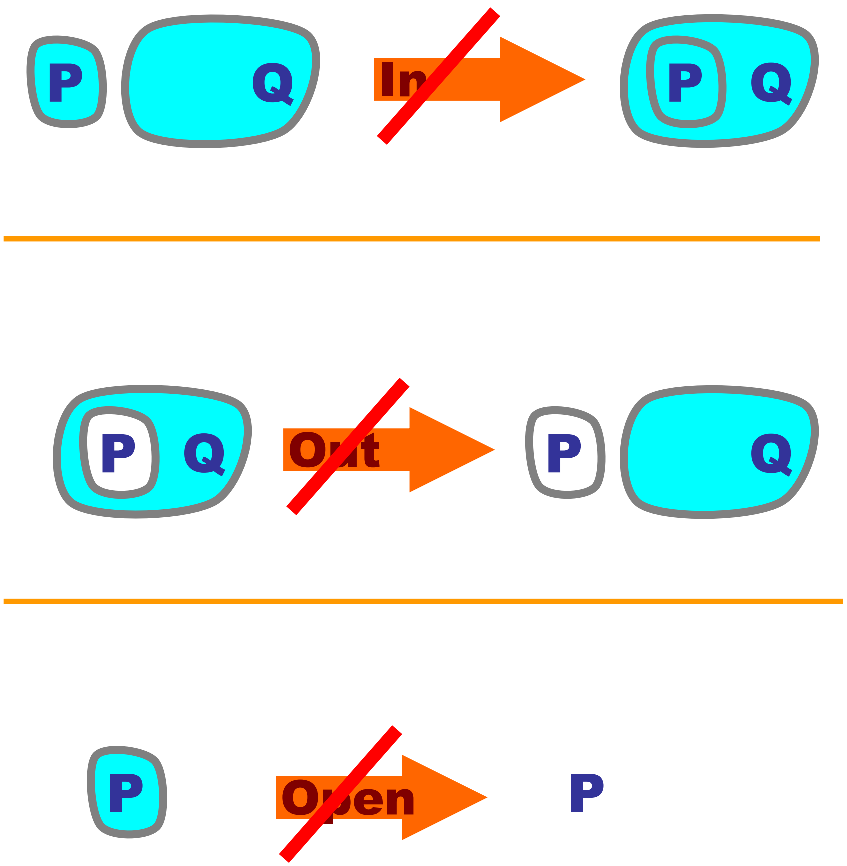


Ex: flooding in context violates bitonality:

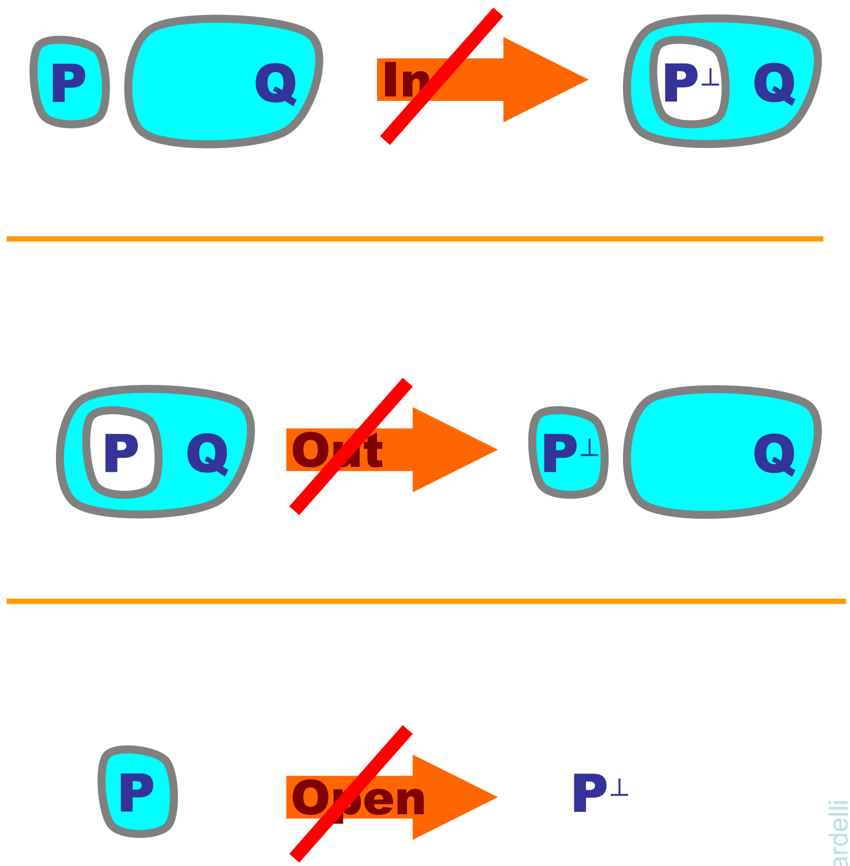


× Ambients

Violate bitonality



Preserve bitonality, but violate stability for subsystem P (i.e. all membranes of P must be "flipped" inside-out).



