SECOND HALF

- First pass: Bitonal membrane systems
  - A warm-up exercise in model construction. Not a calculus; more like an algebra.
  - Bitonality notion not actually used in second pass, but helps guide the "instruction set".
  - Ends with a theorem and a related prediction.
- Second pass: Brane Calculi
  - Process calculi for membrane systems, with real "mechanics".
  - Main example: virus replication.

Bitonal Membrane Systems

A high-level descriptive view
of basic membrane properties
but with very little "mechanism"

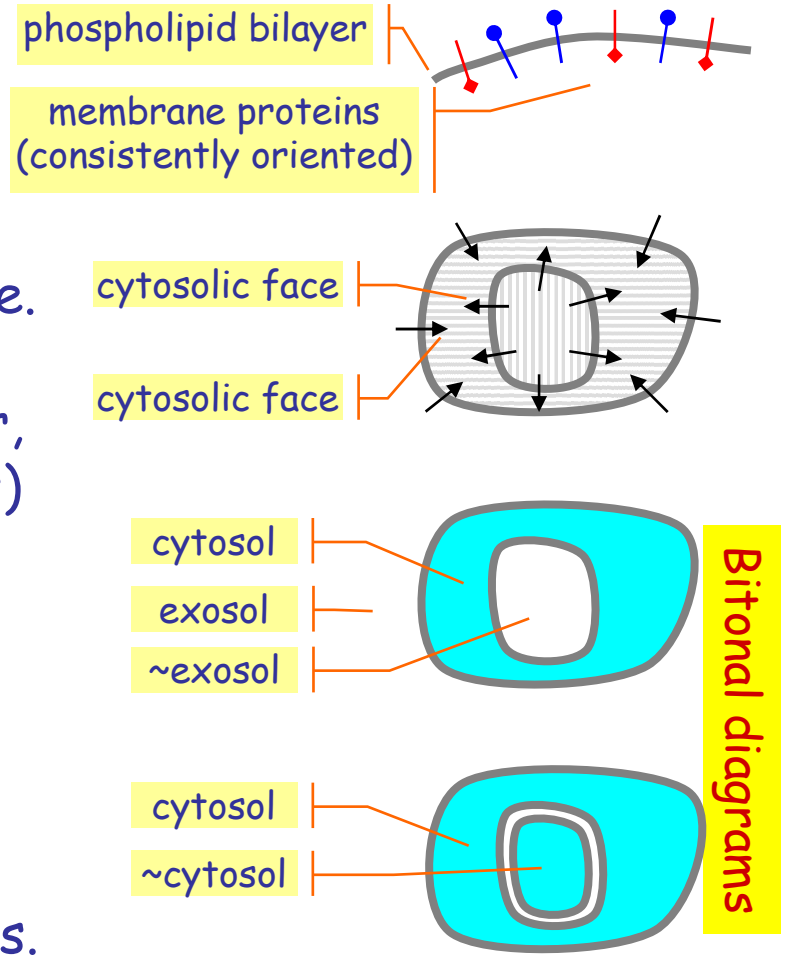
Systems of Oriented Membranes

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.



(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.

