The best material model of a cat is another, or preferably the same, cat. A Rosenbleuth.

Artificial Biochemistry

Bitonal Membrane Systems

Luca Cardelli

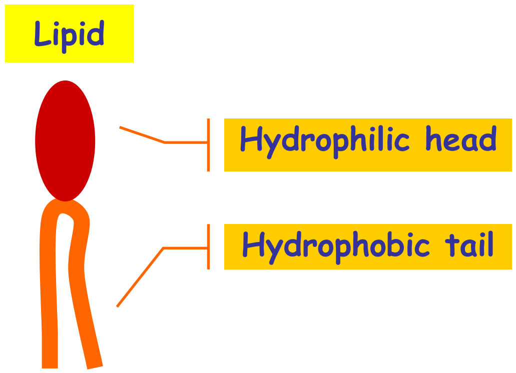
Microsoft Research

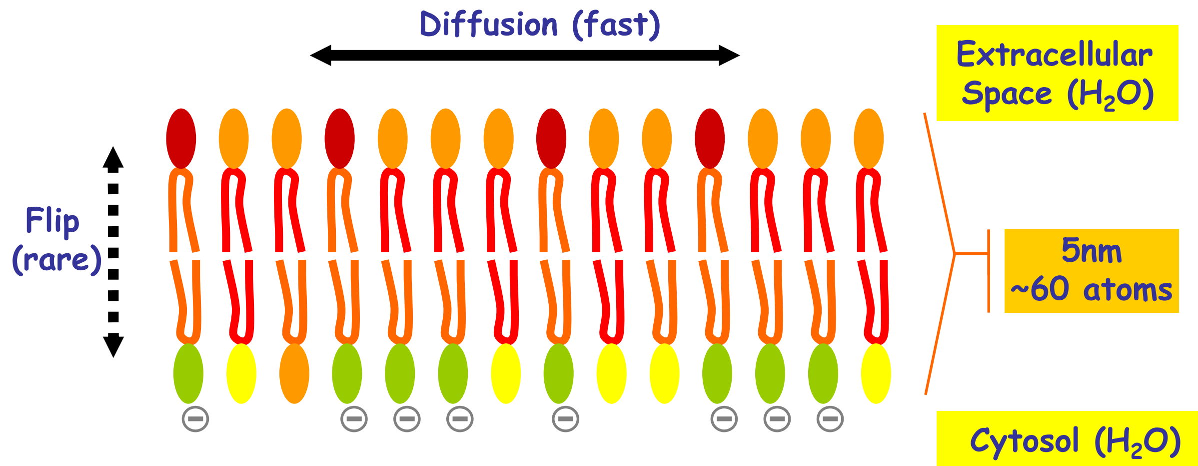
The Microsoft Research - University of Trento
Centre for Computational and Systems Biology

Trento, 2006-05-22..26

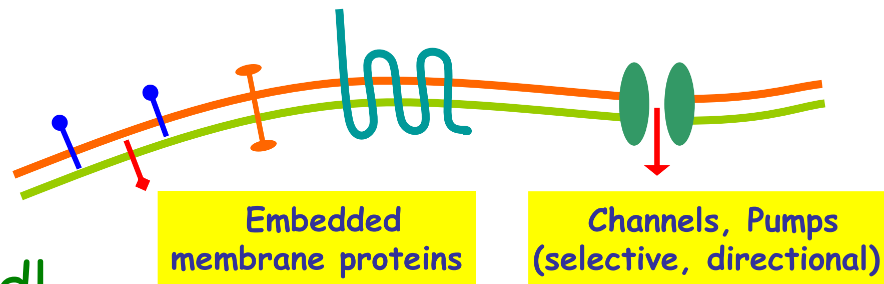
www.luca.demon.co.uk/ArtificialBiochemistry.htm

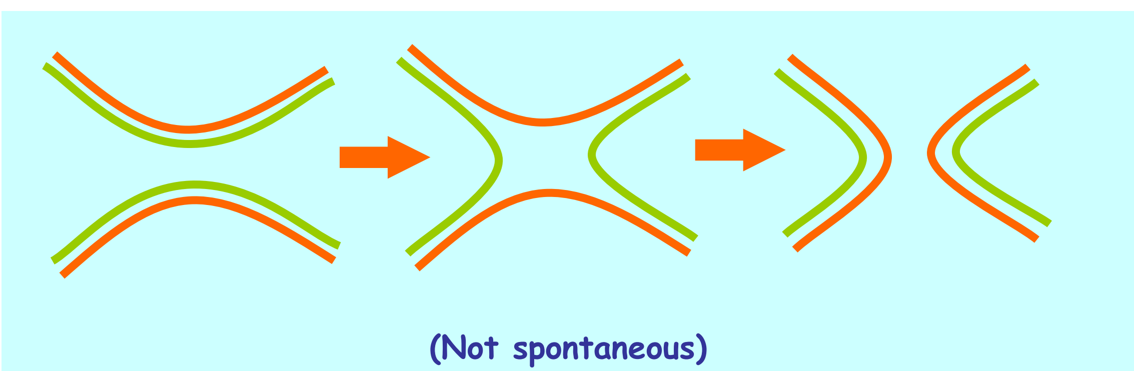
Membranes are Oriented 2D Surfaces

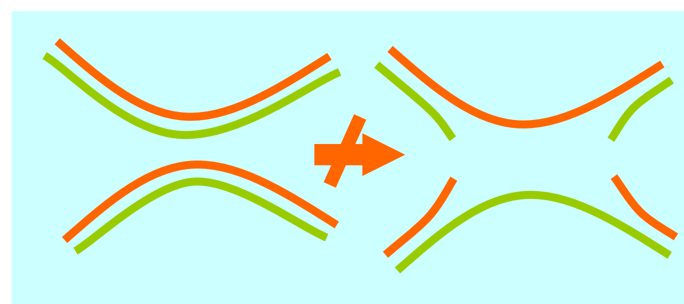




Lipid Bilayer
Self-assembling
Largely impermeable
Asymmetrical (in real cells)
With embedded proteins
A 2D fluid inside a 3D fluid!

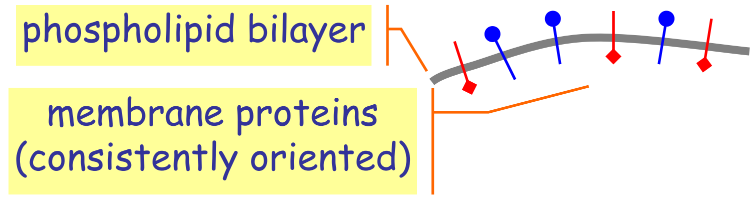




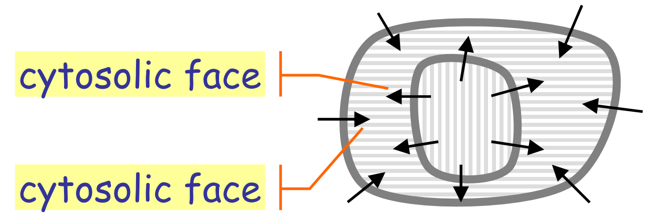


Systems of Oriented Membranes

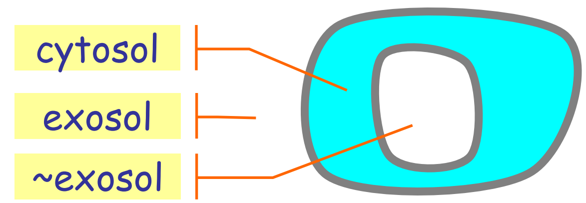
Membranes are closed non-intersecting curves, with an orientation[1].



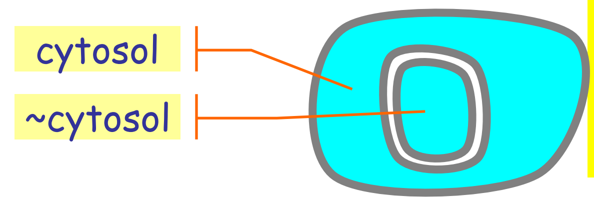
Each membrane has two faces. A cytosolic (~*inner*) face and an exoplasmic (~*outer*) face.
Nested membranes alternate orientation.
(E.g. cytosolic faces always face each other, by definition, or by fusion/fission dynamics)



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



Double membranes (e.g. the nuclear membrane) gives us blue-in-blue components.



Bitonal diagrams

(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.

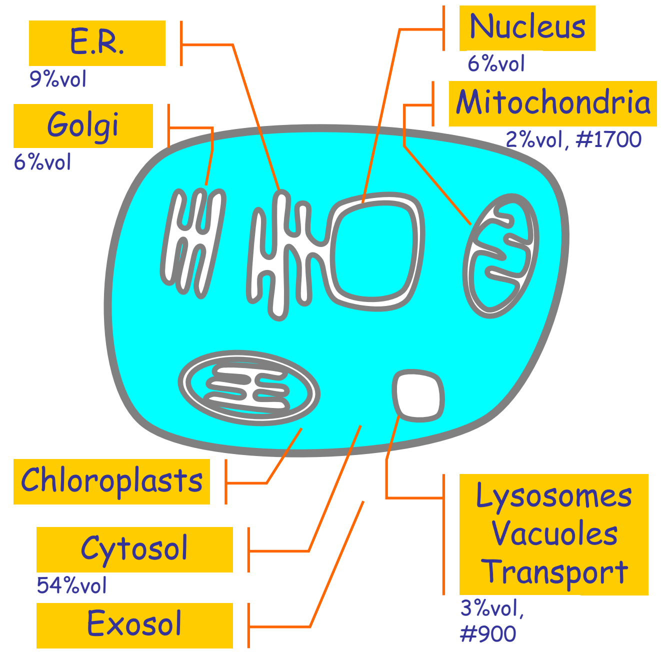
Bitonal Invariant

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

Bitonal Duality

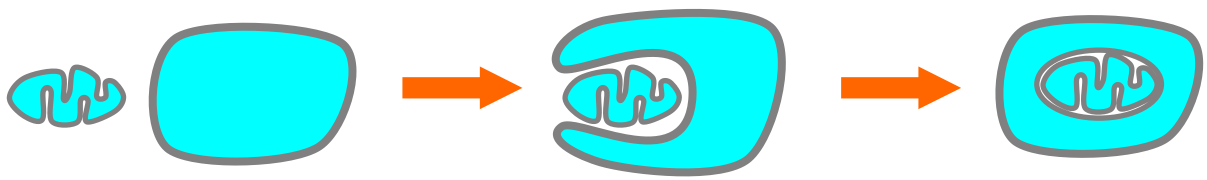
Reactions come in complementary-tone versions.

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

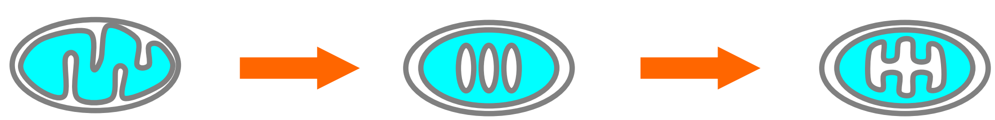


Evolutionary explanations of bitonal structure

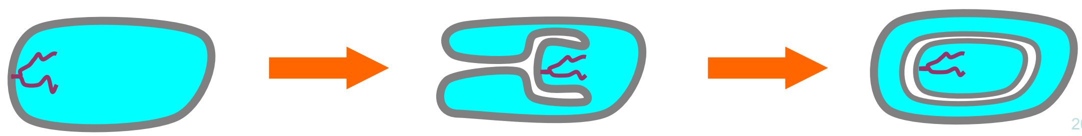
Mitochondria acquisition



Mitochondria to Chloroplasts



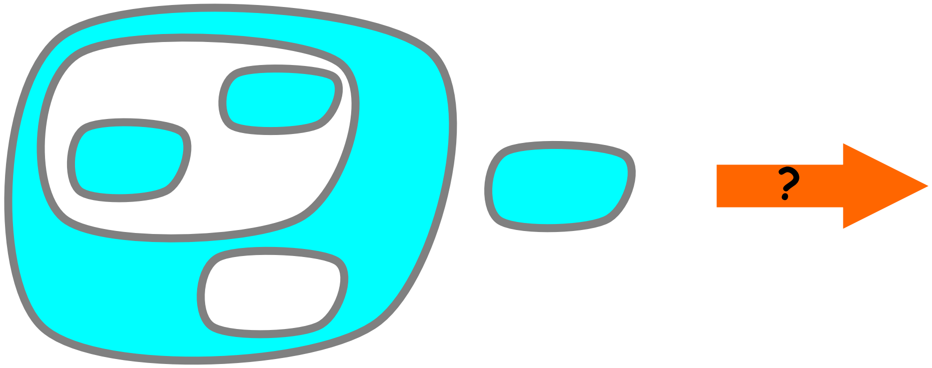
Pre-Eukarya to Eukarya



Gradual Transformations of Membrane Systems

Locally Realizable Reactions

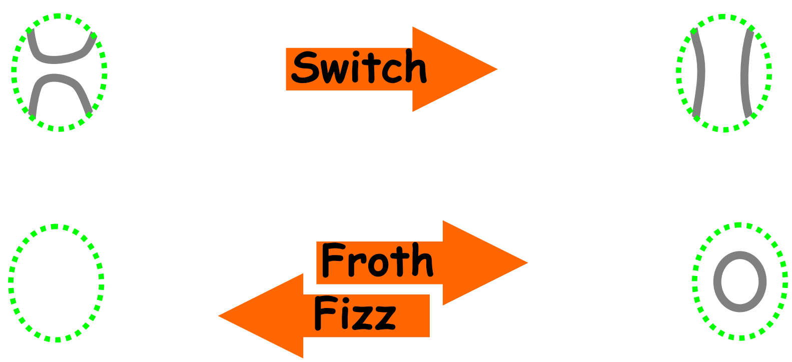
Membrane System



What transformations "make sense"?

Local (Patch) Reactions

Reactions 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 membrane systems (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.)

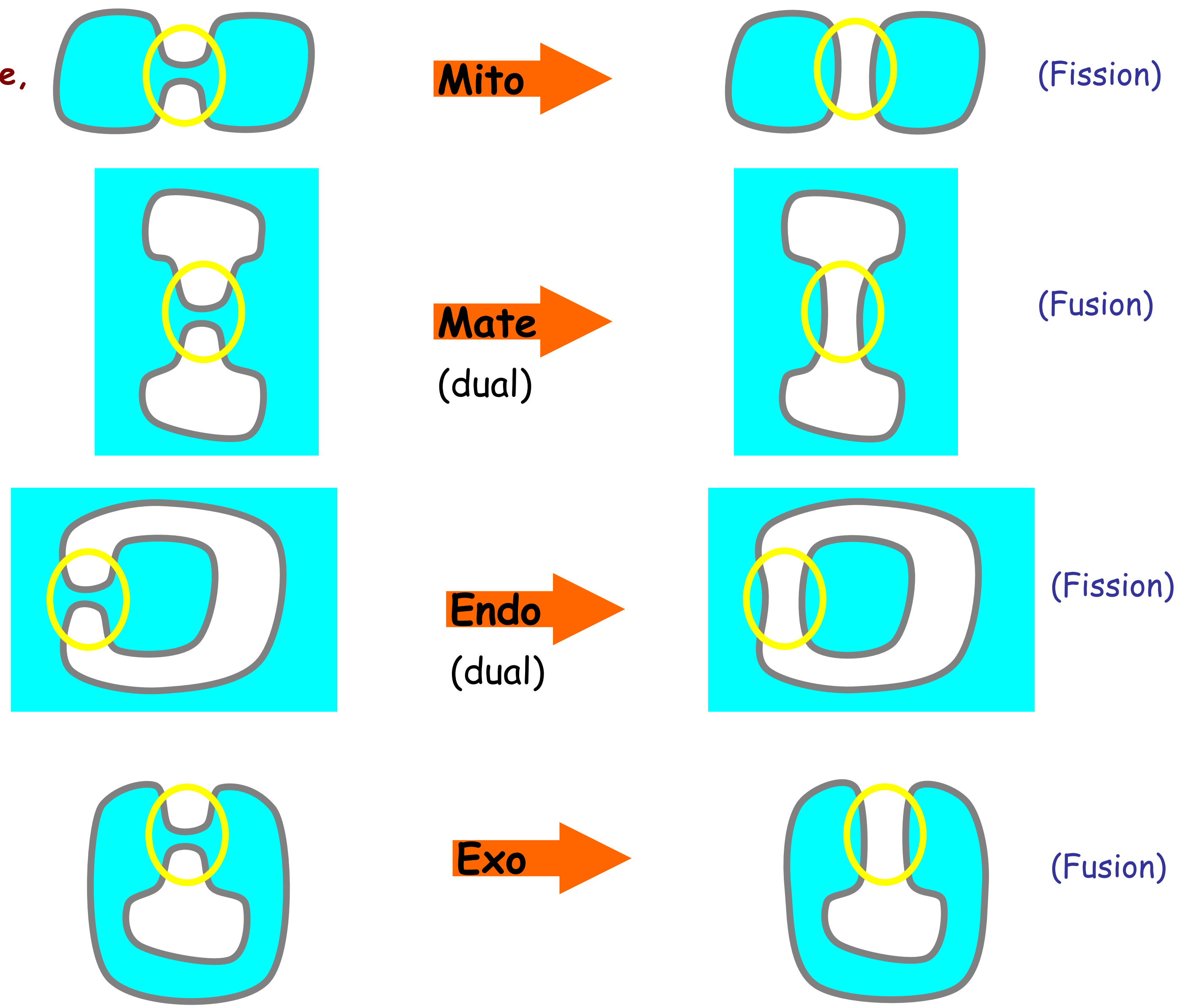
- A specific set of global reactions that are "biologically meaningful"
  (e.g. *mitosis*, *endocytosis*) and hence presumably gradually implemented.