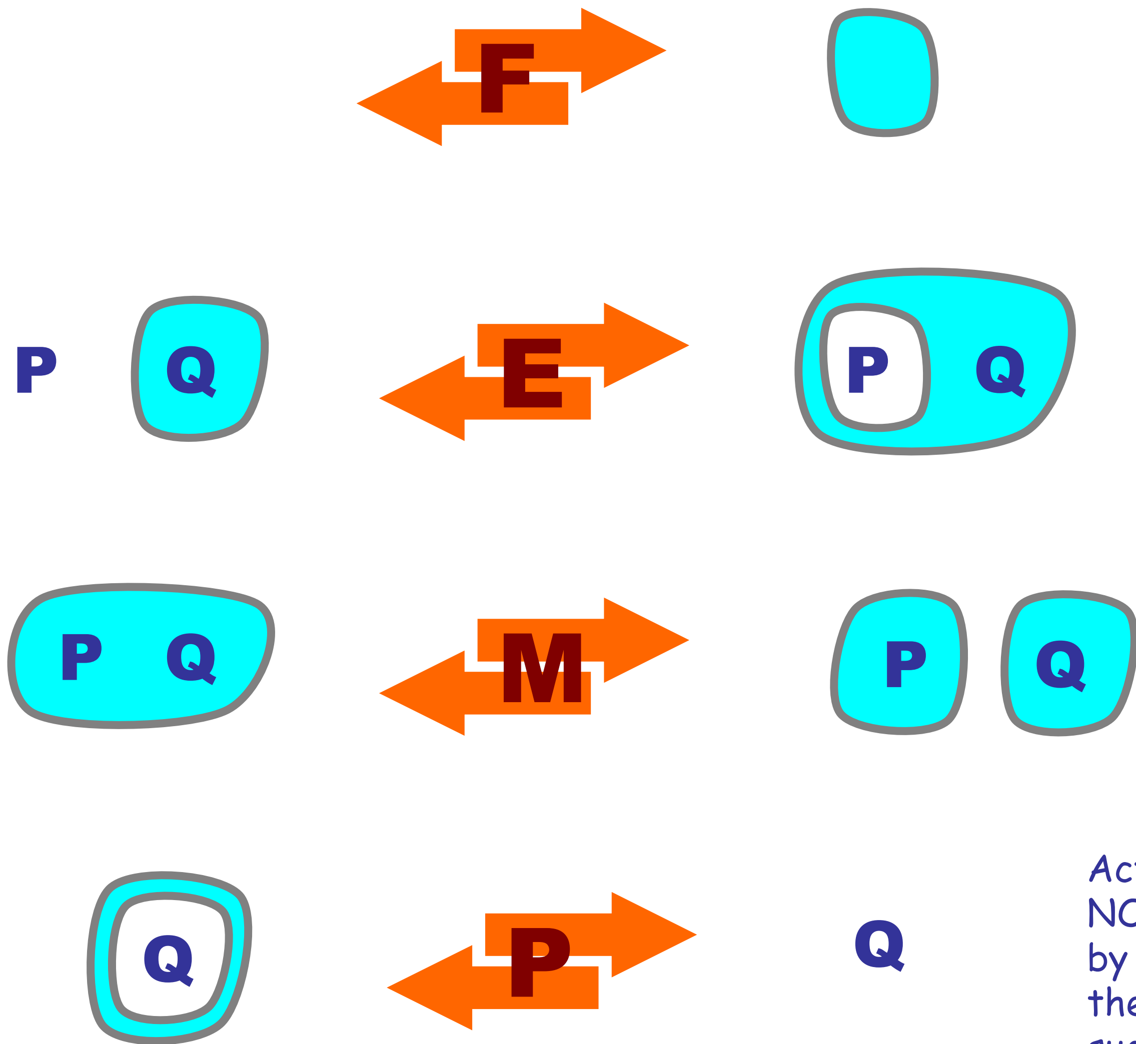
Summary: At Least Four Good Reactions

Froth/Fizz

Endo/Exo

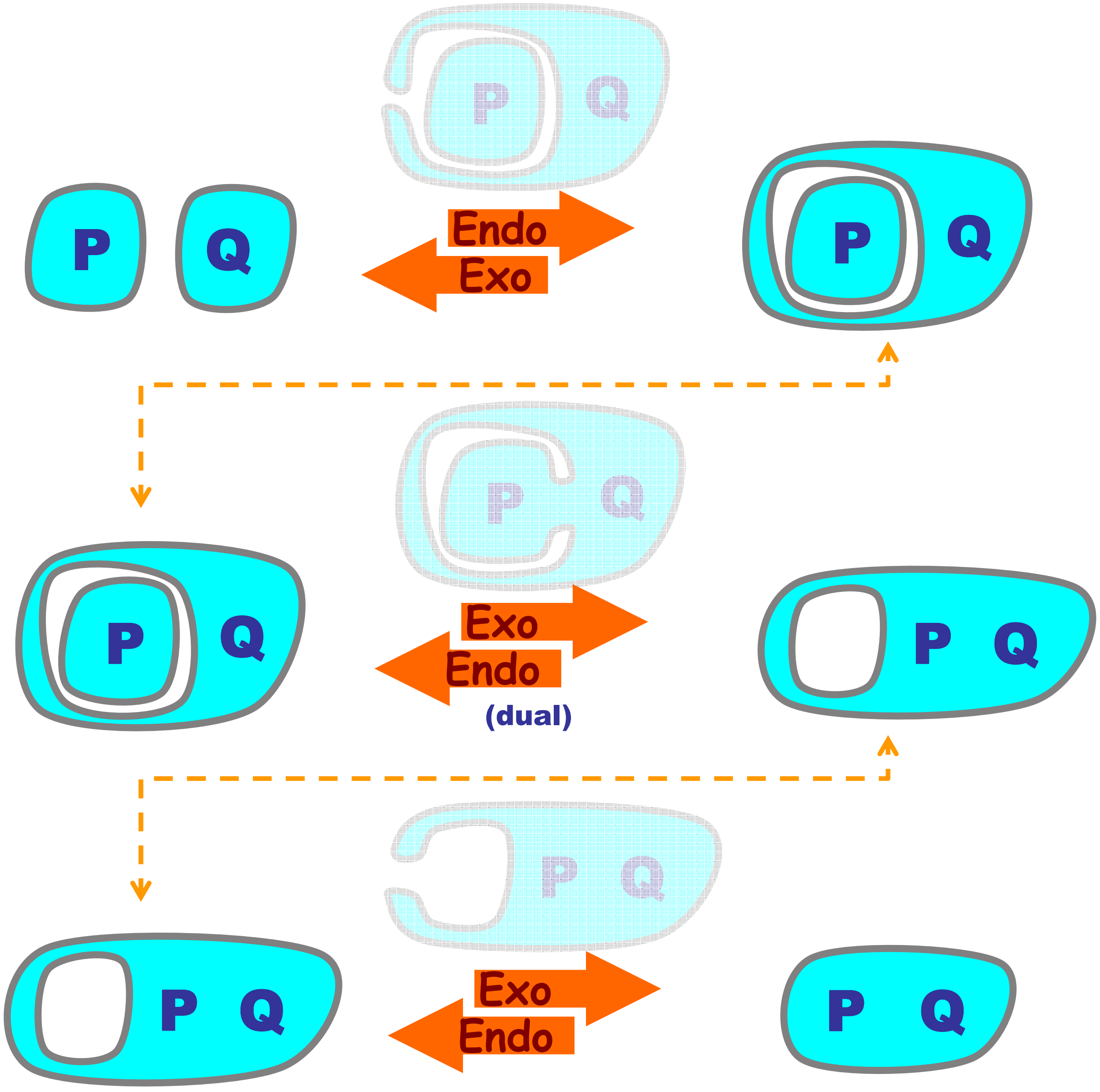
Mito/Mate

Peel/Pad

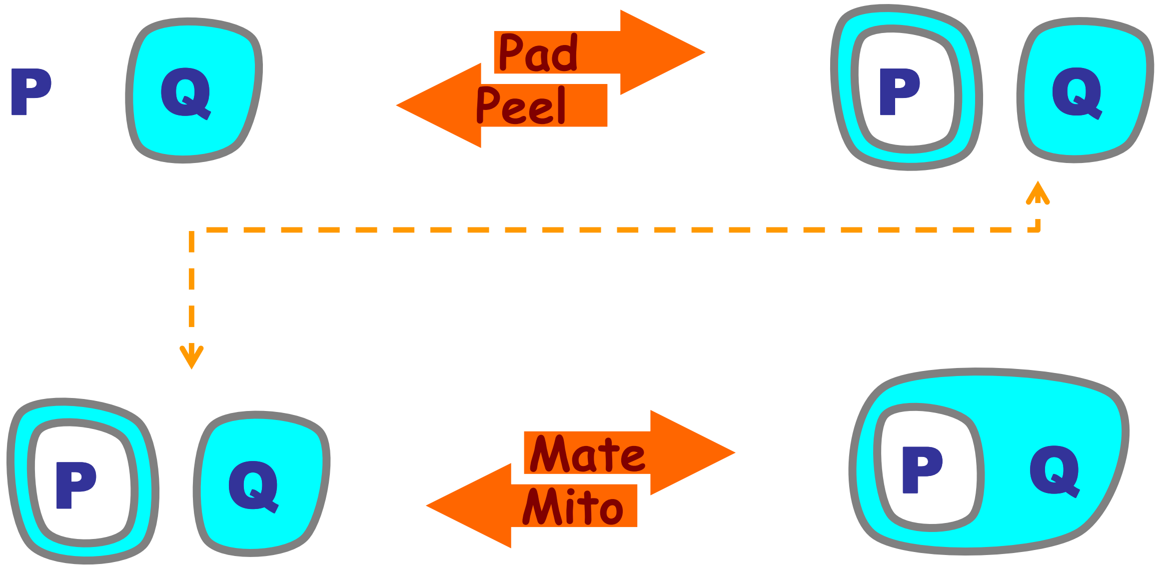


Actually, Peel/Pad is NOT a bitonal *reaction* by my definition, but is the composition of two such. Good enough.