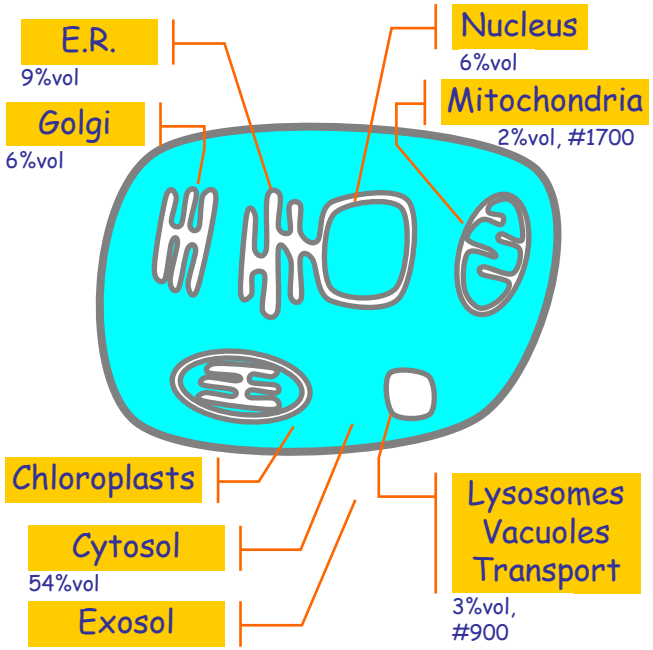
Bitonal Invariant

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

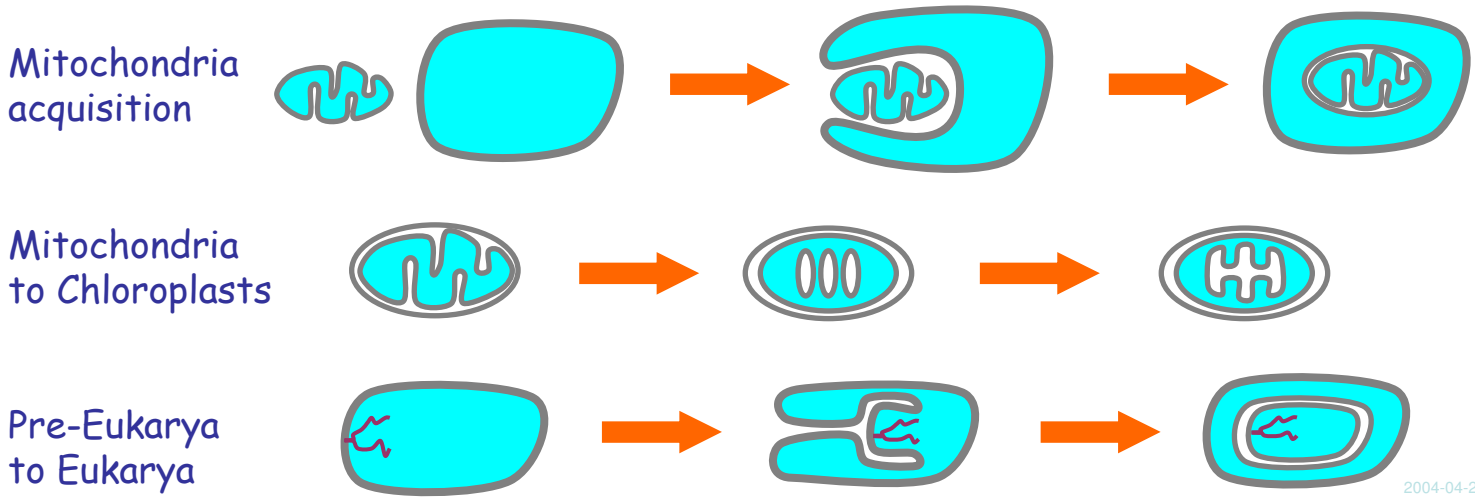
Bitonal Duality

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.