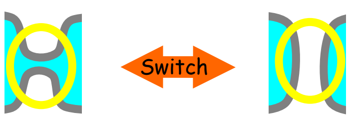
- The gradual transformation of "small areas" of a membrane system
  in ways that do not "mix fluids" on a large scale.

These turn out to be equivalent!

Those Global Reactions are Local Reactions

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



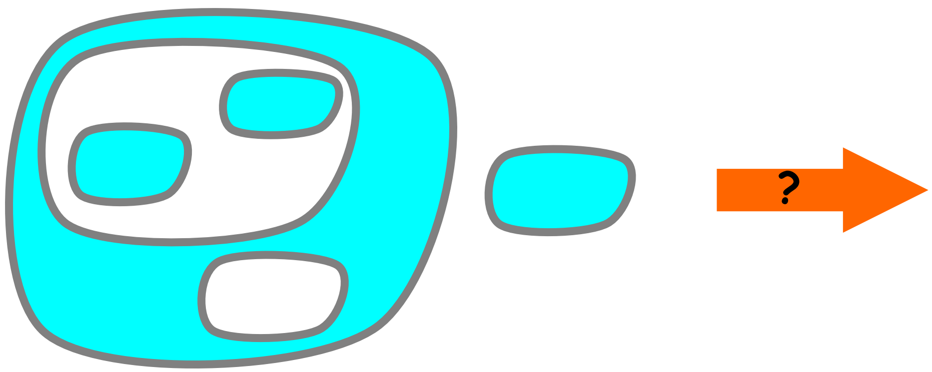


Same Local View!

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 and "well-being".)

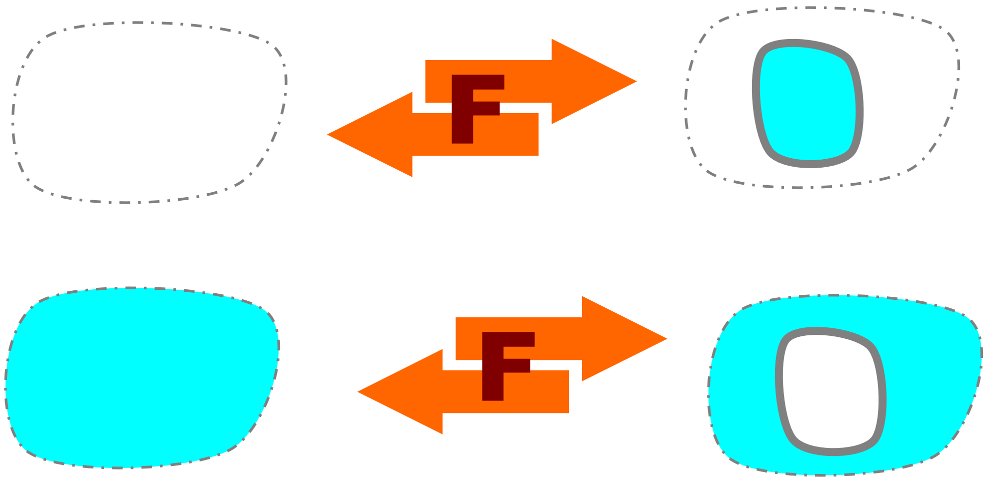


✓ Froth/Fizz Reaction

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

White expanse

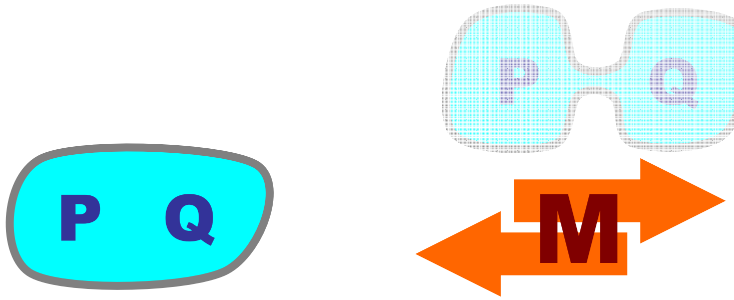
Blue expanse



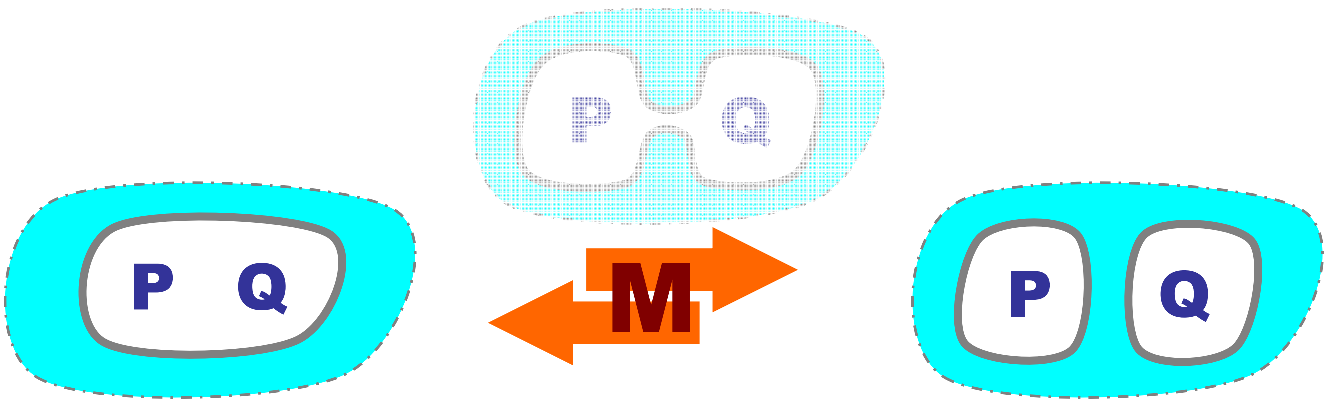
* Phospholipid molecules automatically assemble into closed membranes.

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.

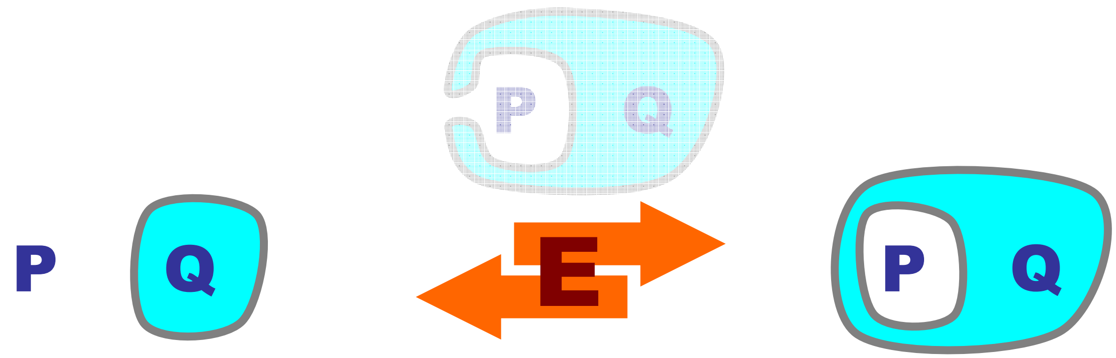
✓ Mito/Mate Reaction



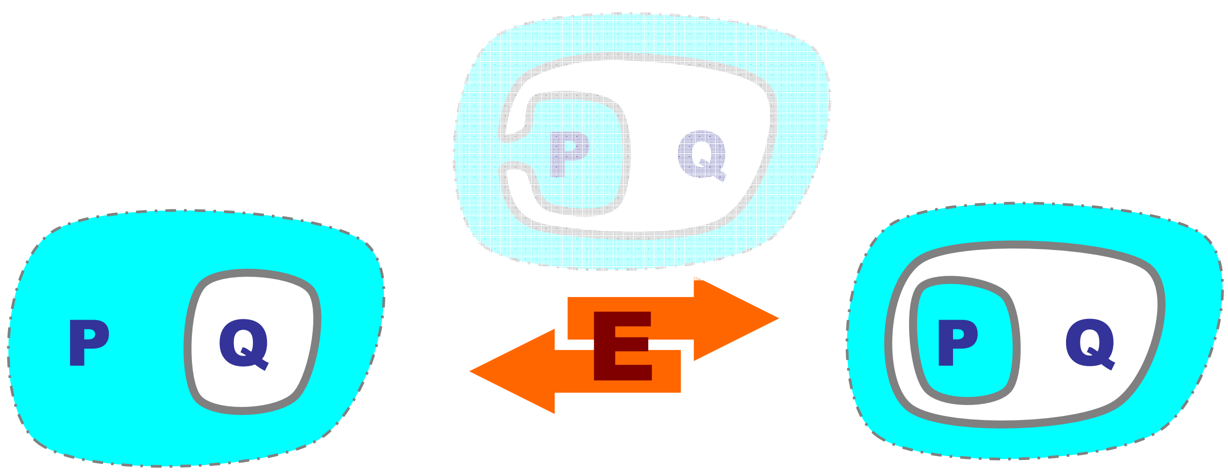
Dual:



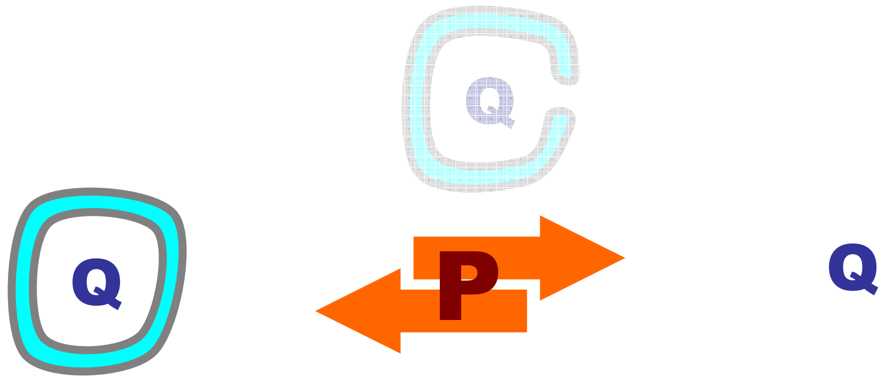
✓ Endo/Exo Reaction



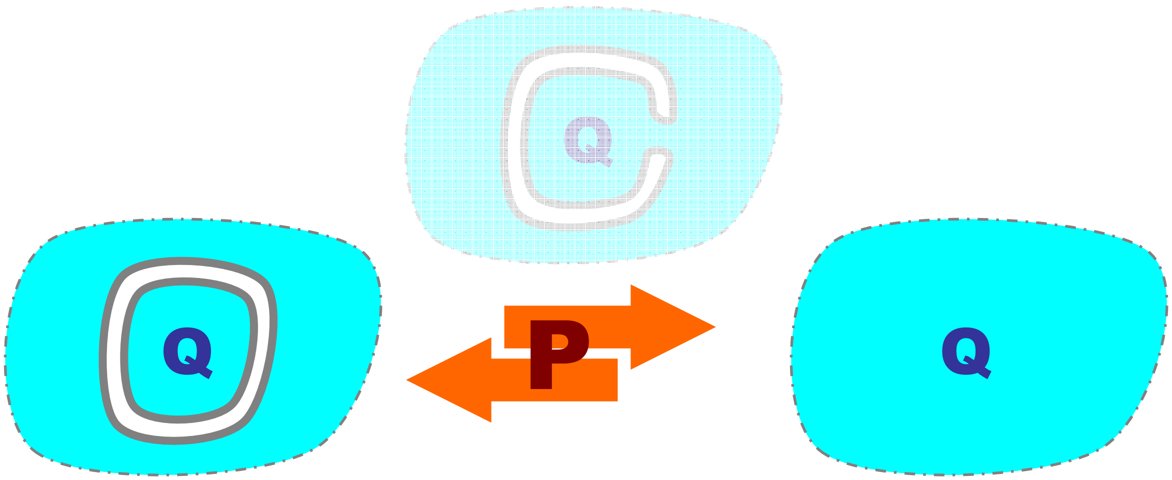
Dual:



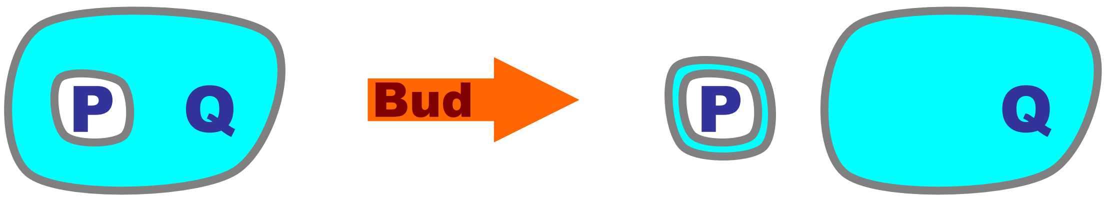
✓ Peel/Pad Reaction



Dual:

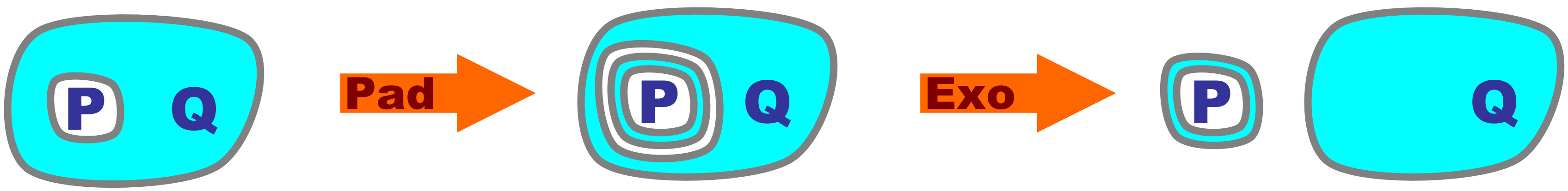


✓ Bud Reaction



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

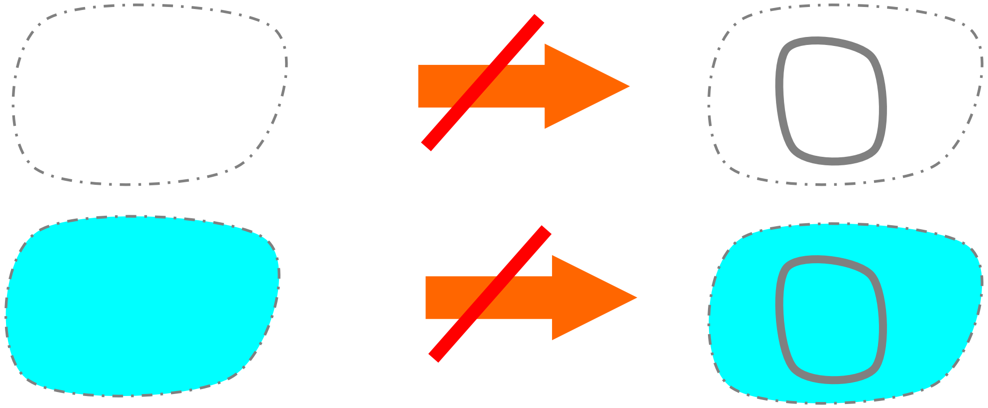
Can also be seen as Pad + Exo:



✘ Bad Bubbles

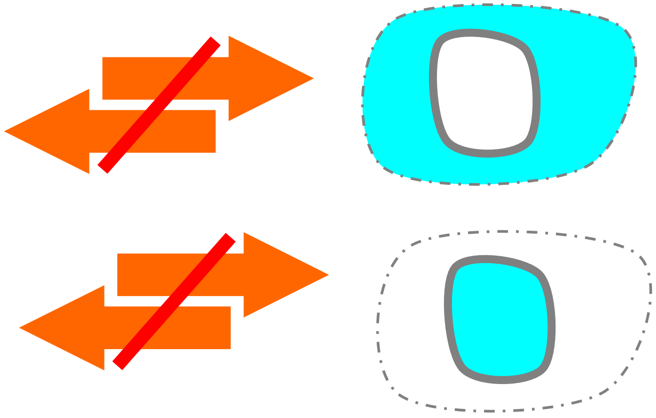
Violates bitonality.