Mito/Mate by 3 Endo/Exo

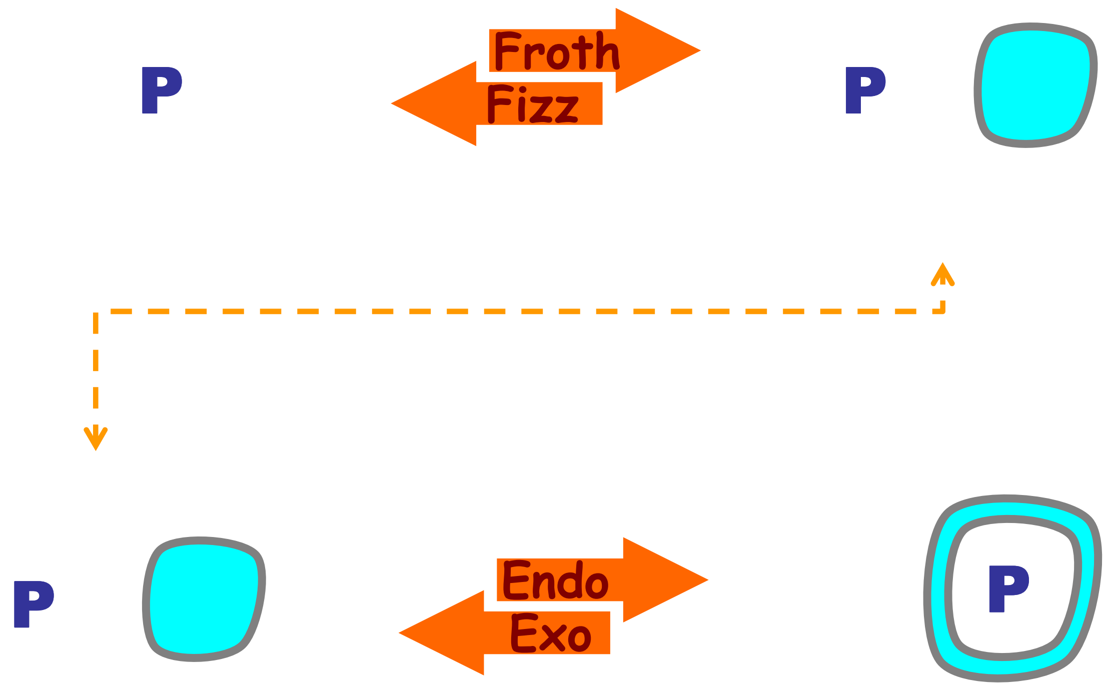


Endo/Exo by Mito/Mate and Peel/Pad



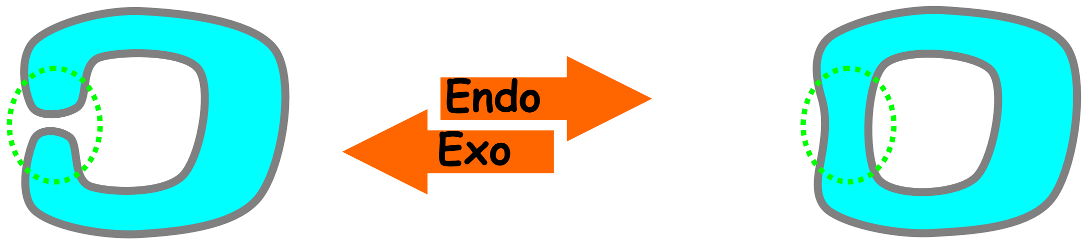
Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.

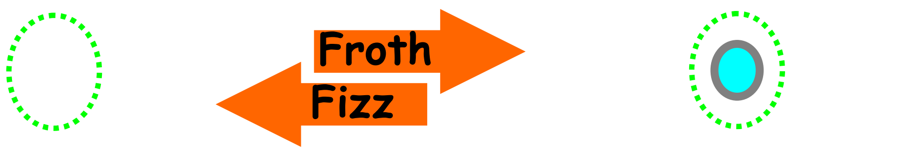
Peel/Pad by Froth/Fizz and Endo/Exo



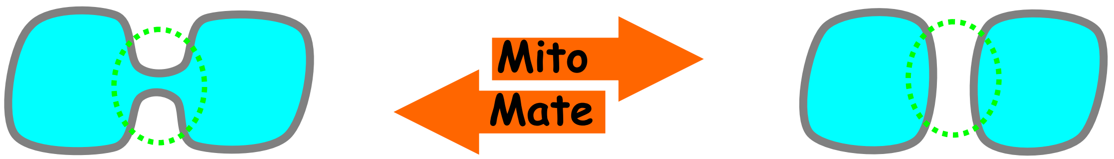
A (Turing) Complete Set of Reactions

[Busi, Gorrieri]





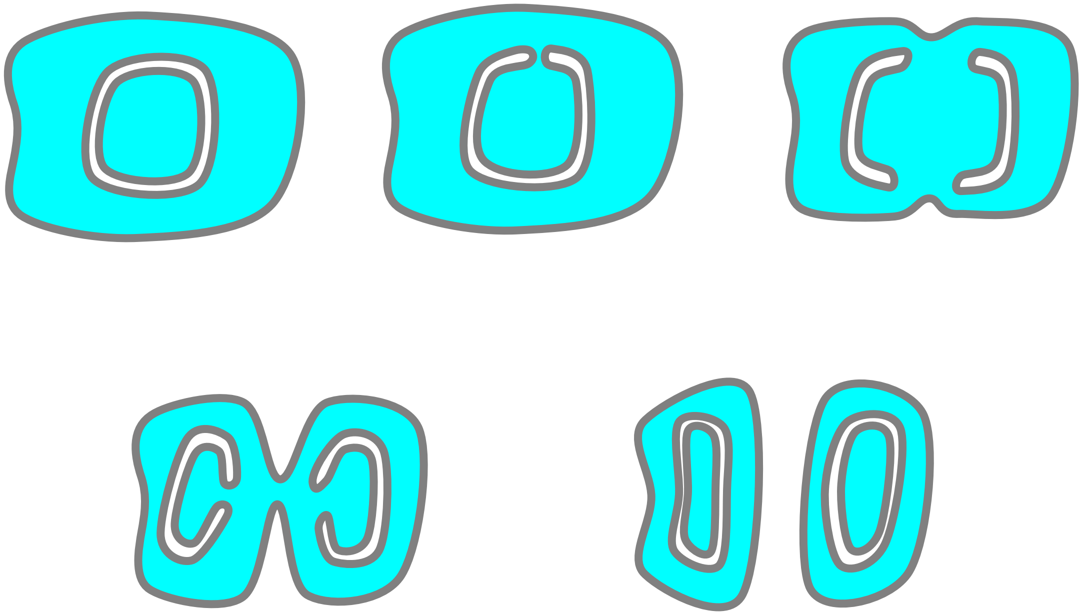
Others bitonal reactions are Derivable, e.g.:



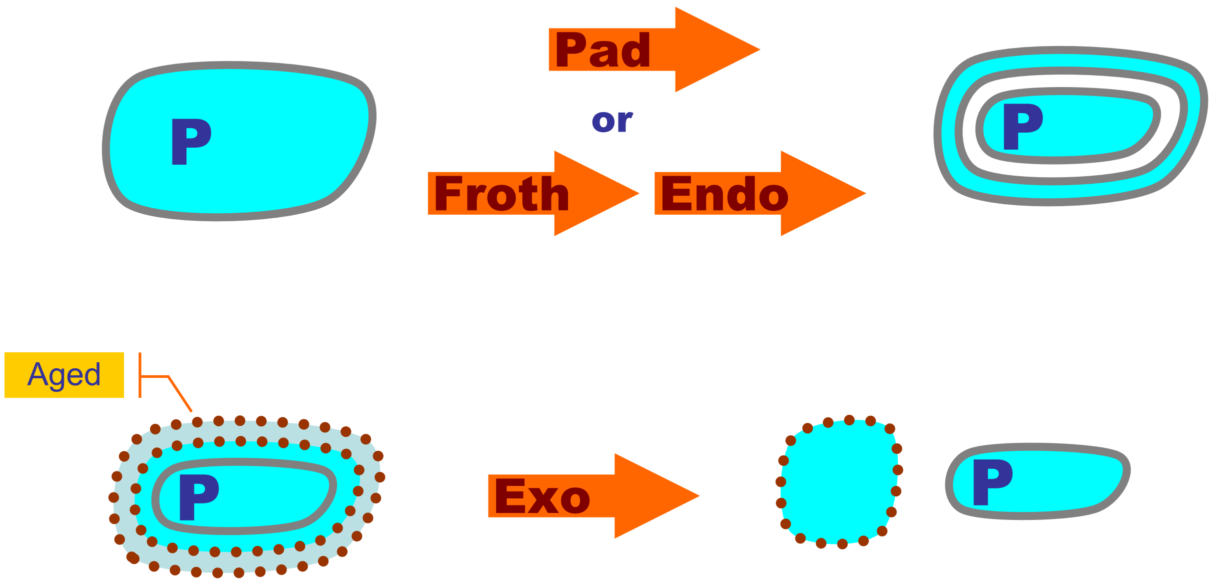
Are *all* other derivable? YES!