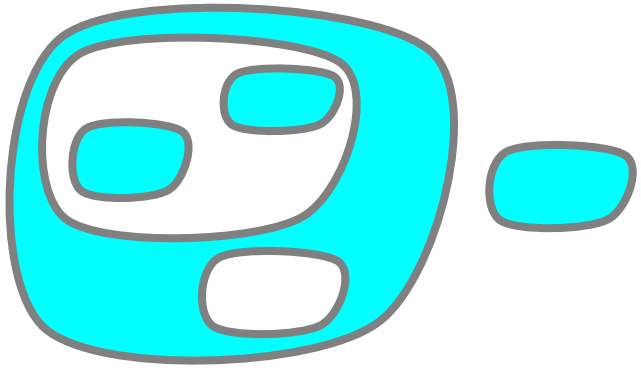


Evolutionary explanations of bitonal structure



Membrane Reactions

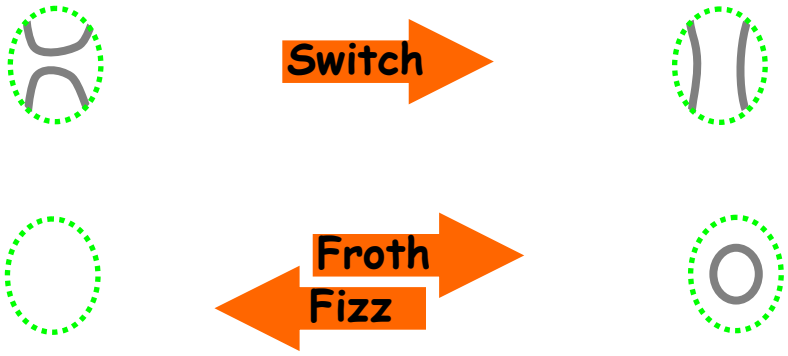
Membrane System



What reactions "make sense"?

Local (Patch) Reactions

Reactions that "make sense" from a local, molecular viewpoint

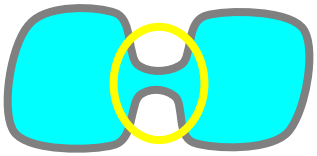


(Symmetric by 90° rotation.)

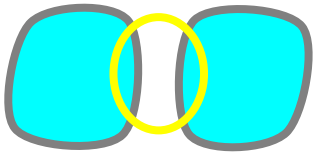
(Phospholipids thrown in water self-assemble into empty vesicles)

Global Reactions

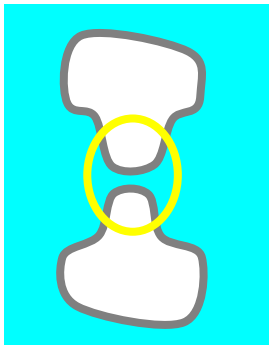
Reactions that "make sense" from a descriptive, global viewpoint



Mito

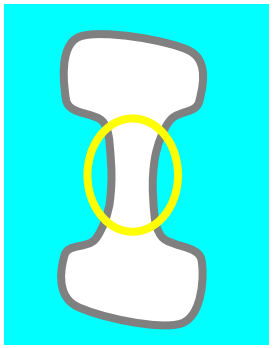


(Fission)

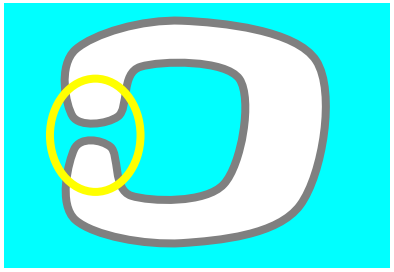


Mate

(dual)

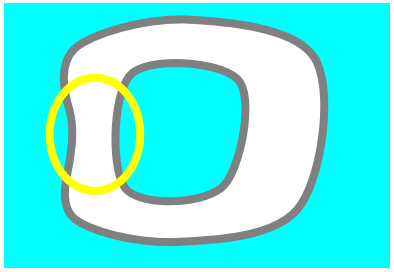


(Fusion)

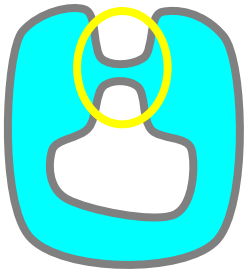


Endo

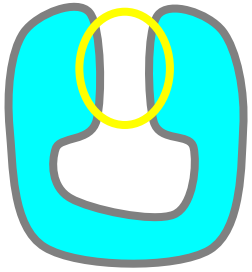
(dual)



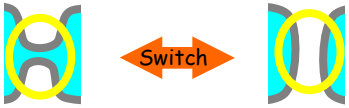
(Fission)