Wrong bubbles:



Bubble catastrophe:

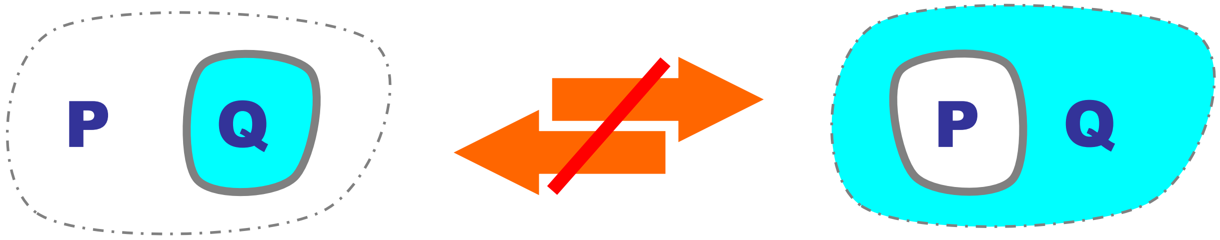
Violates bitonality in context.
Also, ill-toned reaction arrow.



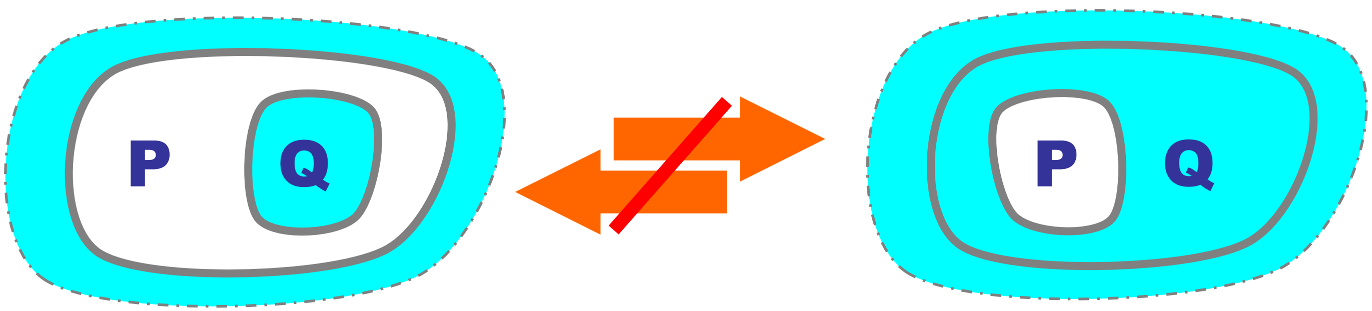
× Flooding

Flooding

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

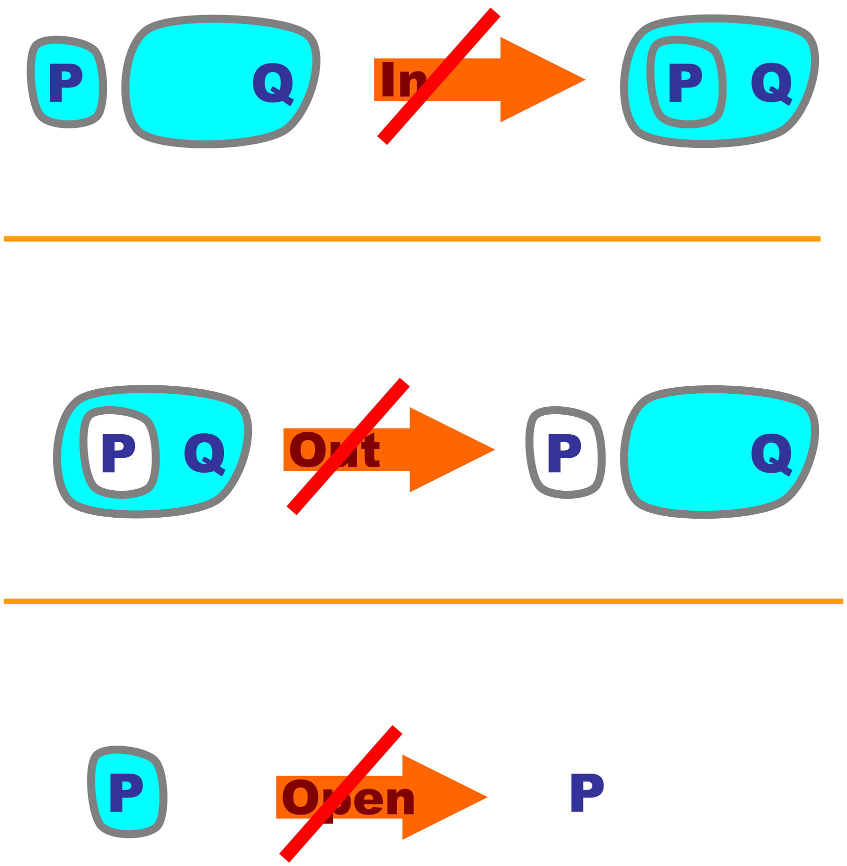


Flooding in context violates bitonality:

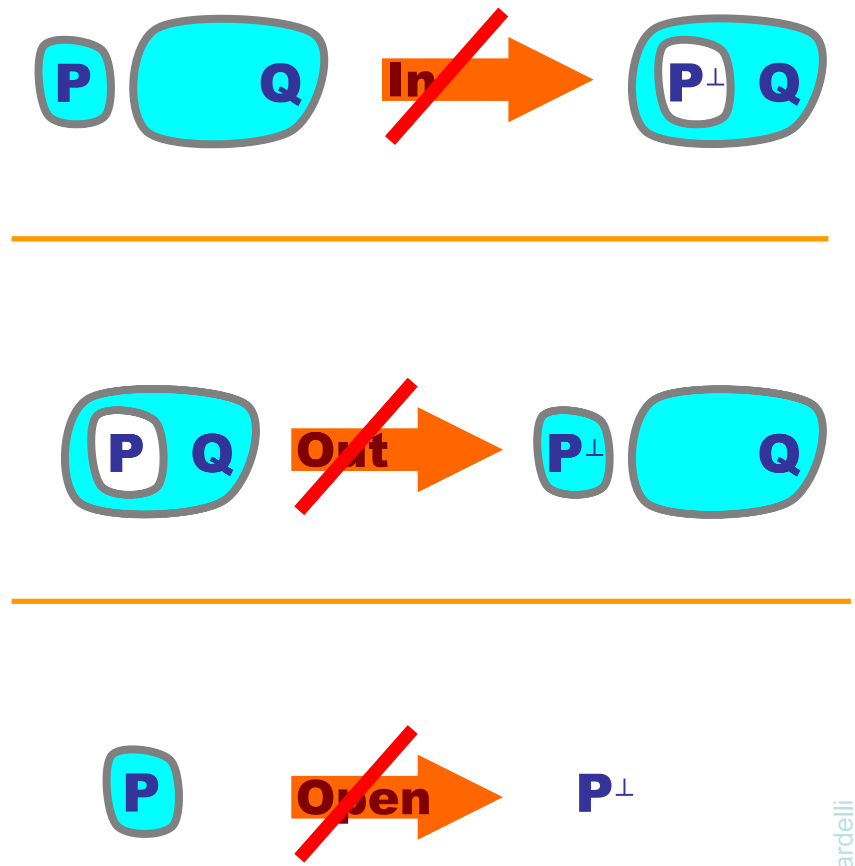


× Ambients

Violate bitonality



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



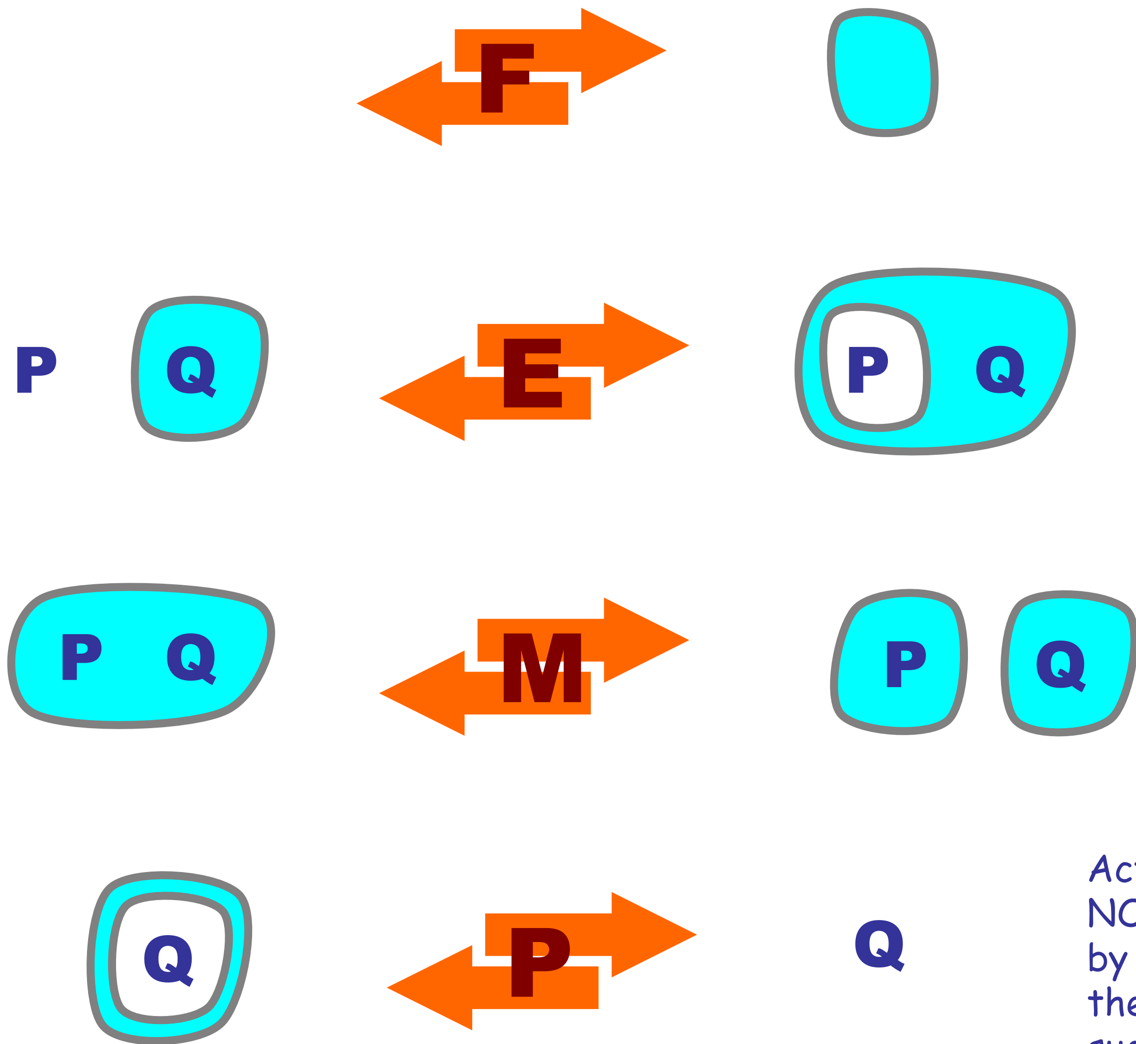
Summary: At Least Four Good Reactions

Froth/Fizz

Endo/Exo

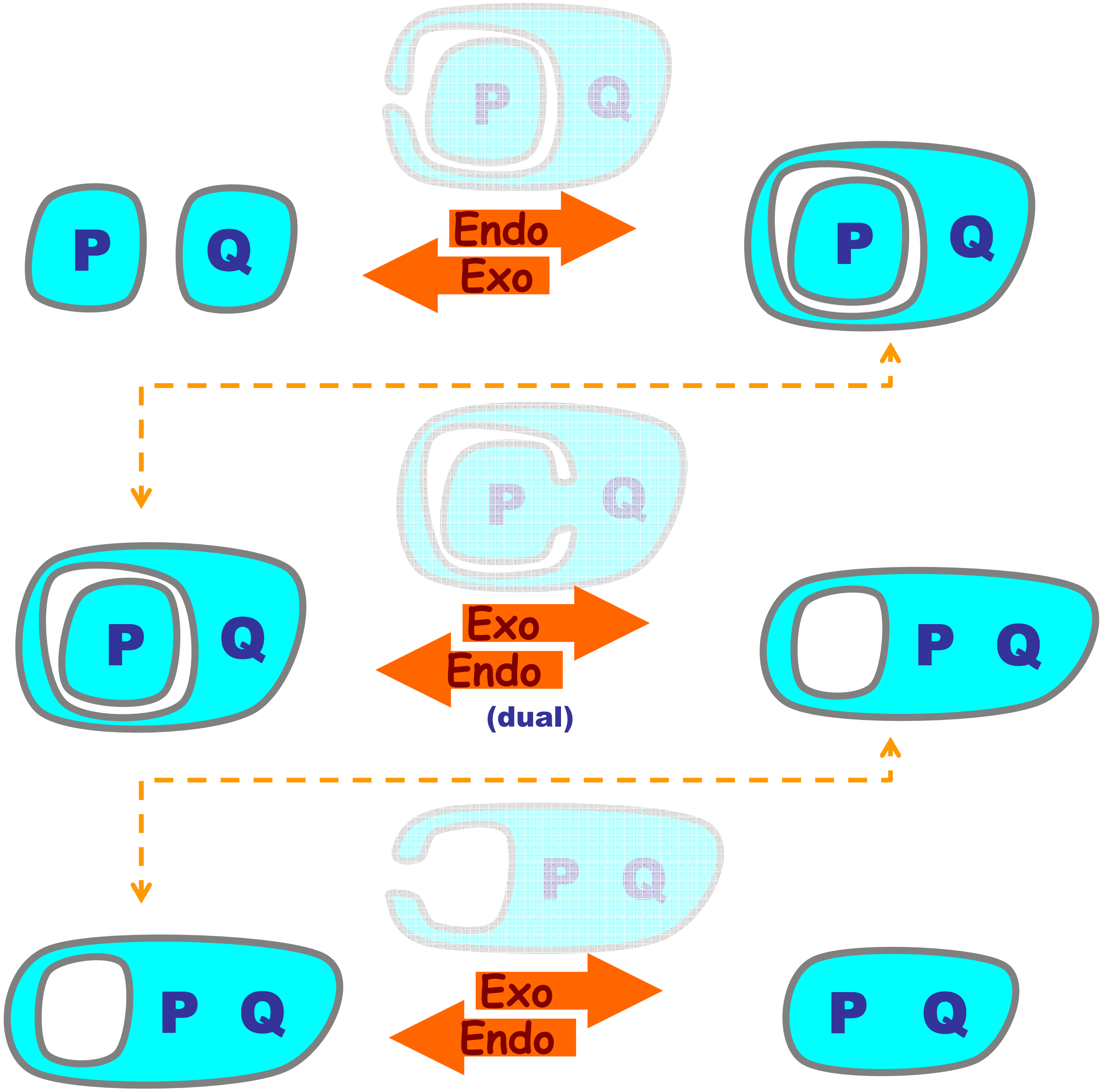
Mito/Mate

Peel/Pad

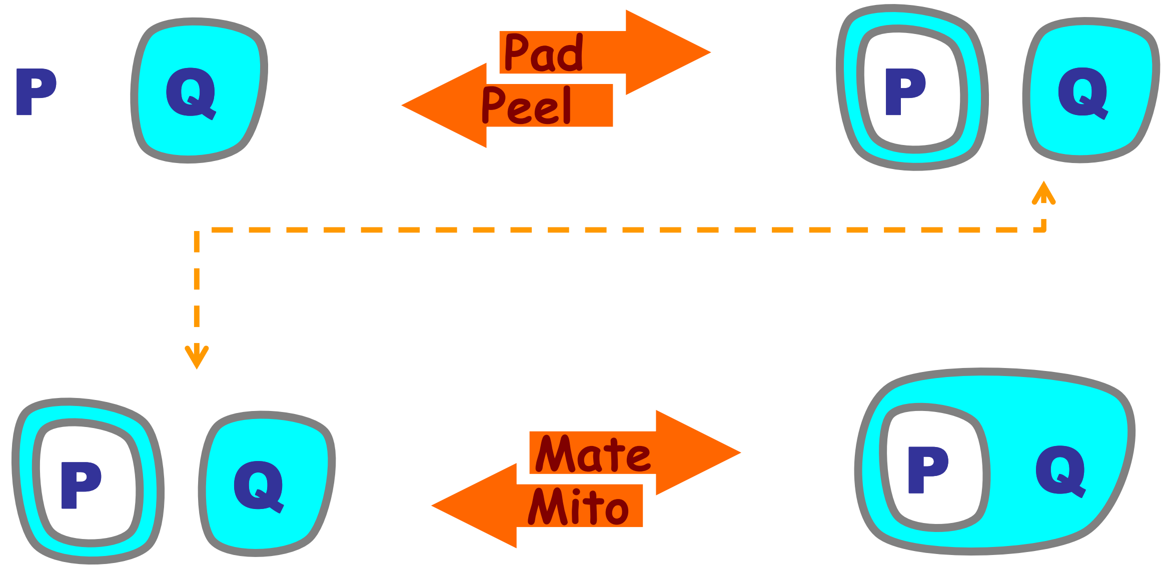


Actually, Peel/Pad is NOT a bitonal *reaction* by my definition, but is the composition of two such. Good enough.