Some Examples

Ex: Eukaryotic Mitosis

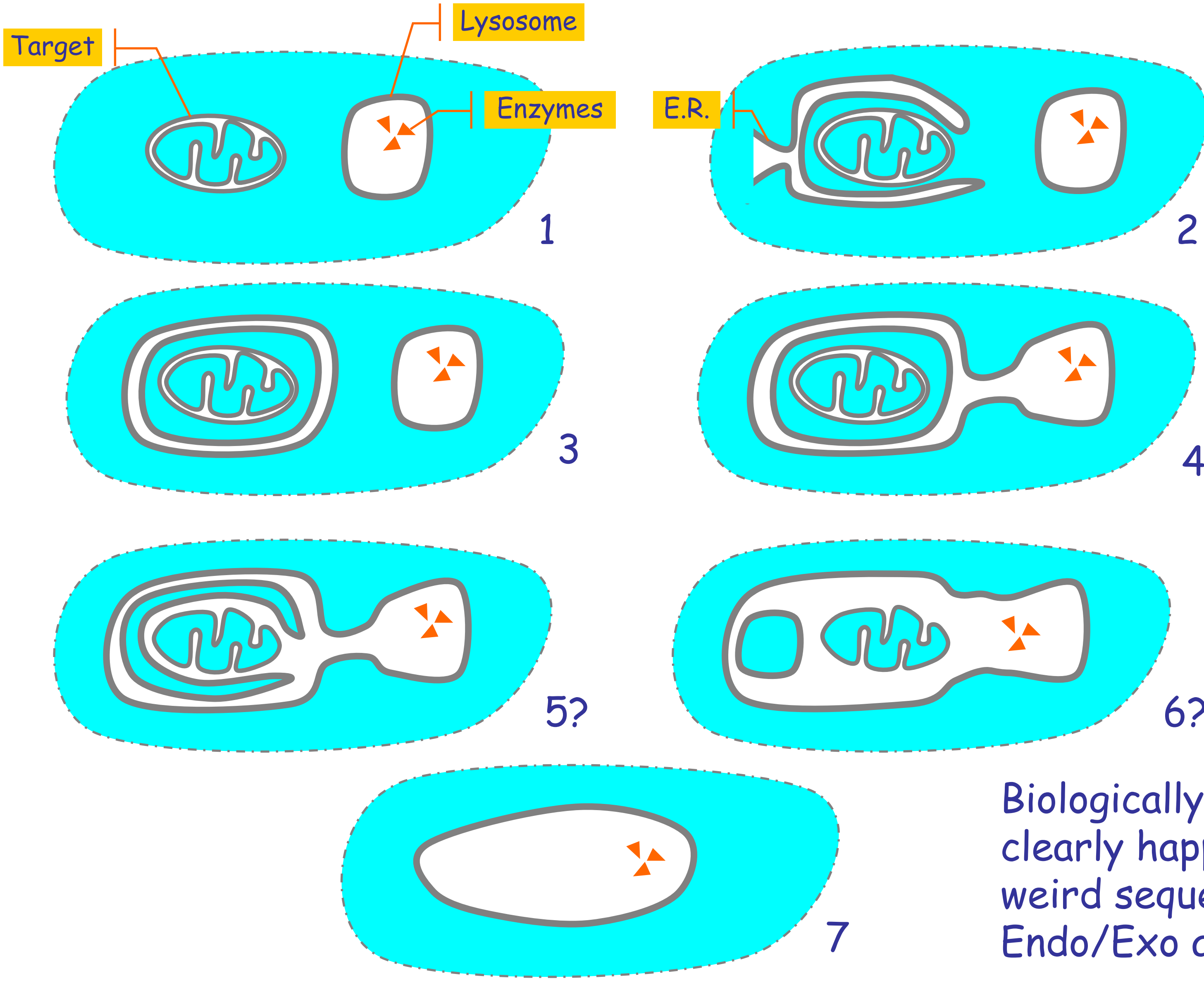


Ex: Molting



Ex: Autophagic Process

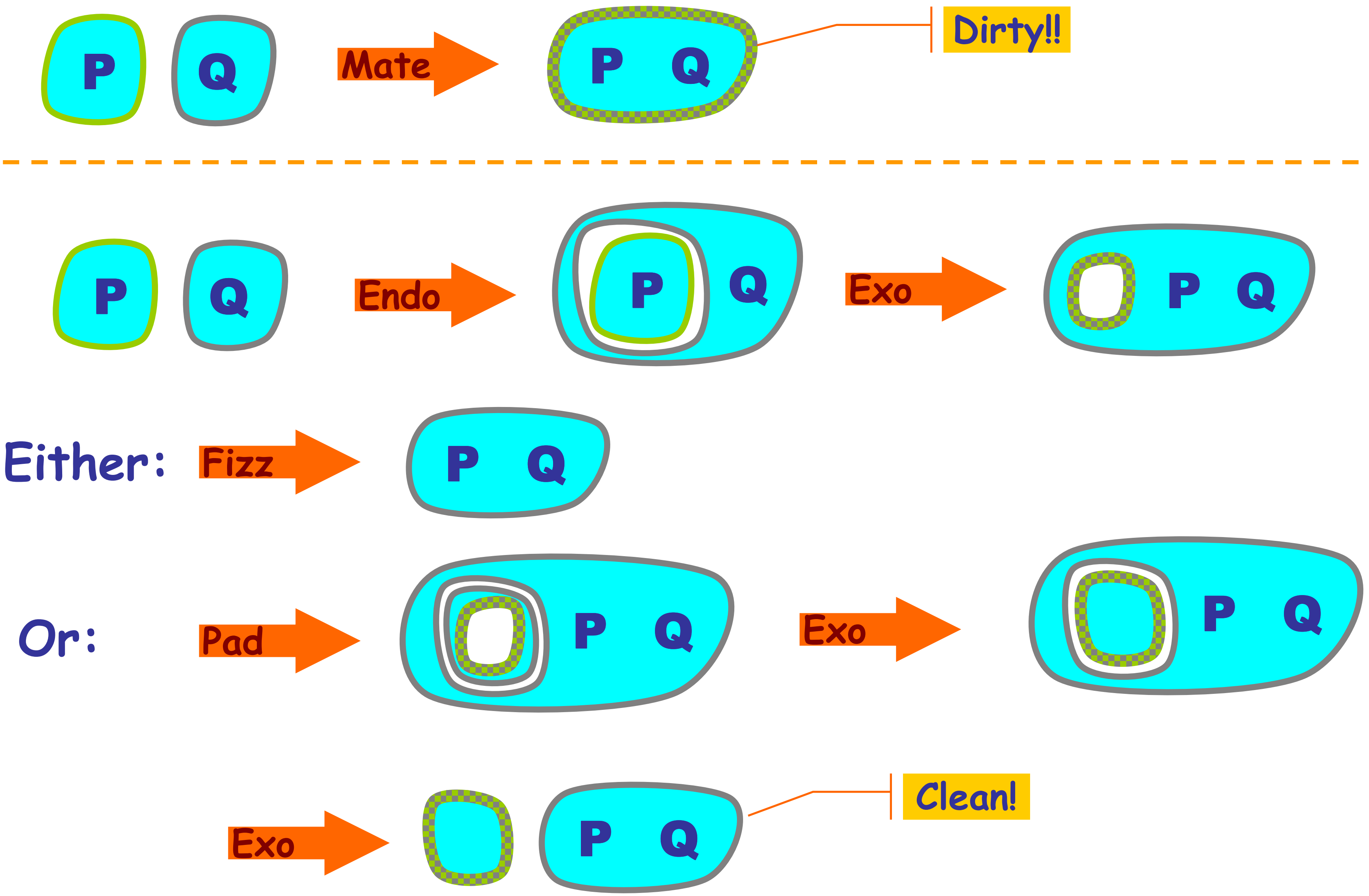
Lysosome and target don't just merge.