Exo

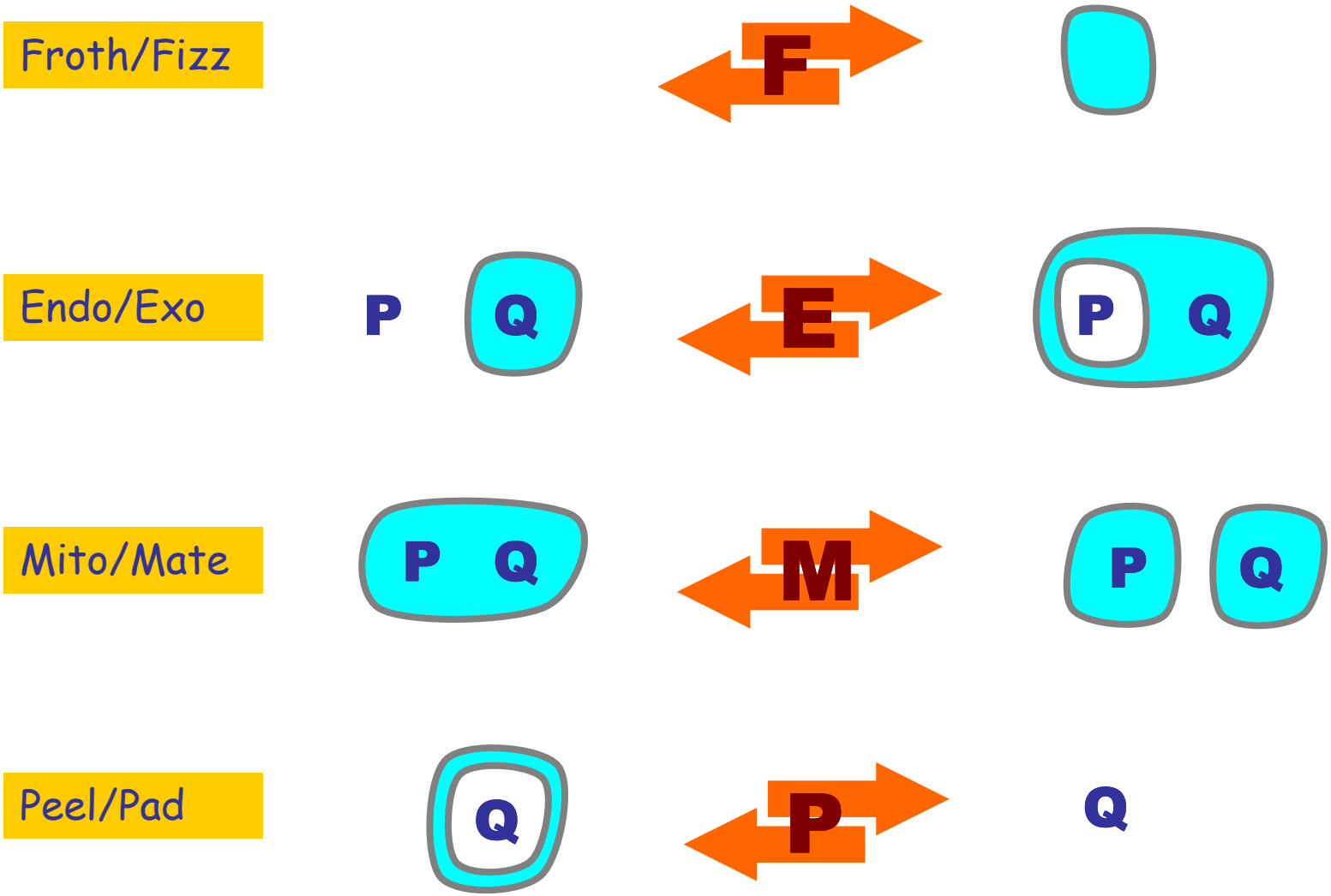


(Fusion)