Mito/Mate by 3 Endo/Exo

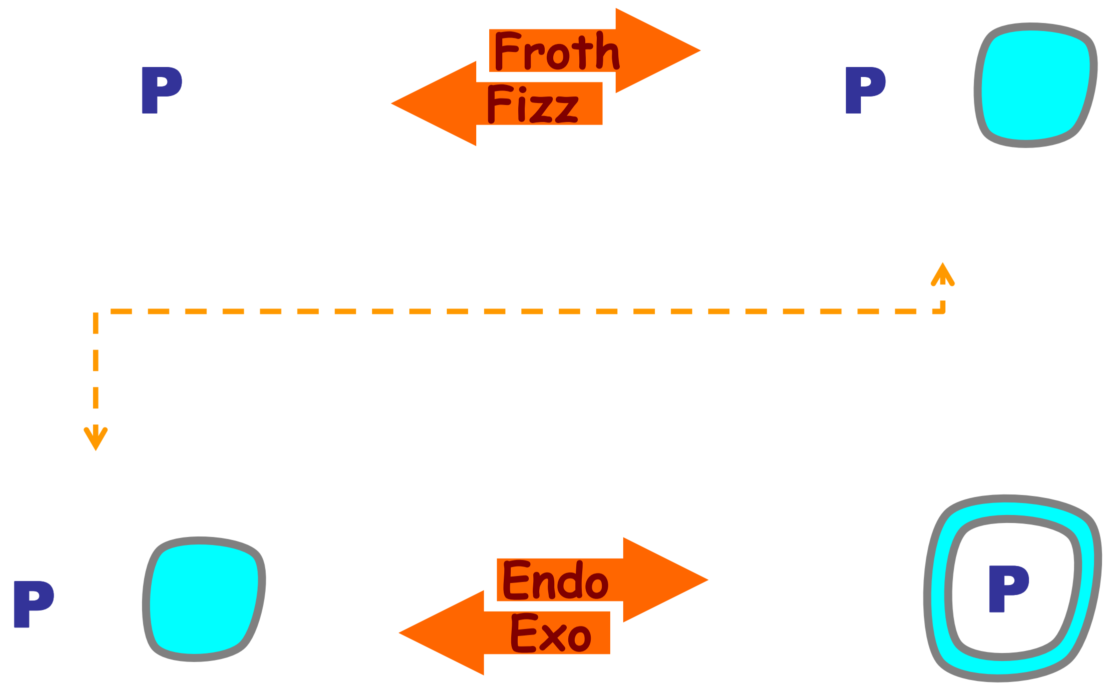


Endo/Exo by Mito/Mate and Peel/Pad

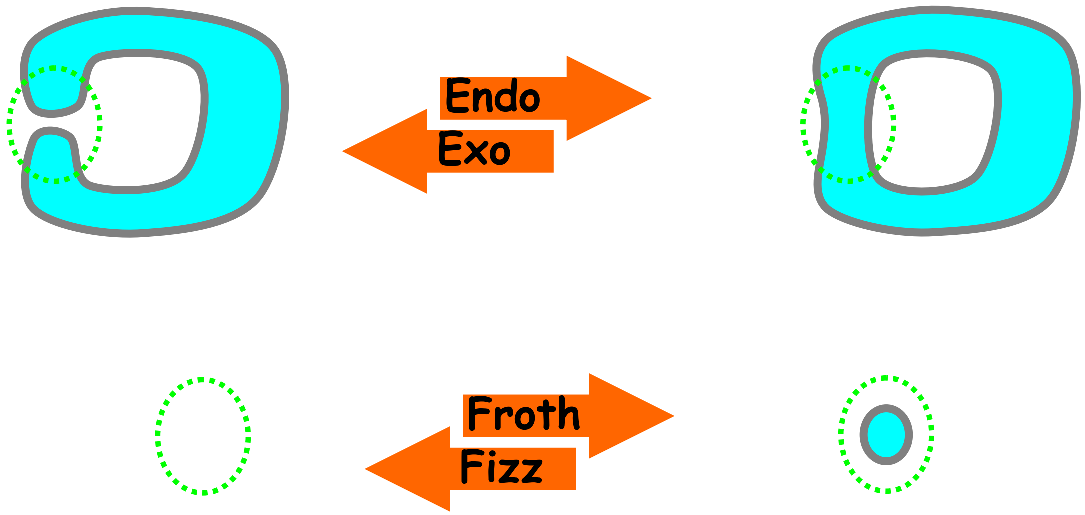


Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.

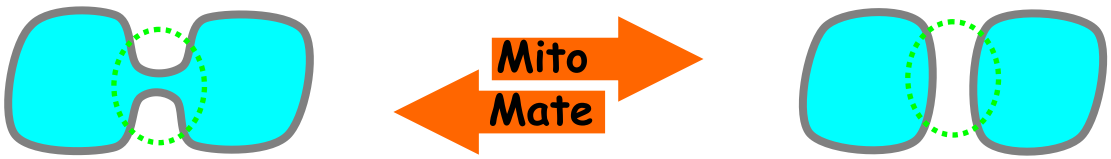
Peel/Pad by Froth/Fizz and Endo/Exo



An (Turing) Complete Set of Reactions

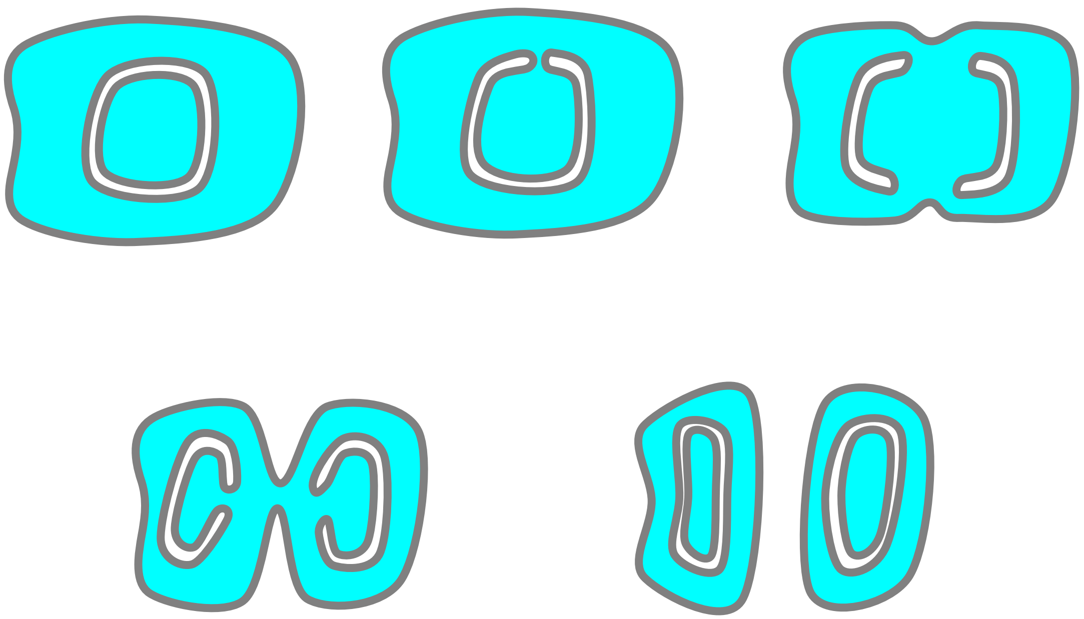


Others bitonal reactions are Derivable, e.g.:



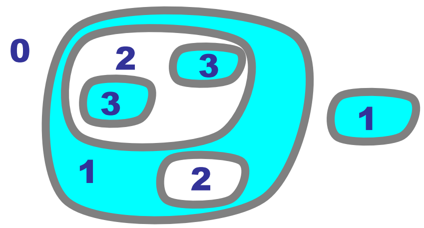
Are *all* other derivable? YES!

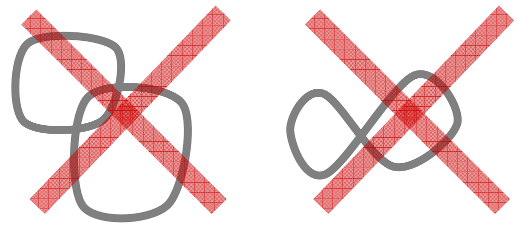
Ex: Eukaryotic Mitosis



Bitonal Transformations: Topological View

Depth and Tonality

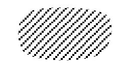


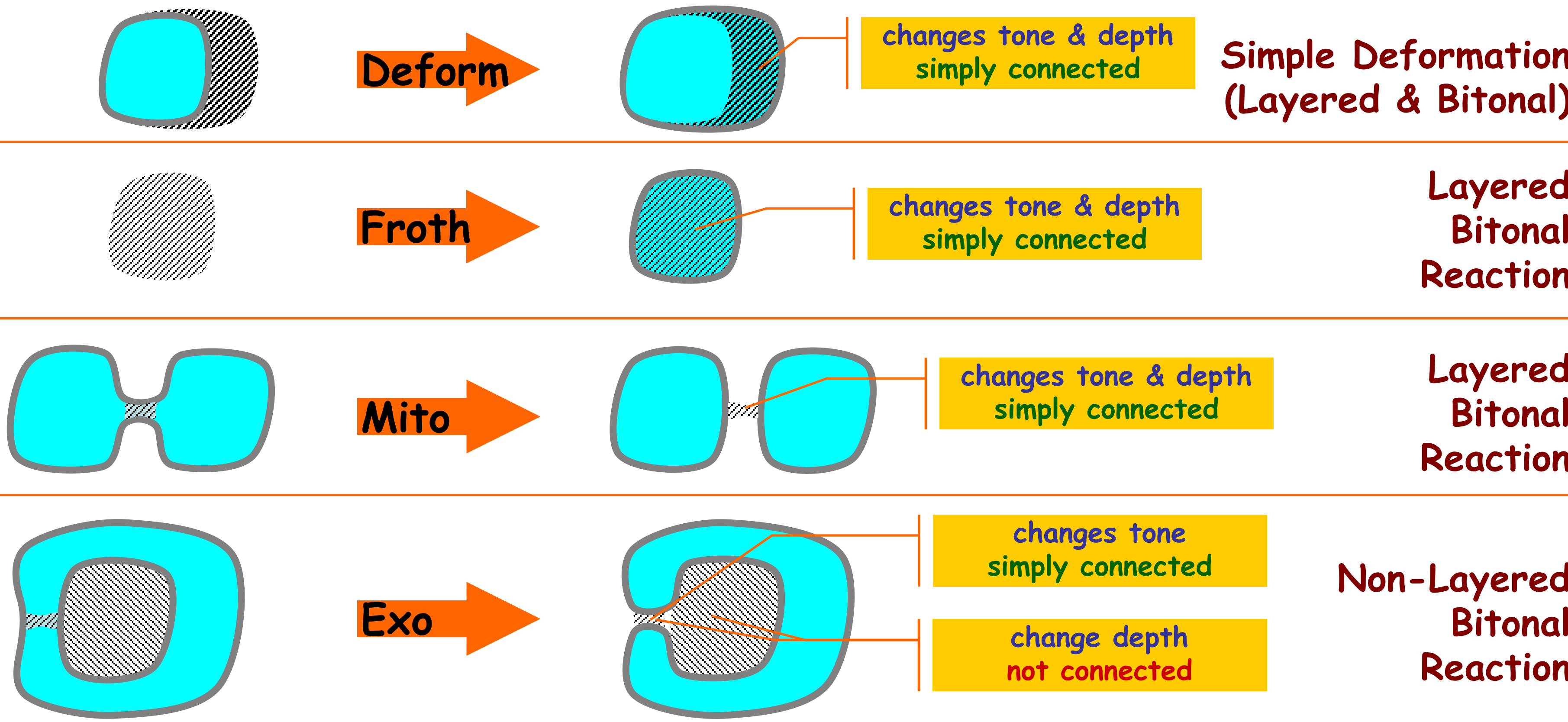


The *depth* of a point is the number of membranes that contain it.
The *tonality* of a point is white/blue iff its depth is even/odd.

Def: Bitonal Reactions

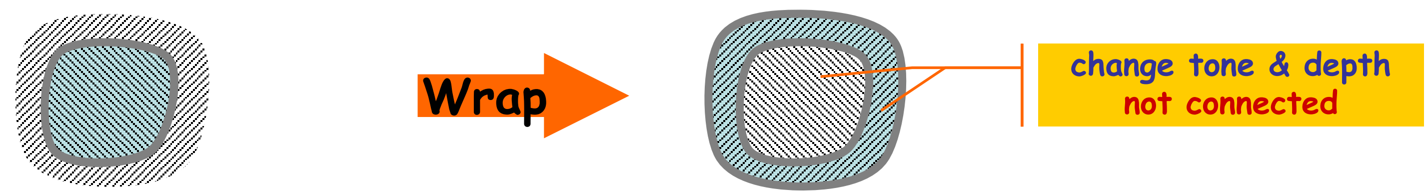
A *bitonal (resp. layered) reaction* is a pair of membrane systems ‹M,M'› such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes). (Layered ⇒ Bitonal)

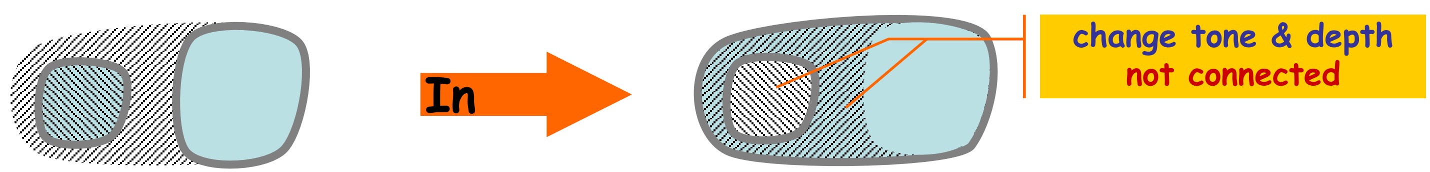


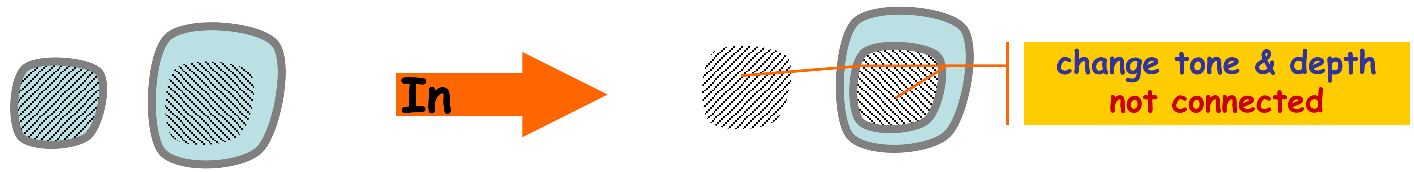


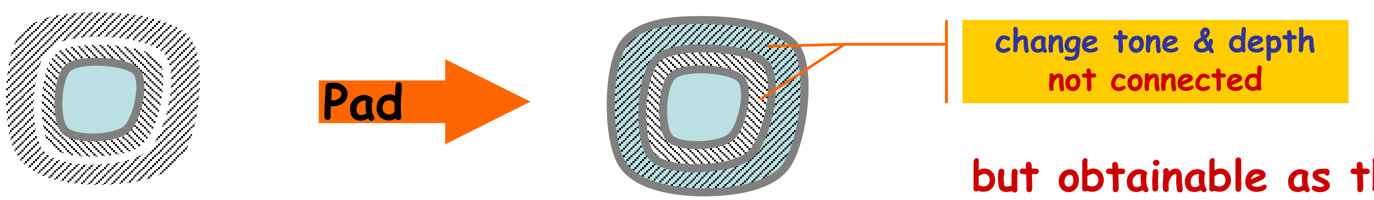
Non-Bitonal Reactions

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).