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

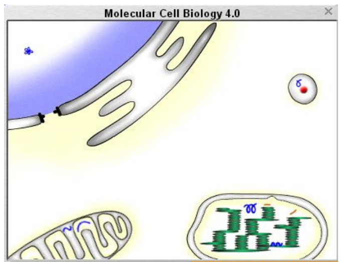
(fake) Ex: Clean Eating

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

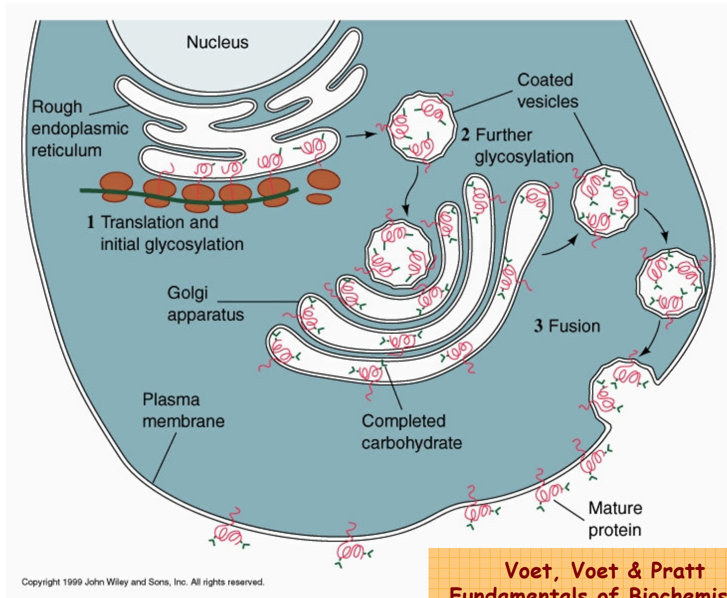


Membrane Algorithms

Protein Production and Secretion

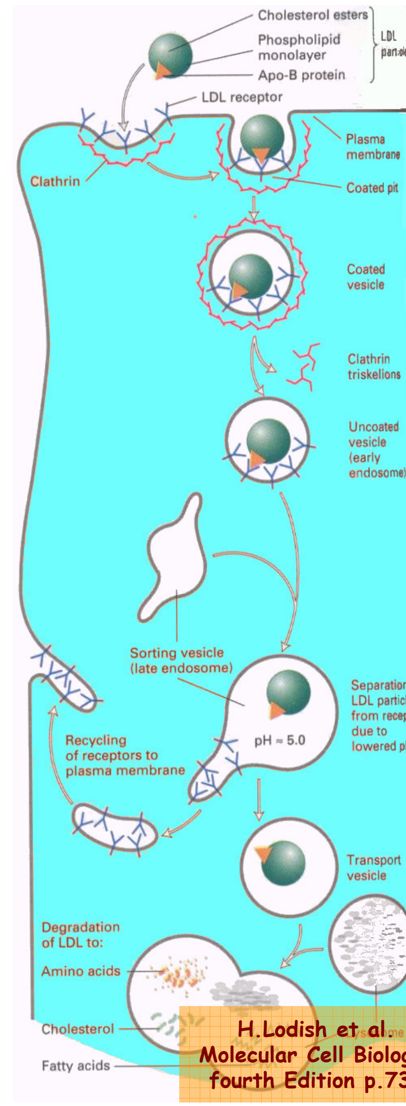


Taken from MCB CD



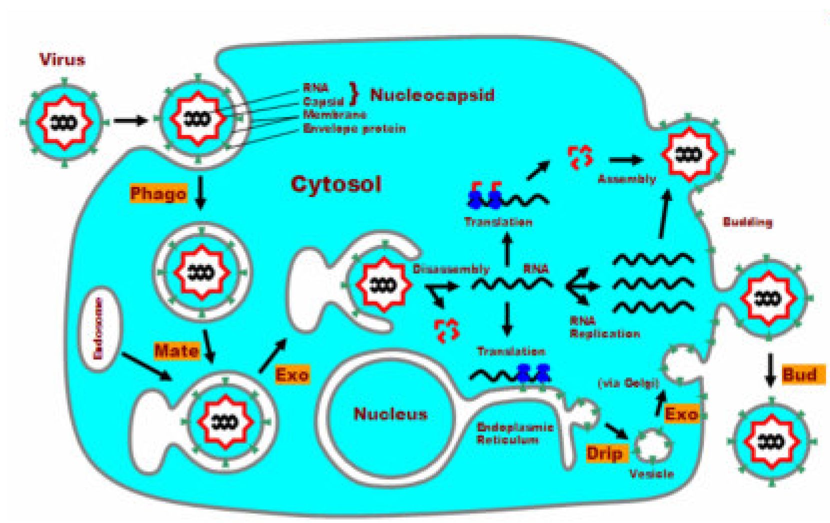
Voet, Voet & Pratt
Fundamentals of Biochemistry
Wiley 1999. Ch10 Fig 10-22.

LDL-Cholesterol Degradation



H.Lodish et al.
Molecular Cell Biology.
fourth Edition p.730.

Viral Replication



Adapted from: B.Alberts et al.
Molecular Biology of the Cell
third edition p.279.

A Note on Locality

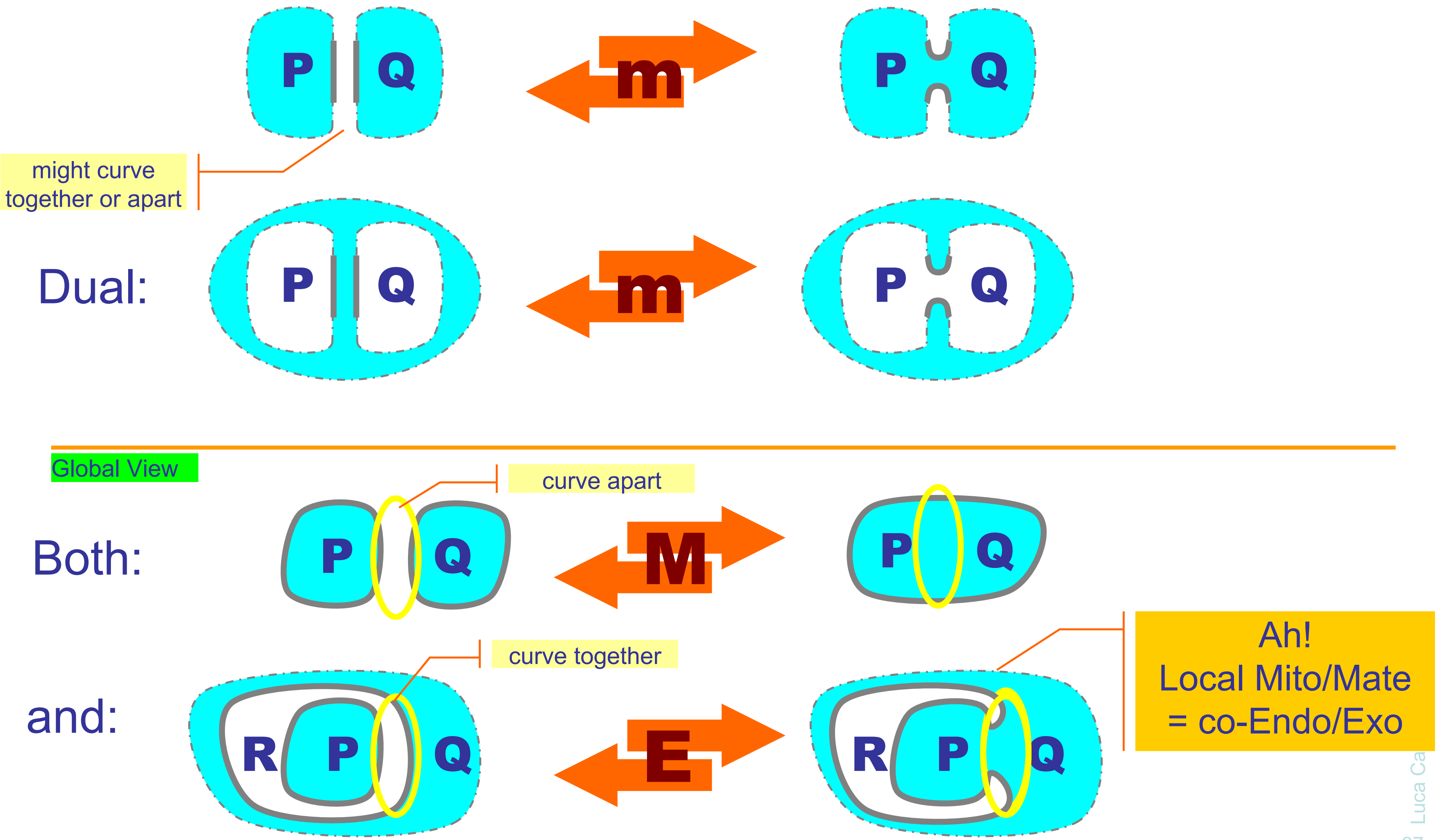
Locality

Locality Postulate

Interactions should be local to small membrane patches (to be biologically implementable).

E.g., they should be independent of global membrane properties such as overall curvature that cannot be observed locally.