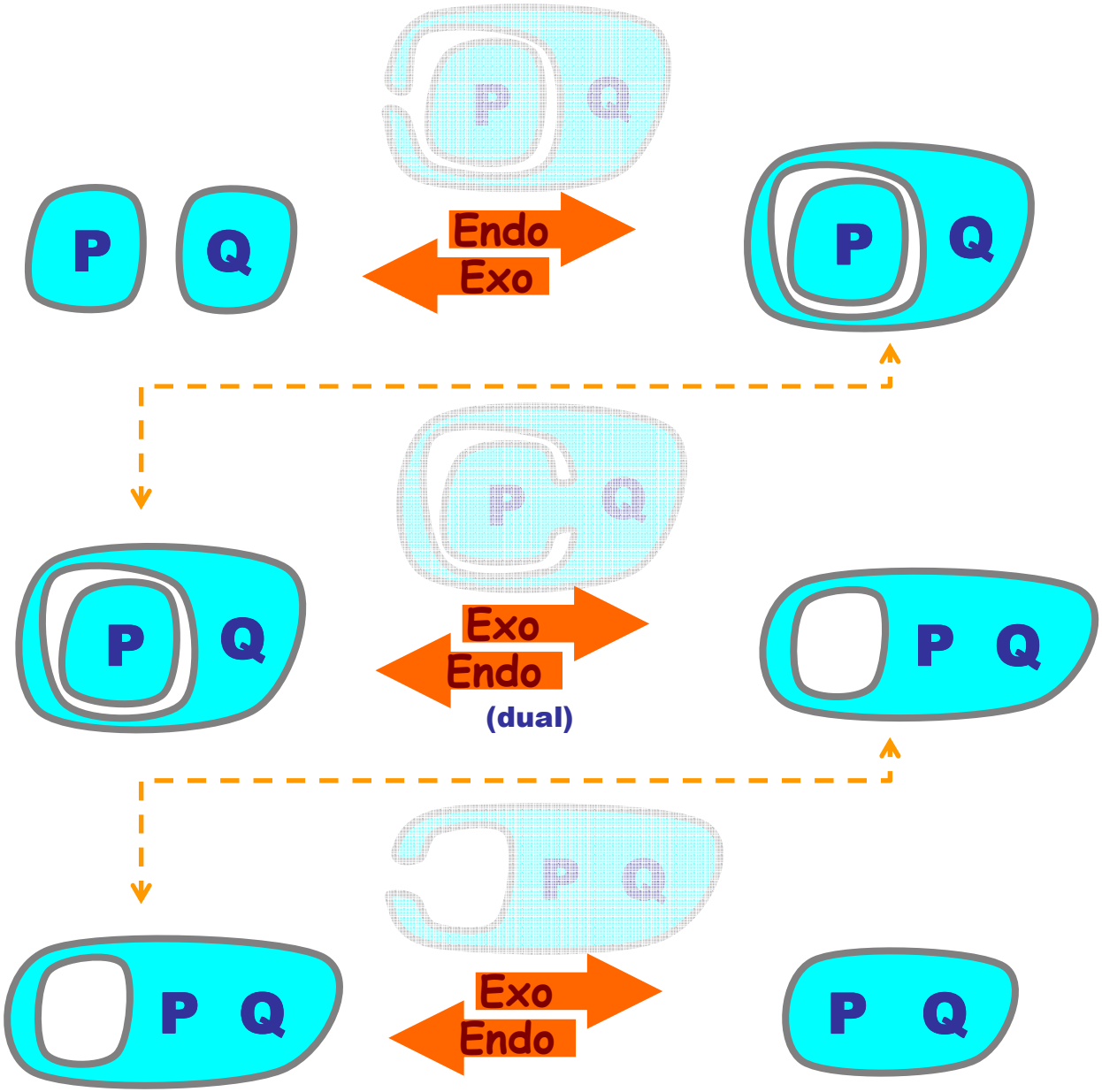


Same Local View!