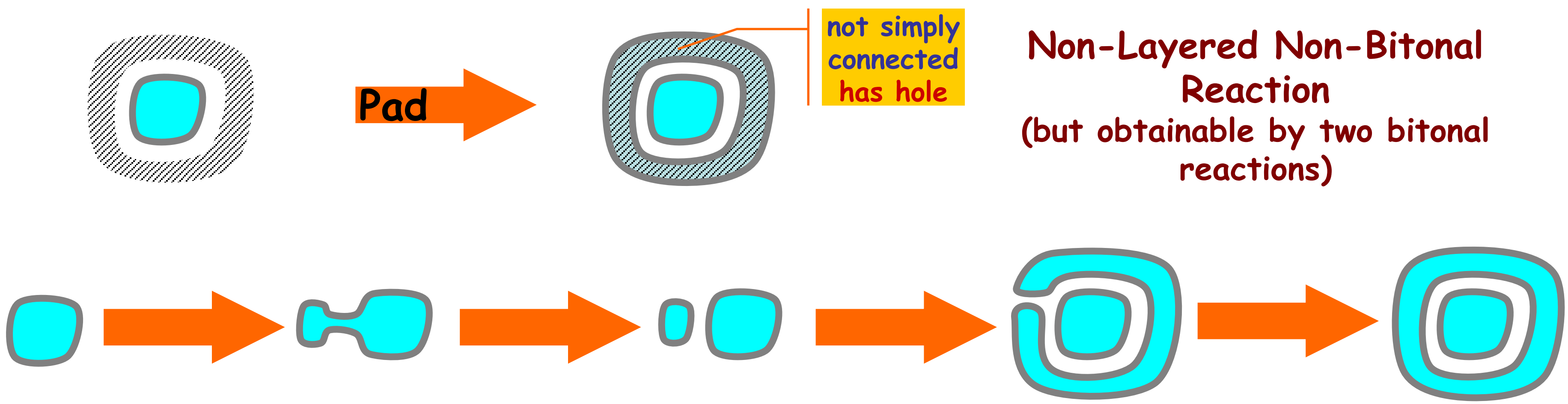




but obtainable as the composition of two bitonal reactions (Froth+Endo)

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:

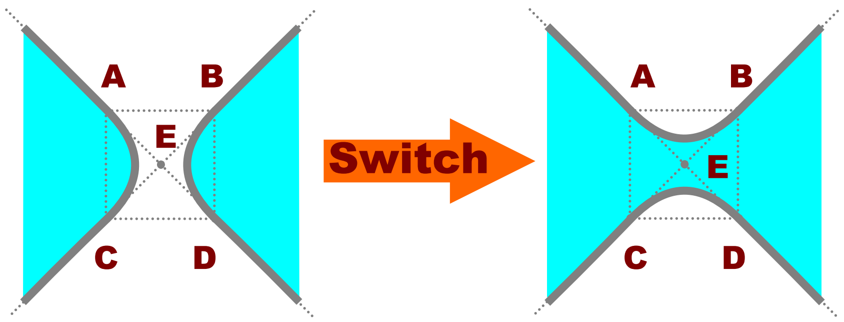


- Some transformations are inherently non-bitonal.

Characterization

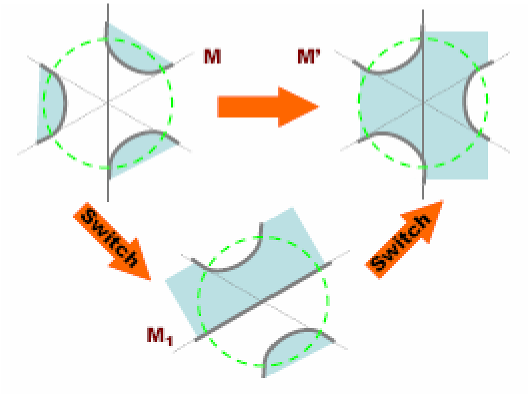
- Soundness and Completeness Theorem
  - A transformation of membrane systems:
    - **is locally realizable**
      (realizable by a sequence of switch + froth/fizz)
    - **iff it is bitonal**
      (changes tone of at most a simply-connected region at a time)
    - **iff it is fusion/fission-realizable**
      (realizable by a sequence of endo/exo + froth/fizz)

- Proof Sketch
  1. All local reactions are bitonal reaction. E.g., Switch:
     - By cases on the external connectivity of A,B,C,D.



2. All bitonal reactions can be obtained by sequences of local reactions (switch/froth/fizz) and deformations.

   - By analysis of the simply connected regions that change tonality, and induction on the number of membranes that cross such a region.



3. Endo/Exo and Mito/Mate are bitonal reactions.

   - They can all be locally implemented by Switch, which is bitonal.

4. Any instance of Switch is an instance of either Endo, Exo, Mito, or Mate, plus deformations.

   - By cases on A,B,C,D connectivity around Switch.

5. Mito/Mate can be encoded by Endo/Exo.

- Therefore, any bitonal transformation can be written as a sequence of local reactions, and hence as a sequence of Endo/Exo/Froth/Fizz plus deformations. Conversely, and such sequence is a bitonal transformation.

Bitonal Calculus
A Prototype for Membrane Calculi

Bitonal Calculus

Systems

X ::= ◇ | X∘X | ⦇X⦈ — membrane

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

Axioms

◇ ∘ is a comm. monoid

F/F: ◇ ⇆ ⦇◇⦈

E/E: X∘⦇Y⦈ ⇆ ⦇⦇X⦈∘Y⦈

Facts

M/M: (without using commutativity)

⦇X⦈∘⦇X'⦈ ⇆ ⦇⦇⦇X⦈⦈∘X'⦈ ⇆ ⦇⦇◇∘⦇X⦈⦈∘X'⦈
⇆ ⦇⦇◇⦈∘X∘X'⦈ ⇆ ◇∘⦇X∘X'⦈ ⇆ ⦇X∘X'⦈

P/P:

X ⇆ X∘◇ ⇆ X∘⦇◇⦈
⇆ ⦇⦇X⦈∘◇⦈ ⇆ ⦇⦇X⦈⦈

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

◇ ⇆ ⦇◆⦈

X∘⦇Y⦈ ⇆ ⦇❨X❩•Y⦈

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: ⦇◇⦈ ⇆ ◇∘⦇◇⦈ ⇆ ⦇⦇◇⦈∘◇⦈ ⇆ ⦇⦇◇⦈⦈ ⇆ ◇

E/E: X∘⦇Y⦈ ⇆ ⦇⦇X⦈⦈∘⦇Y⦈ ⇆ ⦇⦇X⦈∘Y⦈

Atonal Calculus

Systems

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

membrane

Axioms

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

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

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

violates bitonality

Facts

Atonal emulates bitonal (obviously):

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

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"

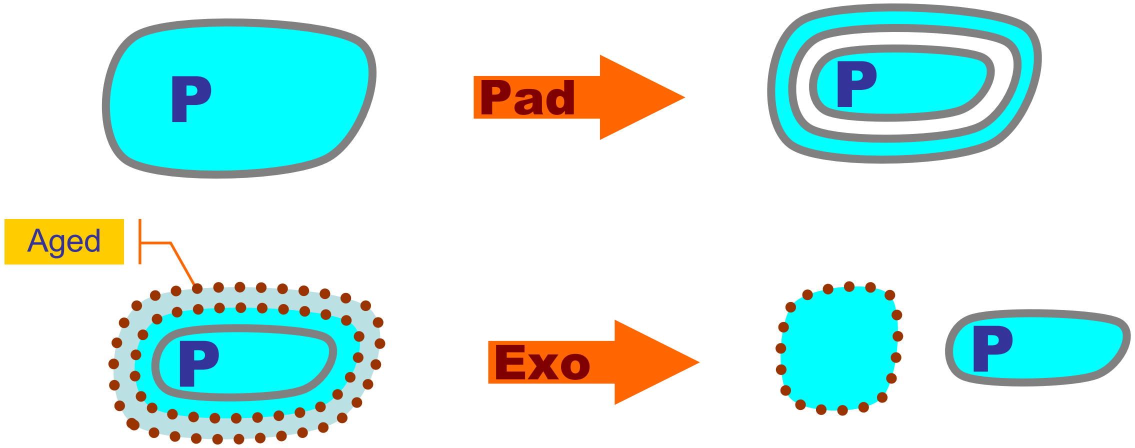
Summary

- 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.

Q?

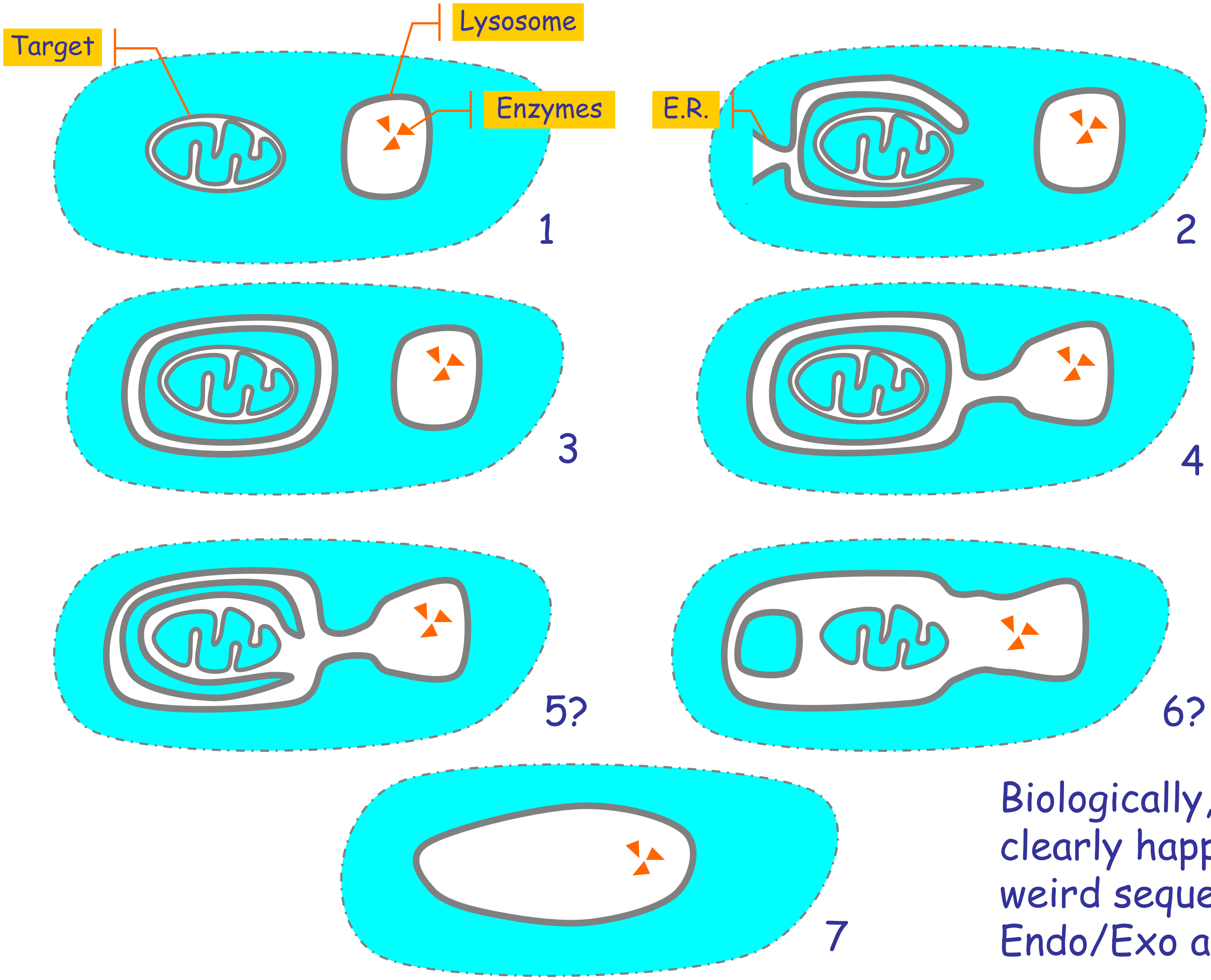
Appendix
More Examples

Ex: Molting



Ex: Autophagic Process

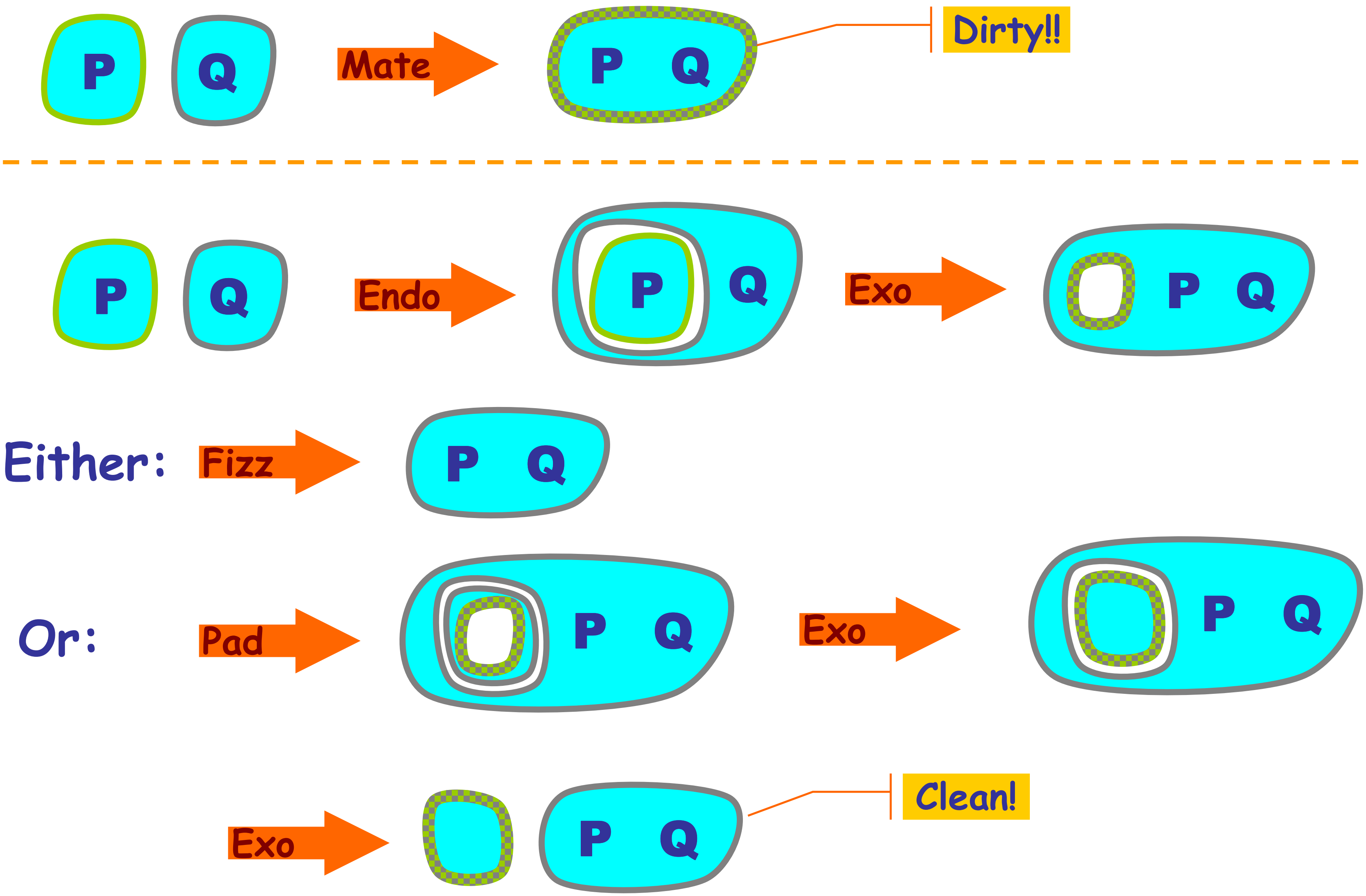
Lysosome and target don't just merge.



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)



Appendix
A Note on Locality

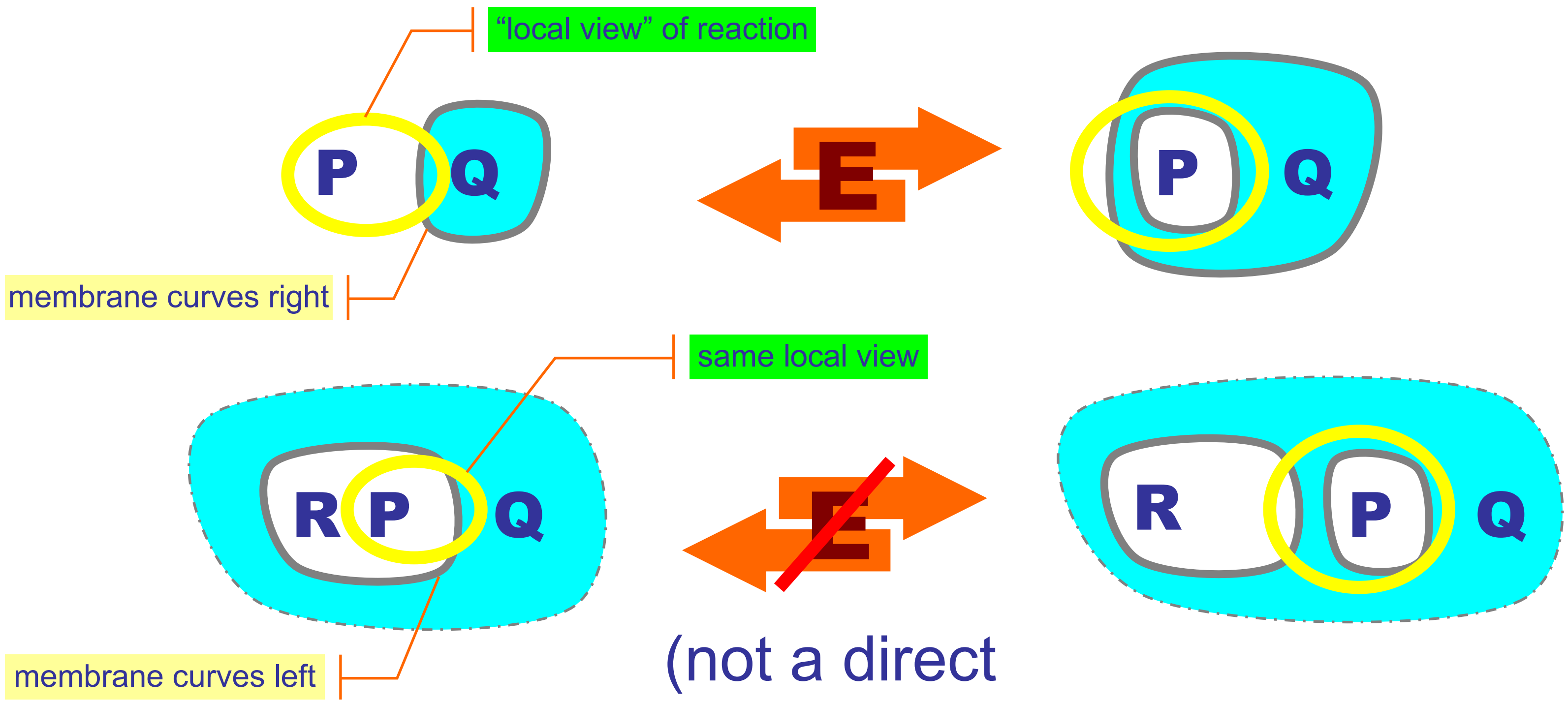
Locality Postulate

Locality Postulate

Interactions should be local to small membrane patches.