Local-view Mito/Mate Reaction

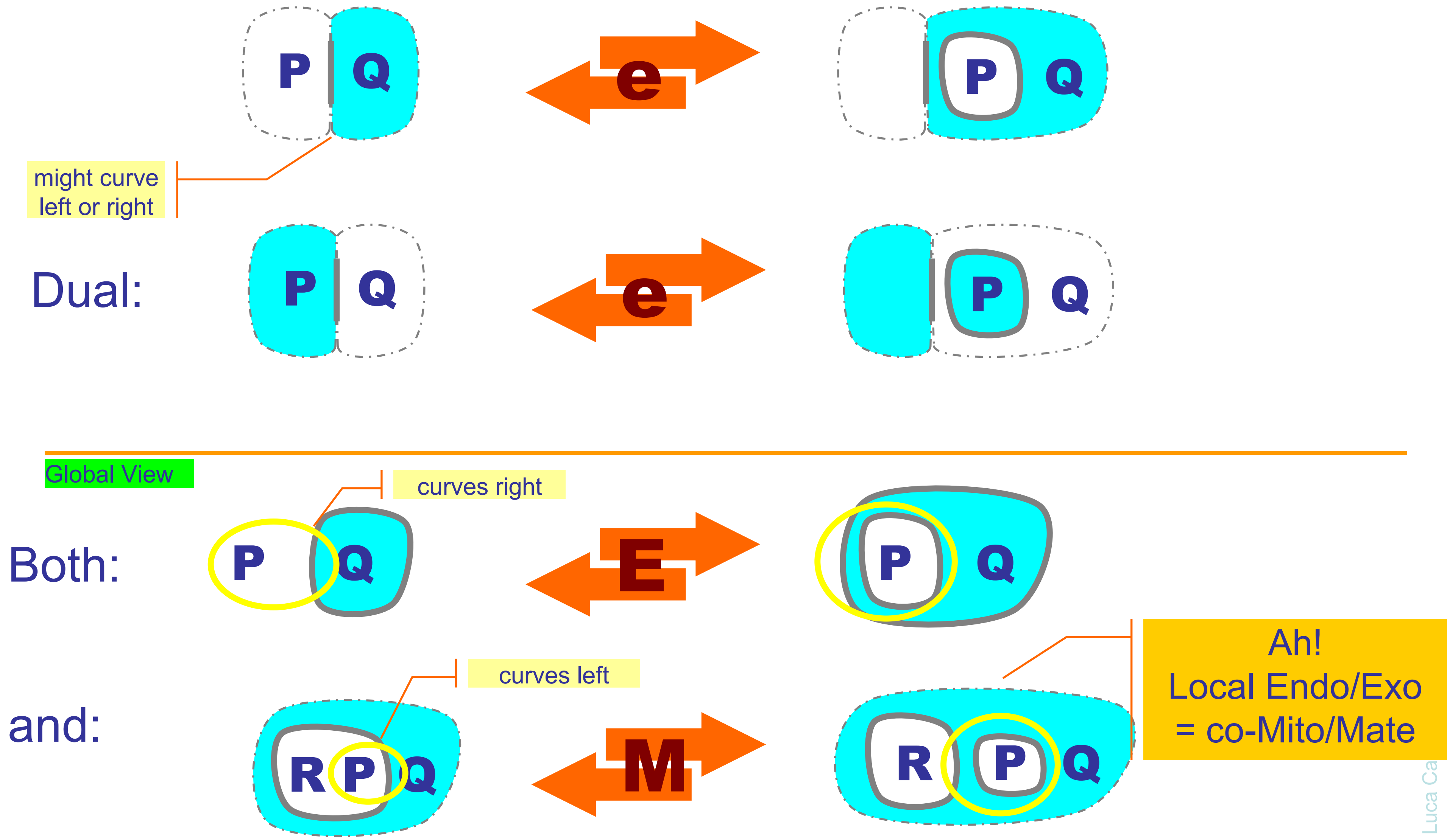


Locality Violated!

Locally, we cannot distinguish between a mito-mate and a co-endo-exo reaction.

Hence, a calculus that includes mito-mate reactions but does not include endo-exo reactions "violates locality", because a local reaction could not distinguish between the two.

Local-view Endo/Exo Reaction



Locality Violated?

Locally, we cannot distinguish between an endo-exo and a co-mito-mate reaction.

But fortunately, (co-)endo-exo can encode (co-)mito-mate. So a calculus with only endo-exo does not *prevent* mito-mate from happening. (As long as the dual reactions are included!)

Locality needs "enough" Global Operations

- 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 better justified after which we may forget about local-view reactions.
- But we cannot go around inventing calculi without considering whether their operations are "locally implementable" even in the sense of making sure we do not have *too few global operations*!

- Problem: how to formally represent the local-view reactions, so that they can be formally related to the global-view reactions, e.g. to prove completeness?

Bitonal Transformations: Relating Local and Global Reactions Through Topology

Membrane Systems

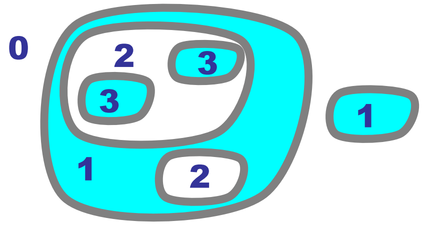
- Def: a curve c (on the plane) is a continous map in $[0,1] \to R^2$.

- Def: a membrane m is a curve that is
  - simple (i.e., injective in the open interval (0,1), hence non-self intersecting and with a non-empty interior).
  - closed (having $m(0)=m(1)$).
  - smooth (infinitely differentiable and with all derivatives coinciding at $m(0), m(1)$). (So that we can tell when a point is inside a membrane.)

- Def: a membrane system M is a finite set of membranes $\{m_1, \ldots, m_n\}$ whose ranges nowhere intersect in R.

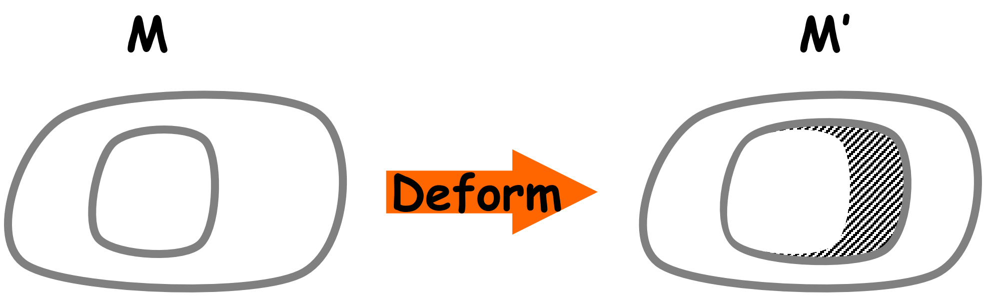
Depth and Tonality

- Def: the *depth* of a point (in a membrane system, and not on a membrane) is the number of membranes that contain it.
- Def: the *tonality* of a point is white/blue iff its depth is even/odd.

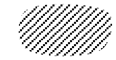


Reactions and Transformations

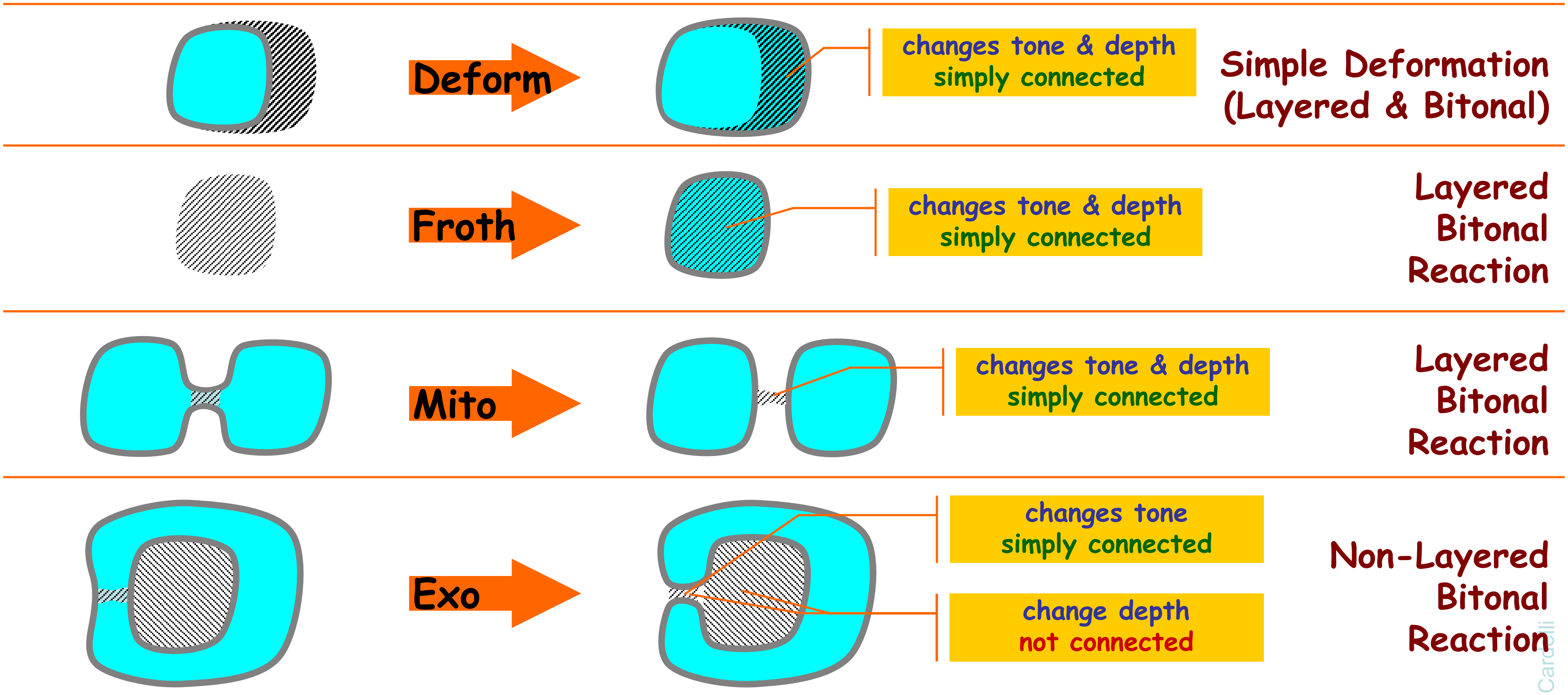
- Def: a reaction is a pair of membrane systems <M,M'>: the one *before* (M) and the one *after* (M') the reaction.
- Def: a deformation is a reaction <M,M'> with a 1-1 mapping between membranes in M,M' that preserves containment.
- Def: a transformation is a finite sequence of zero or more reactions.