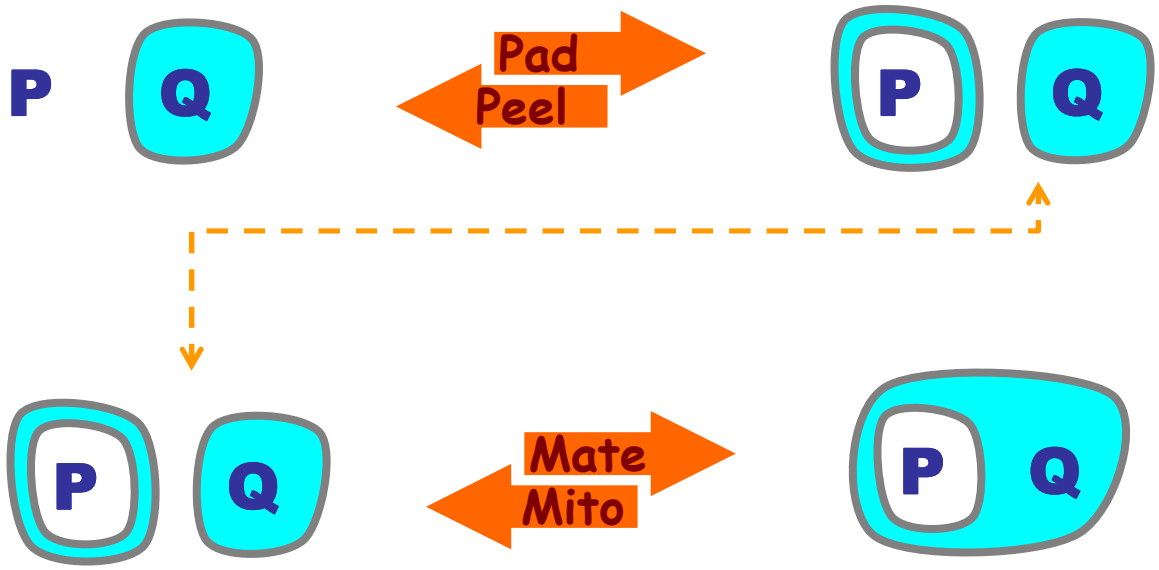
Four Bitonal Reactions



Mito/Mate by 3 Endo/Exo

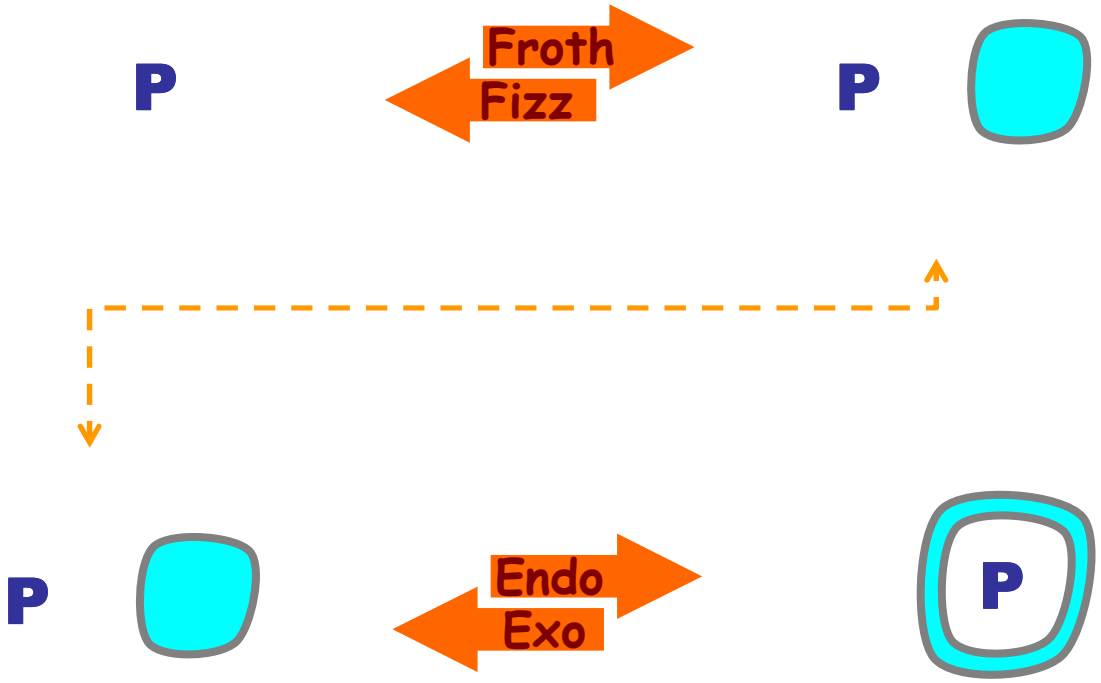


Endo/Exo by Mito/Mate and Peel/Pad