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

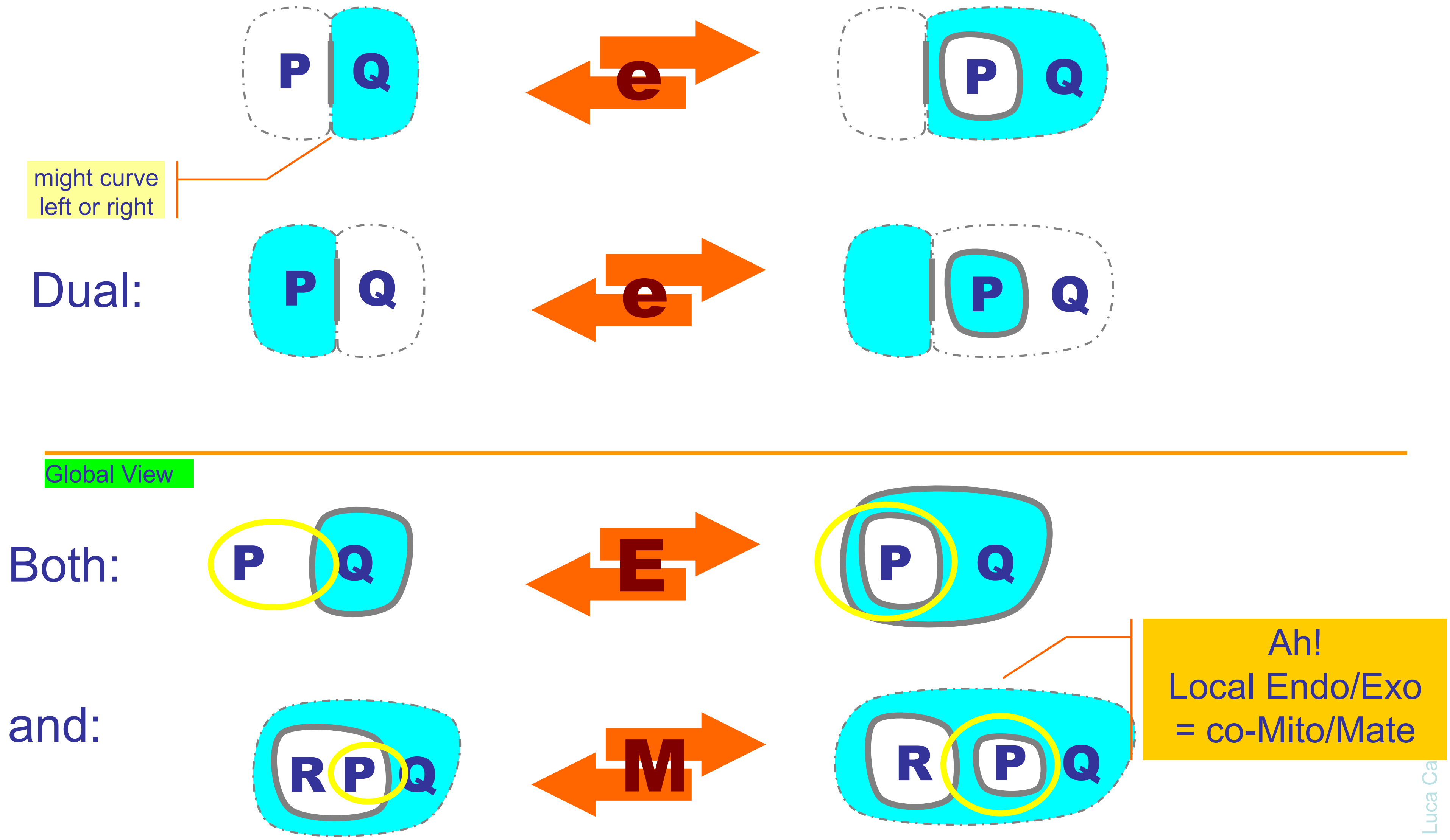
Endo/Exo Violates Locality?



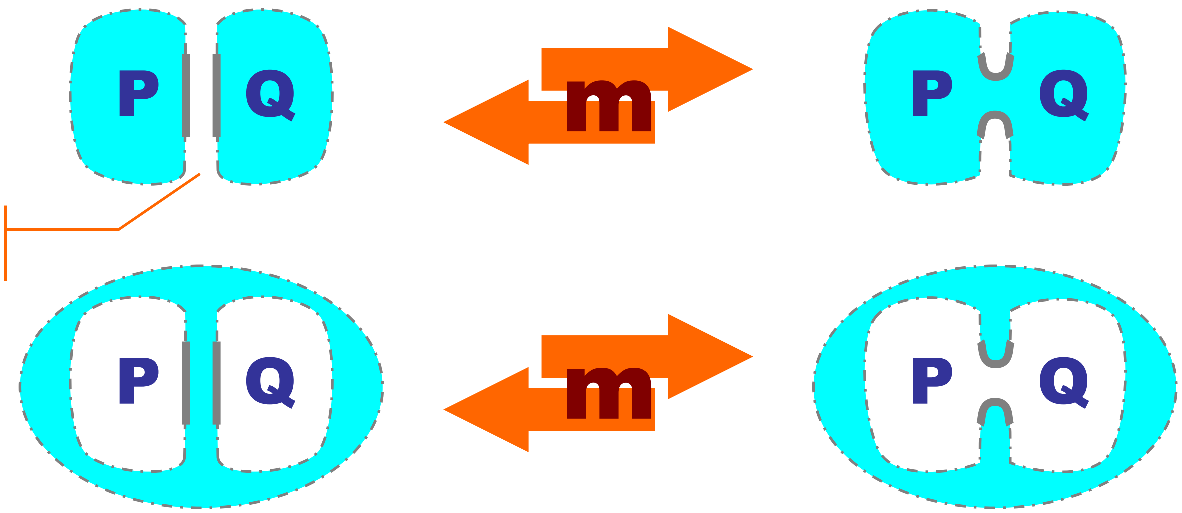
(not a direct instance of endo/exo)

Oops…

✓ Local-view Endo/Exo Reaction



✓ Local-view Mito/Mate Reaction



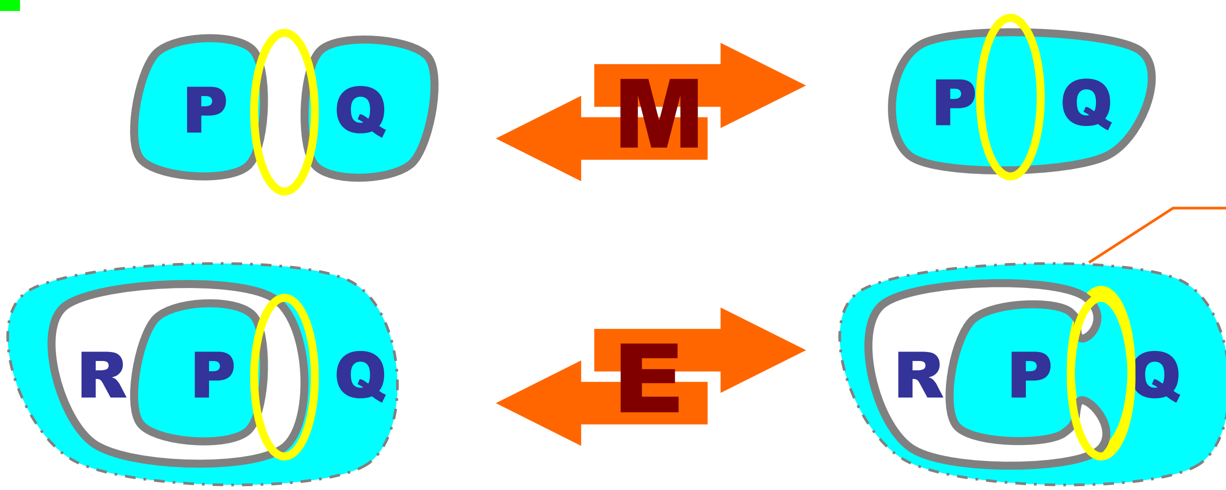
might curve together or apart

Dual:

Global View

Both:

and:



Ah!
Local Mito/Mate
= co-Endo/Exo

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?

Appendix
Molecules as Small Membranes

Molecules as Small Membranes

Mol

$mol_n = mate_n + \circlearrowleft_n$
$Mol_n = mol_n \llparenthesis \diamond \rrparenthesis$

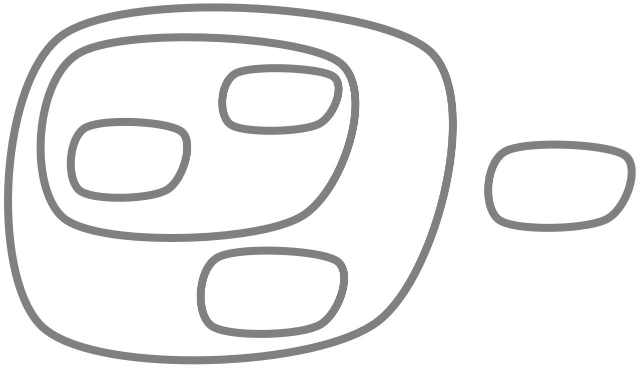
$n(\diamond)\rightrightarrows = mate^{\perp}_n$ $\qquad$ $\rightrightarrows n(\diamond) = drip_n(mol_n)$
$\diamond(n)\rightrightarrows = \circlearrowleft^{\perp}_n$ $\qquad$ $\rightrightarrows\diamond(n) = \circledcirc(mol_n)$

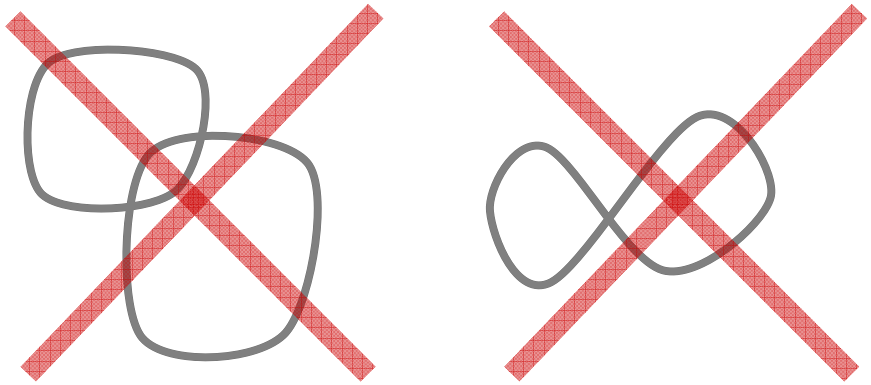
$n(\diamond)\rightrightarrows\diamond(m) = n(\diamond)\rightrightarrows.\rightrightarrows\diamond(m)$ etc.

$$Mol_n \circ n(\diamond)\rightrightarrows.\rightrightarrows\diamond(n).\sigma|\sigma_0\llparenthesis P \rrparenthesis \Rightarrow \sigma|\sigma_0\llparenthesis Mol_n \circ P \rrparenthesis$$

Appendix
Local Membrane Reactions

Membrane Systems

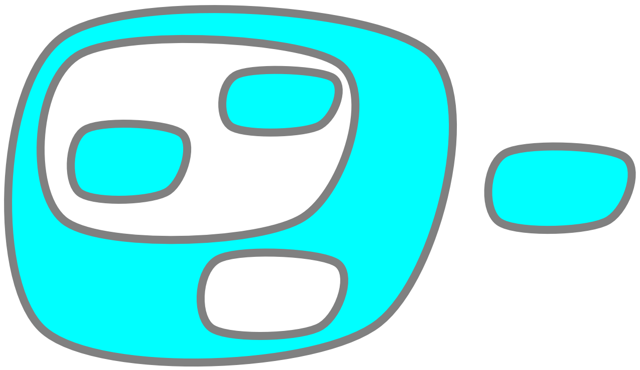


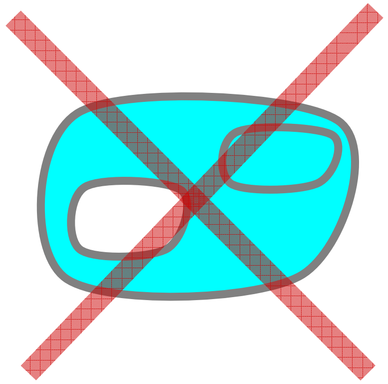


Good Systems
(Closed non-intersecting curves)

Bad Systems

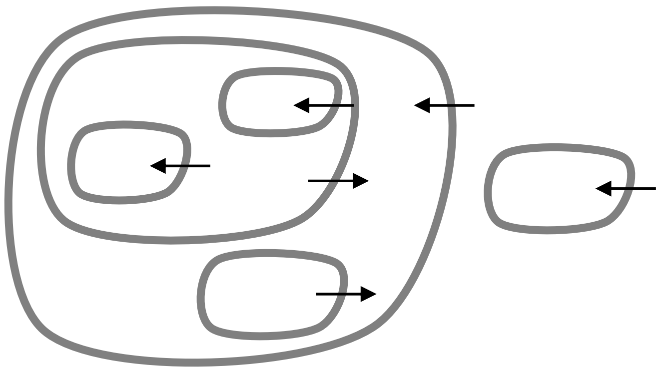
Bitonal Membrane Systems



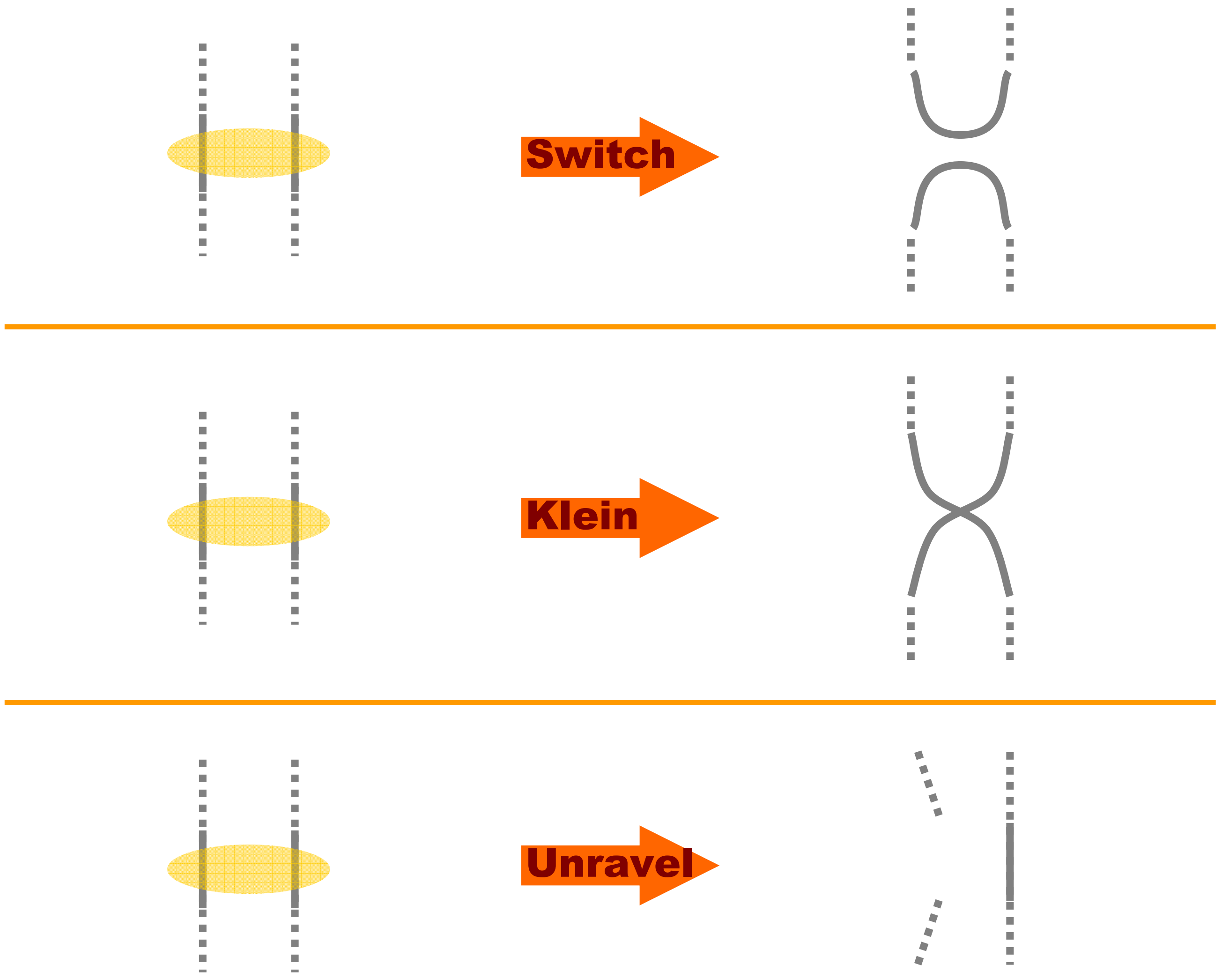


Good Bitonal Systems
(Alternating oriented curves)