Layered and Bitonal Reactions

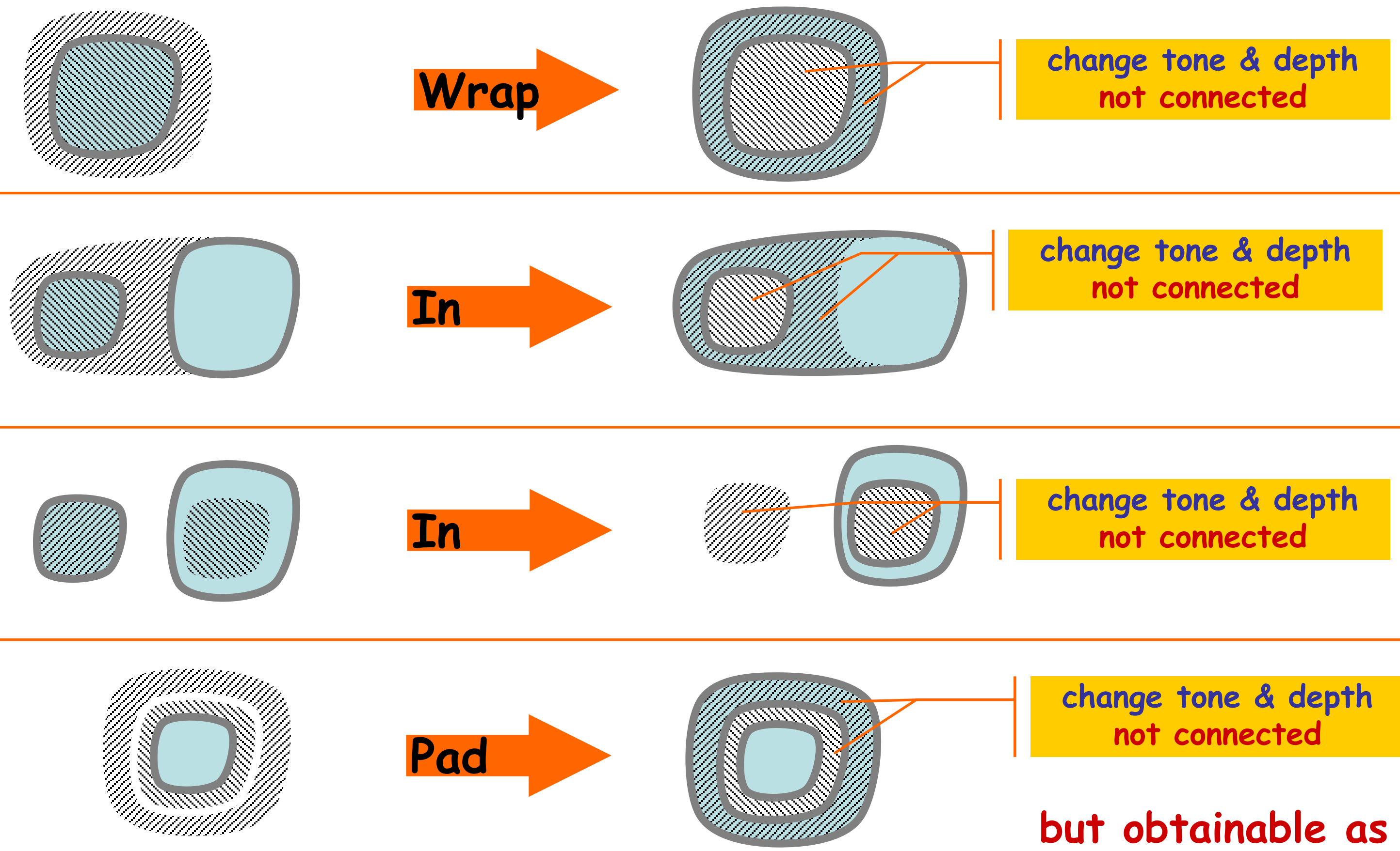
Def: A *bitonal (resp. layered) reaction* is a pair of membrane systems <M,M'> such that the points that change tone (resp. depth) form a simply-connected  region of the plane (a region not separated by membranes).

(N.B.: Layered ⇒ Bitonal)



Non-Bitonal Reactions

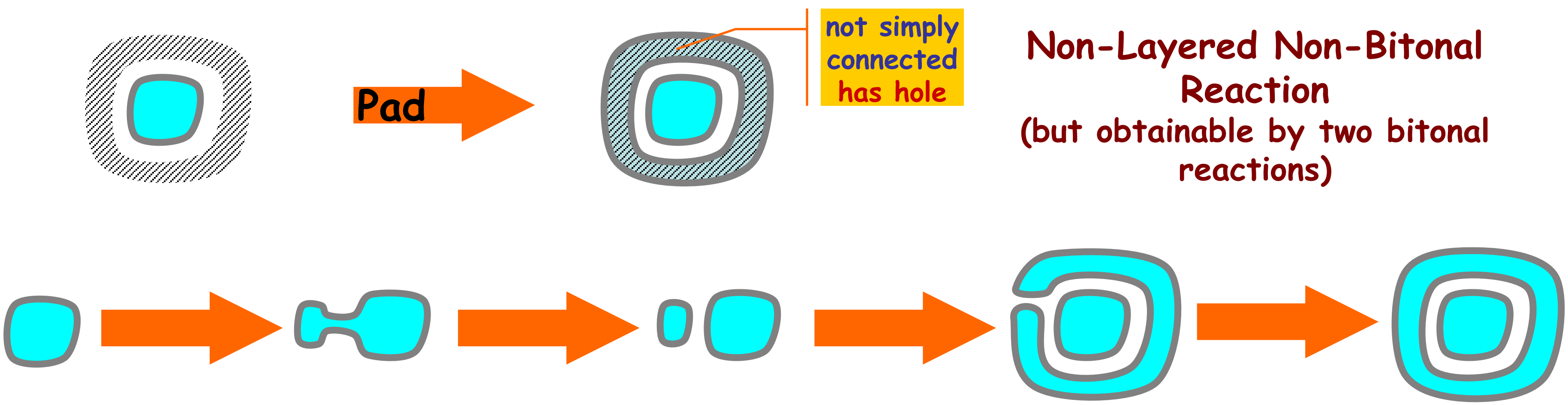
A *bitonal (resp. layered) reaction* is a pair of membrane systems <M,M'> such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes).



but obtainable as the composition of two bitonal reactions (Froth+Endo)

Bitonal Transformations

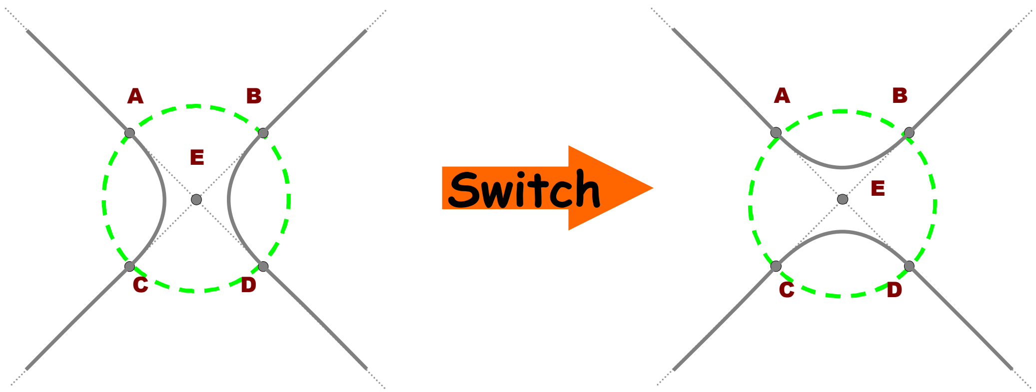
- *A transformation* is a finite sequence of reactions. *A bitonal transformation* is a finite sequence of bitonal reactions.
- We want all "legal" transformations to be bitonal transformations (and hence "gradual" transformations). E.g.: padding:



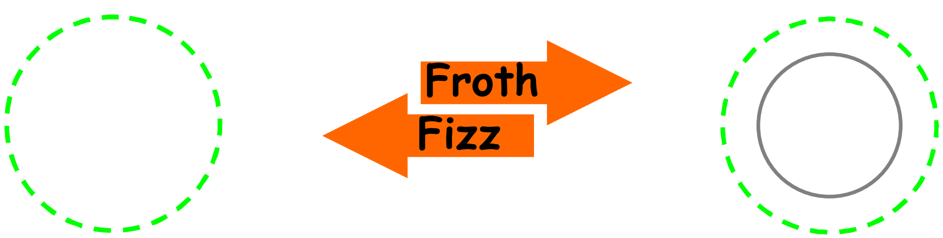
- Some transformations are inherently non-bitonal.