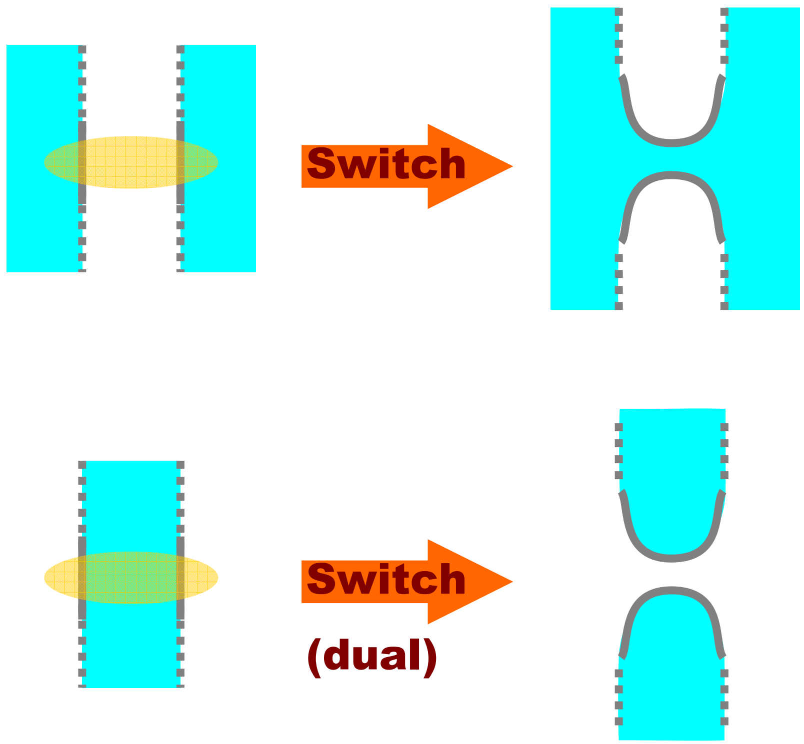
Bad Bitonal Systems



Local Unoriented Interactions



Switch as a Bitonal Reaction



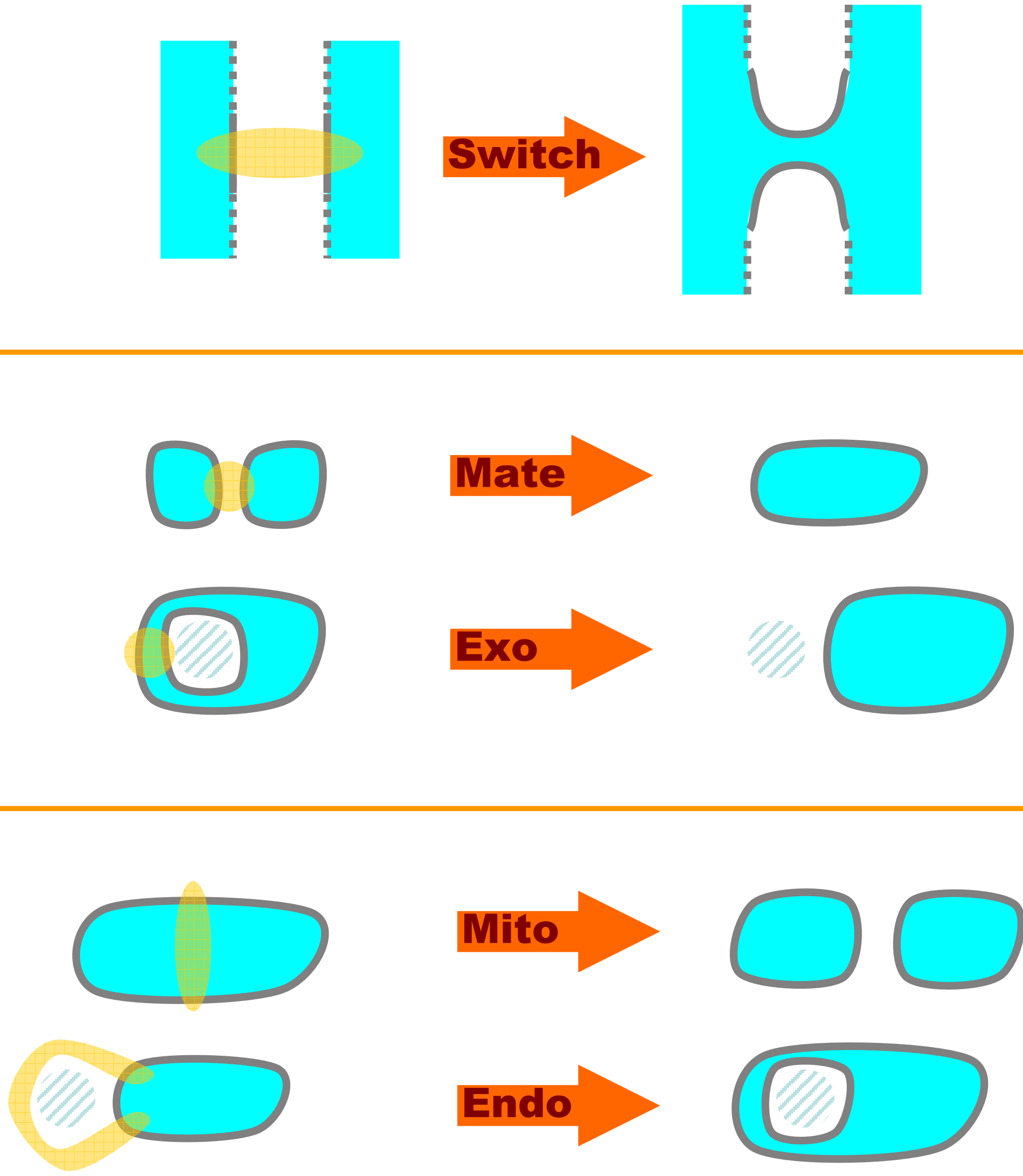
Global Effects of Switch

Preserves Bitonality

Decreases Cardinality

Increases Cardinality

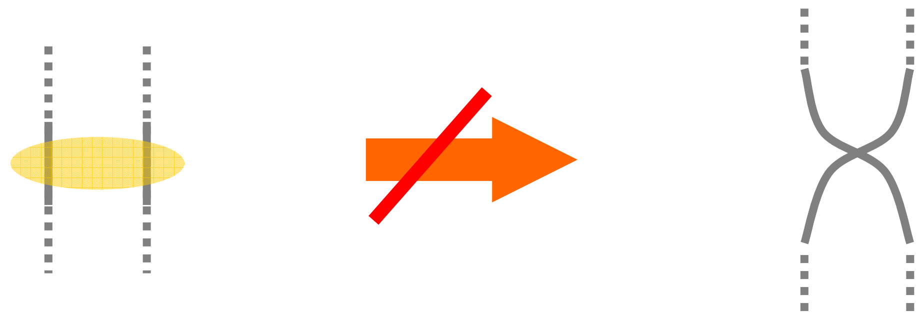
(self-reactions)



(In 3D these might create a torus: require elaborate staging)