Local Reactions (on the plane)

- Def: A switch is (up to deformations) a reaction that changes a membrane system M only as indicated (say, in the unit circle):

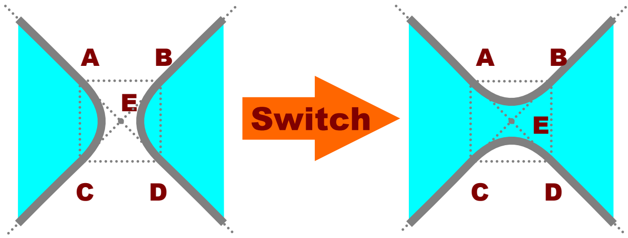


- Def: a froth (fizz) is (up to deformations) a reaction that changes a membrane sytem M only as indicated:

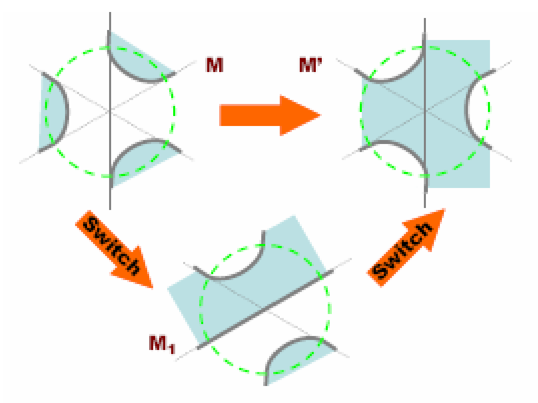


Local = Bitonal

- Prop: In any membrane system, a switch is a bitonal reaction. (So is froth and fizz.)
  - That is, switch changes tonality of only a simply connected region of the plane. Proof by cases on the external connectivity of switch end-points.



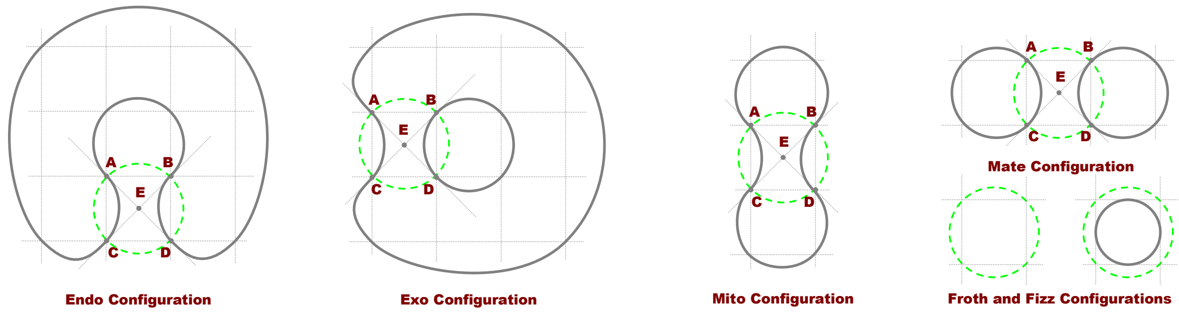
- Prop: All bitonal reactions can be obtained as a finite sequence of switch, froth, fizz, and deformations.
  - By analysis of the simply connected region that changes tonality, and by induction on the number of membranes that cross such a region (using switch for the induction step, and froth,fizz for the base case).



- Th 1: Local Transformations = Bitonal Transformations.

Soundness and Completeness of Global Operations

- Def: "global" Endo, Exo, Mito, Mate, Froth, Fizz are the following normalized starting configurations and related reactions (up to deformations):



- Soundness: Any Endo, Exo, Mito, Mate reaction can be implemented by switch.
  - Proof obvious: a single switch will do it in each case (plus deformations).

- Completeness: any switch in a membrane system can be represented as either an Endo, Exo, Mito, or Mate global reaction.
  - Proof by cases on the external connectivity of switch end-points.
  - Further, a sequence of Endo/Exo will suffice, since they can code Mito/Mate.

Global = Bitonal

- Th 2: Global Transformations = Bitonal Transformations.
  - Any bitonal transformation can be expressed as a finite sequence of Endo, Exo, Froth, Fizz, and deformations (because every bitonal reaction can be expressed as local transformations, and those as global ones).
  - Any sequence is of global transformations is bitonal (because each step can be implemented by either switch, froth, fizz, or deformations, which are all bitonal).

Bitonal Calculus
The Most Trivial Prototype
for Membrane Calculi

Bitonal Calculus

Systems

$X ::= \diamond \mid X \circ X \mid \llparenthesis X \rrparenthesis$ — membrane

This algebra is a minimal "subset" of more sophisticated process calculi for membranes that one may devise.

Axioms

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

F/F: $\diamond \leftrightarrows \llparenthesis \diamond \rrparenthesis$

E/E: $X \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ Y \rrparenthesis$

Facts

M/M:

$\llparenthesis X \rrparenthesis \circ \llparenthesis X' \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis \circ X' \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis \diamond \circ \llparenthesis X \rrparenthesis \rrparenthesis \circ X' \rrparenthesis$ (without using commutativity)

$\leftrightarrows \llparenthesis \llparenthesis \diamond \rrparenthesis \circ X \circ X' \rrparenthesis \leftrightarrows \diamond \circ \llparenthesis X \circ X' \rrparenthesis \leftrightarrows \llparenthesis X \circ X' \rrparenthesis$

P/P:

$X \leftrightarrows X \circ \diamond \leftrightarrows X \circ \llparenthesis \diamond \rrparenthesis$

$\leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ \diamond \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis$

Define a simple "type system" that colors brackets and operators with alternating tones.

$\diamond \leftrightarrows \llparenthesis \blacklozenge \rrparenthesis$

$X \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \boldsymbol{\llparenthesis} X \boldsymbol{\rrparenthesis} \bullet Y \rrparenthesis$

Subject reduction theorem. Bitonal coloring is preserve by reductions.

Alternative axiomatization: take M/M and P/P as axioms and derive F/F and E/E as theorems:

F/F: $\llparenthesis \diamond \rrparenthesis \leftrightarrows \diamond \circ \llparenthesis \diamond \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis \diamond \rrparenthesis \circ \diamond \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis \diamond \rrparenthesis \rrparenthesis \leftrightarrows \diamond$

E/E: $X \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ Y \rrparenthesis$

Atonal Calculus

Systems

$X ::= \diamond \mid X \circ X \mid \llparenthesis X \rrparenthesis$

membrane

Axioms

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

F/F: $\diamond \leftrightarrows \llparenthesis \diamond \rrparenthesis$

I/O: $X \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis X \circ Y \rrparenthesis$

violates bitonality

Facts

Atonal emulates bitonal (obviously):

$$X \circ \llparenthesis Y \rrparenthesis \leftrightarrows X \circ \diamond \circ \llparenthesis Y \rrparenthesis \leftrightarrows X \circ \llparenthesis \diamond \rrparenthesis \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis X \circ \diamond \rrparenthesis \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis X \rrparenthesis \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ Y \rrparenthesis$$

Bitonal emulates atonal, based on this translation:

$$\diamond^* = \diamond$$
$$(X \circ Y)^* = X^* \circ Y^*$$
$$\llparenthesis X \rrparenthesis^* = \llparenthesis \llparenthesis X^* \rrparenthesis \rrparenthesis$$ "double walling"

Summary

- Bitonal Membrane Systems
  - Algebraically capturing the notion that cytosol/exosol do not "usually" mix during membrane transformations.
  - Characterization theorem: membrane reactions are locally implementable (switch) iff globally implementable (endo/exo) iff topologically gradual (bitonal).

- Bitonal Calculus
  - A minimalist membrane calculus.
  - Bitonal can emulate atonal.