Global Effects of Klein

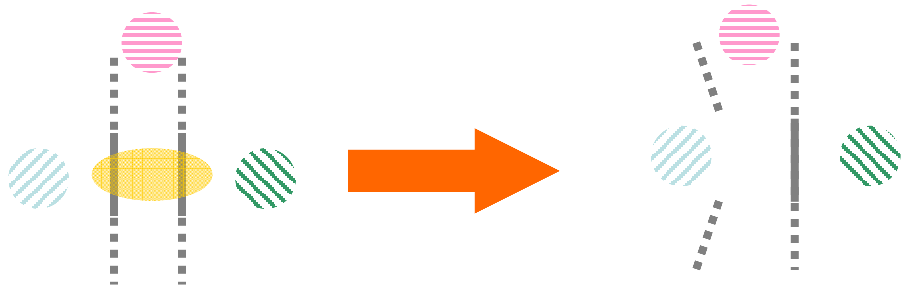
Violates
Proper
Containment



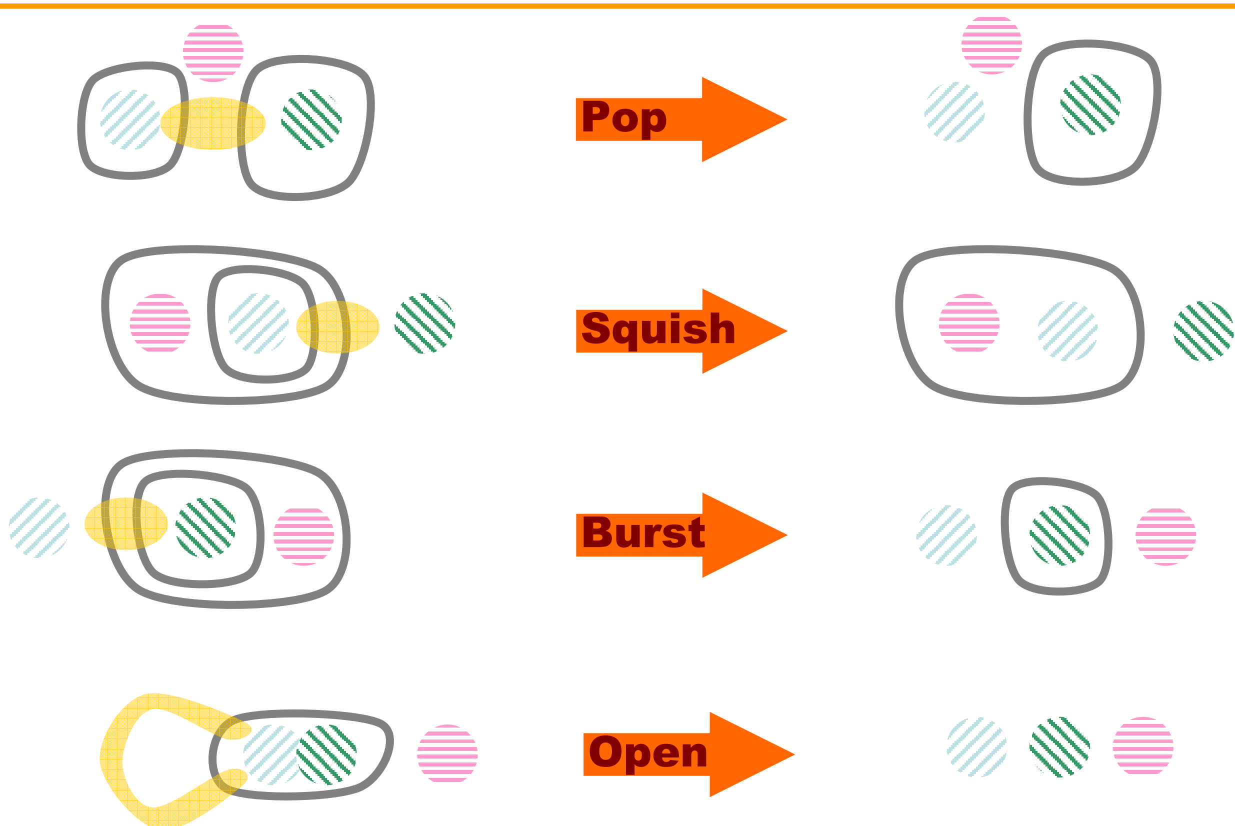
Produces
Unorientable
Curves

Global Effects of Unravel

Violates Bitonality

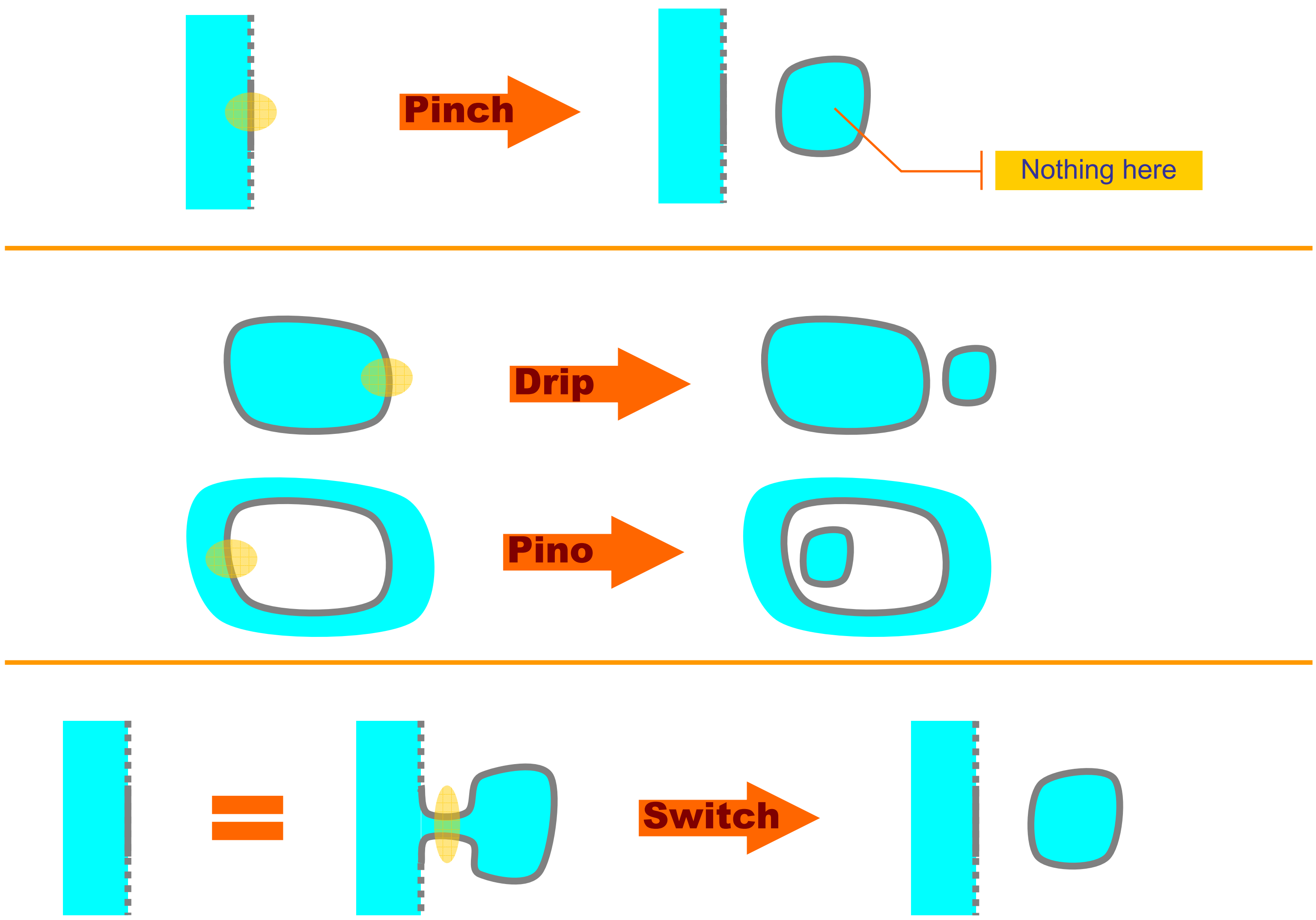


Decreases Cardinality



Global Effects of Pinch

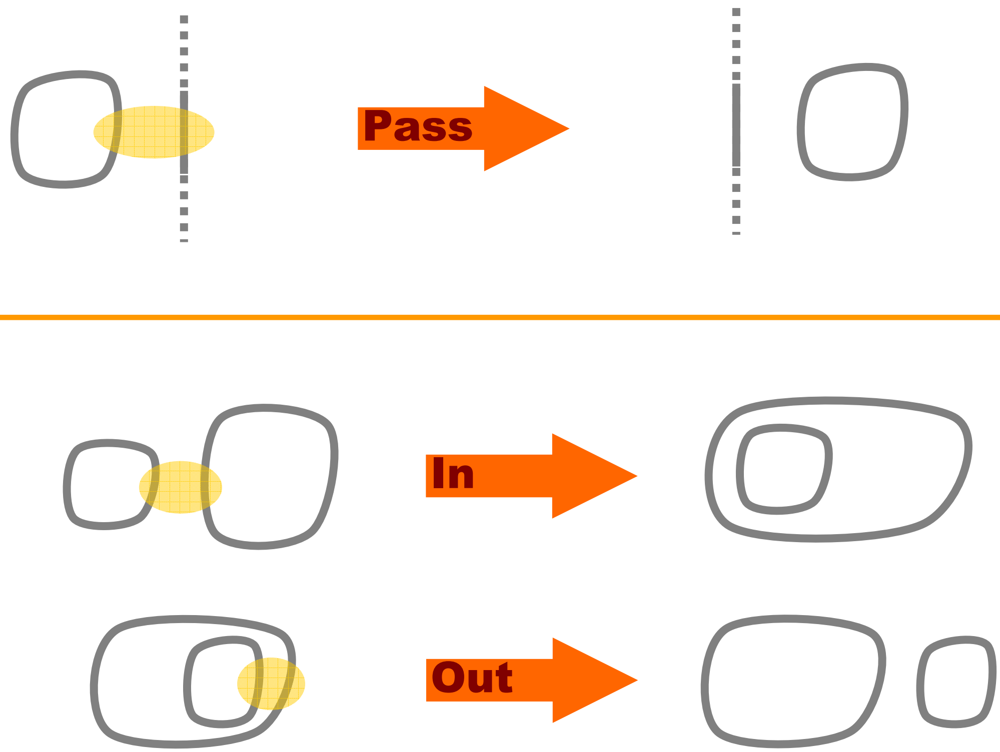
Preserves Bitonality



Global Effects of Pass

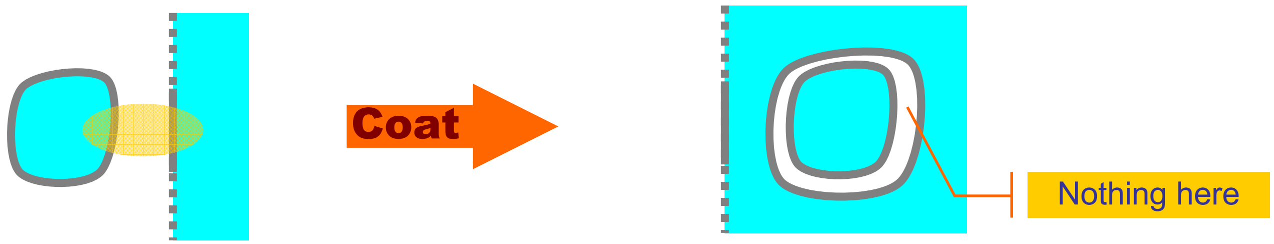
Violates Bitonality

Preserves Cardinality

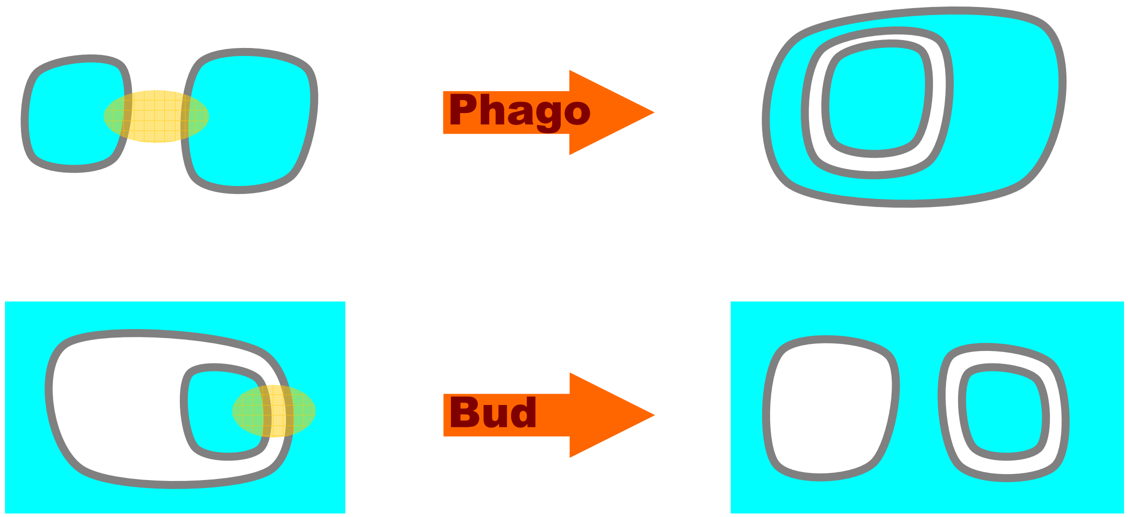


Global Effects of Coat

Preserves Bitonality



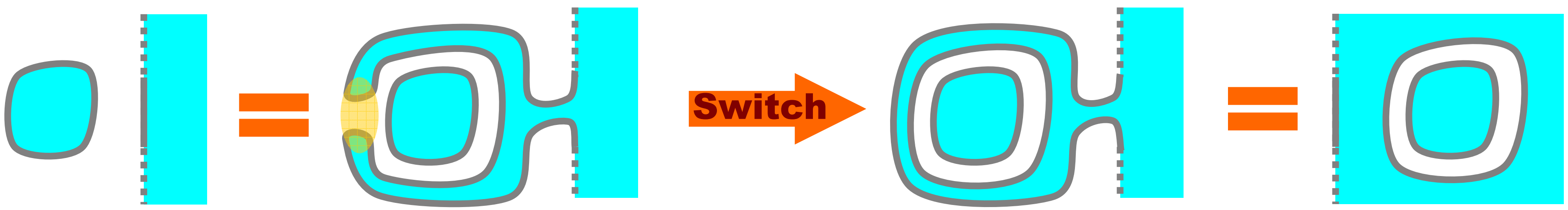
Increases Cardinality



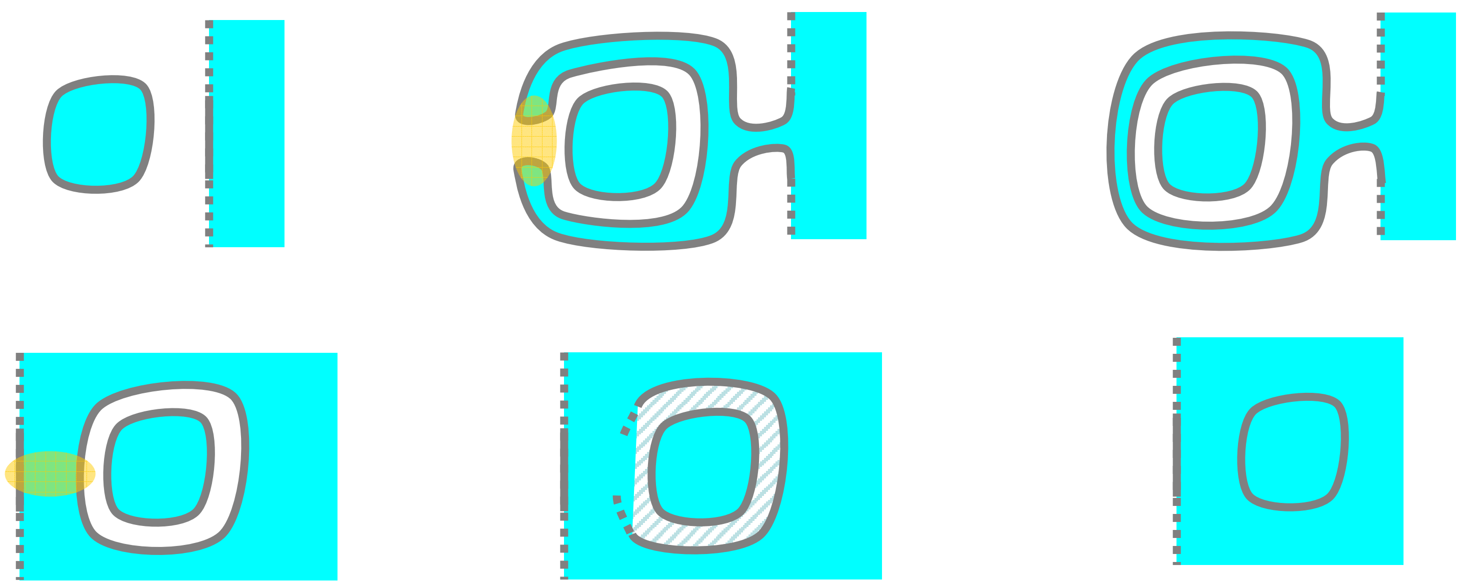
N.B. Pass can be obtained by Coat + Unravel, showing that Pass violates alternation because Unravel violates alternation.

Reductions to Switch

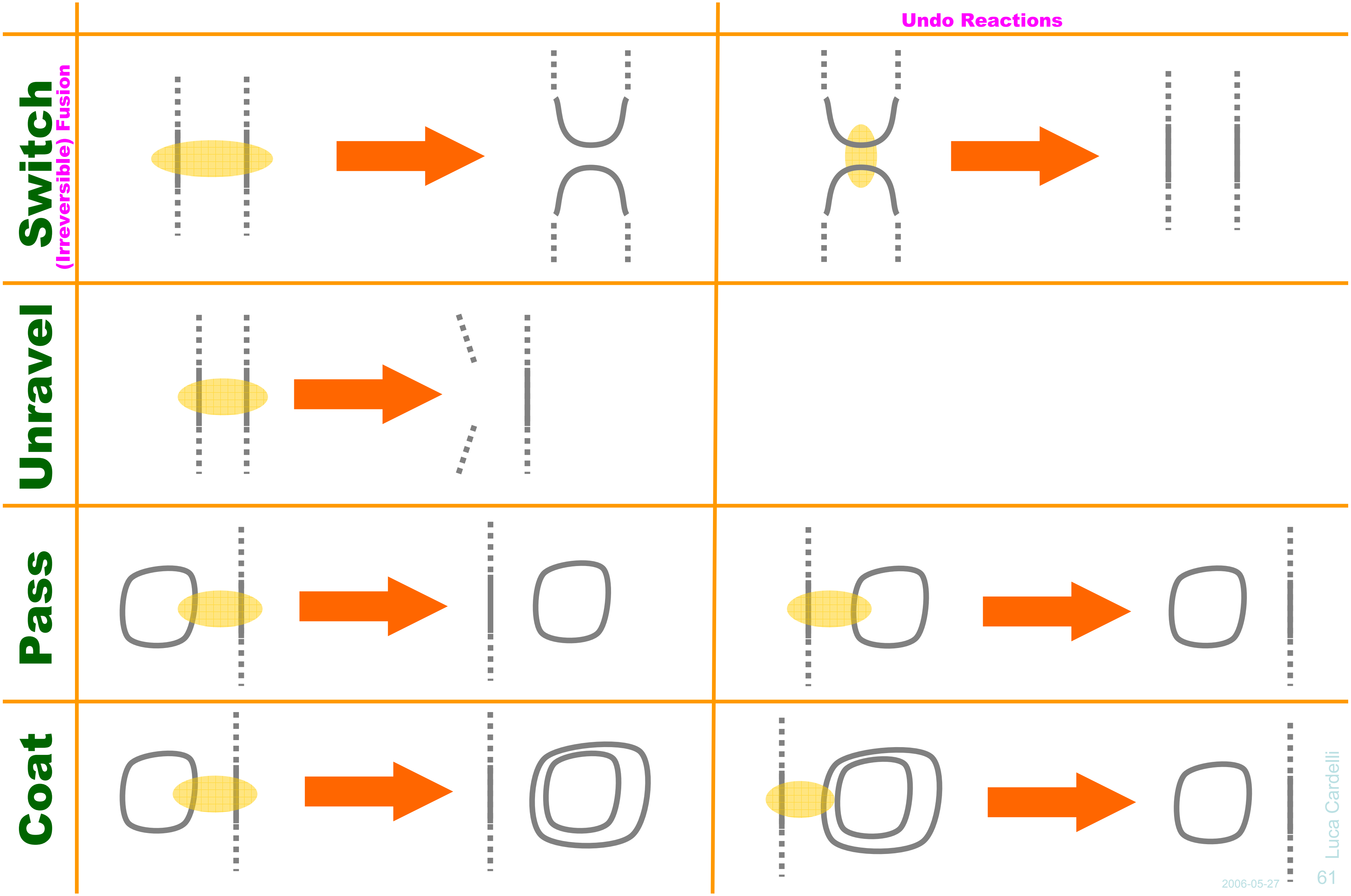
Coat by Switch



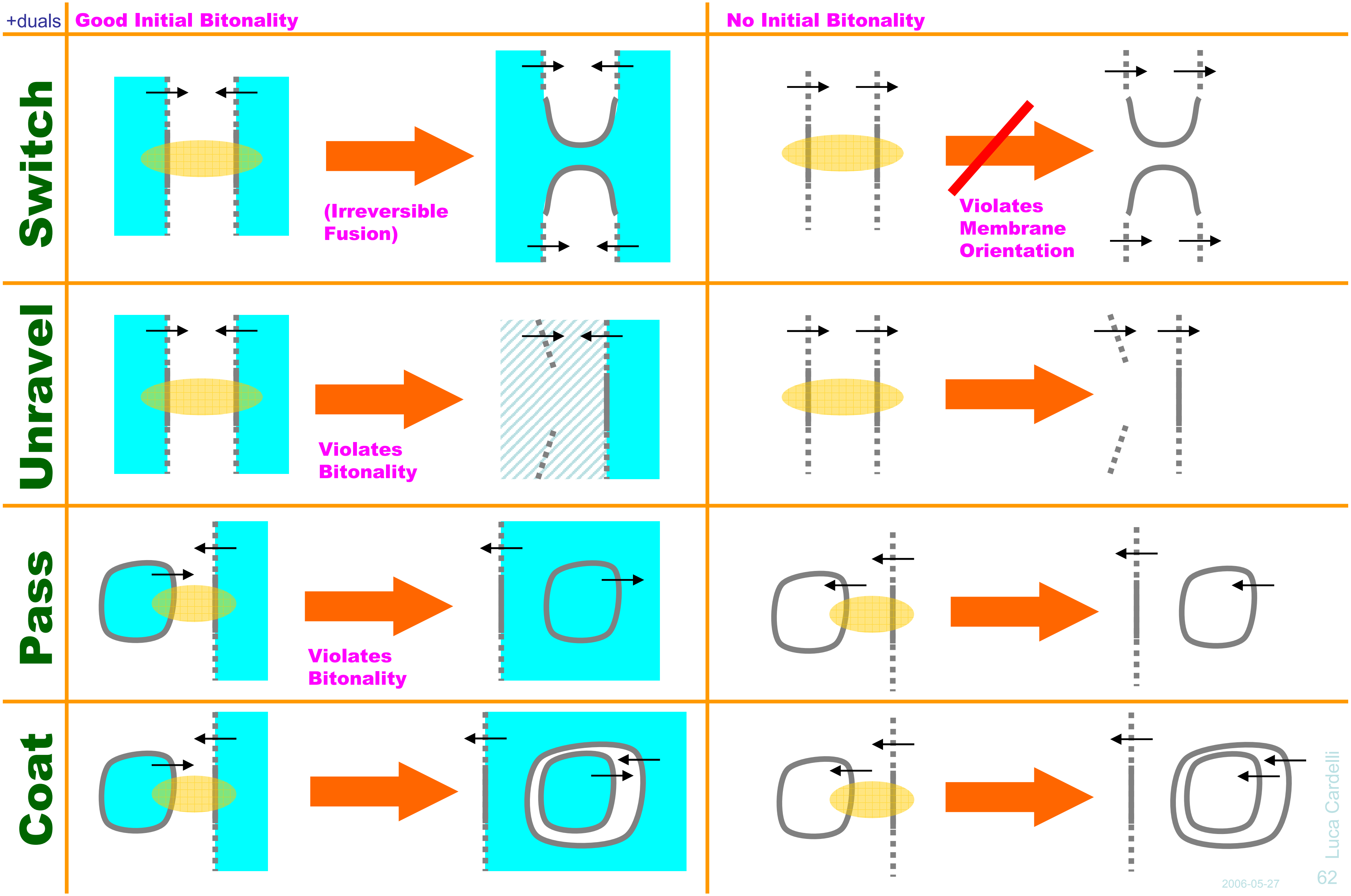
Pass by Switch and Unravel



Unoriented Local Reactions



Oriented Local Reactions



Local Brane Algebra?

- Hence, Switch and Coat are the "good" oriented reactions.
- Moreover, Coat can be obtained by Switch, and Pass can be obtained by Coat and Unravel.
- Can we build a membrane algebra just out of local operations such as Switch and Unravel?