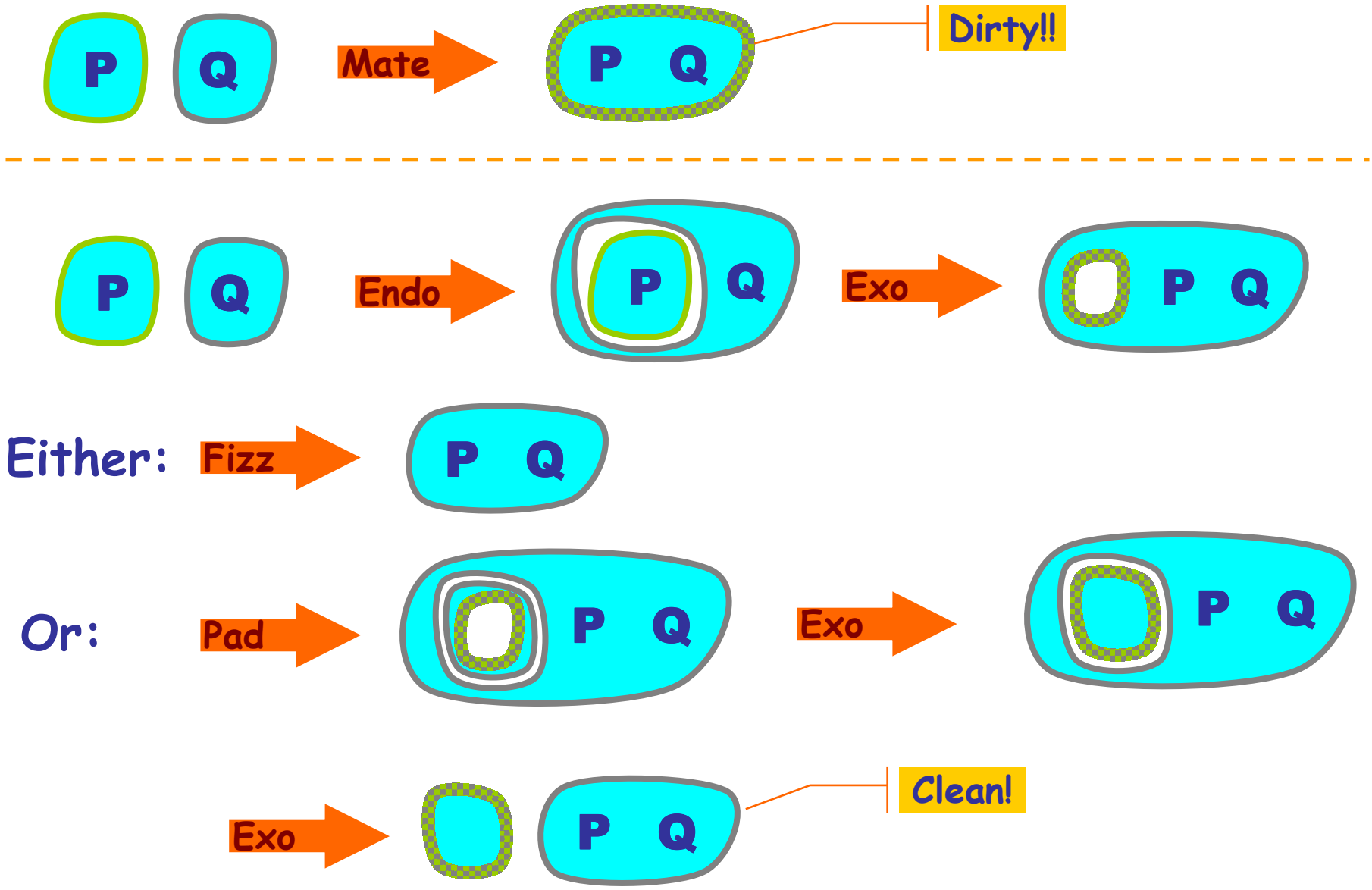
Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.

Peel/Pad by Froth/Fizz and Endo/Exo



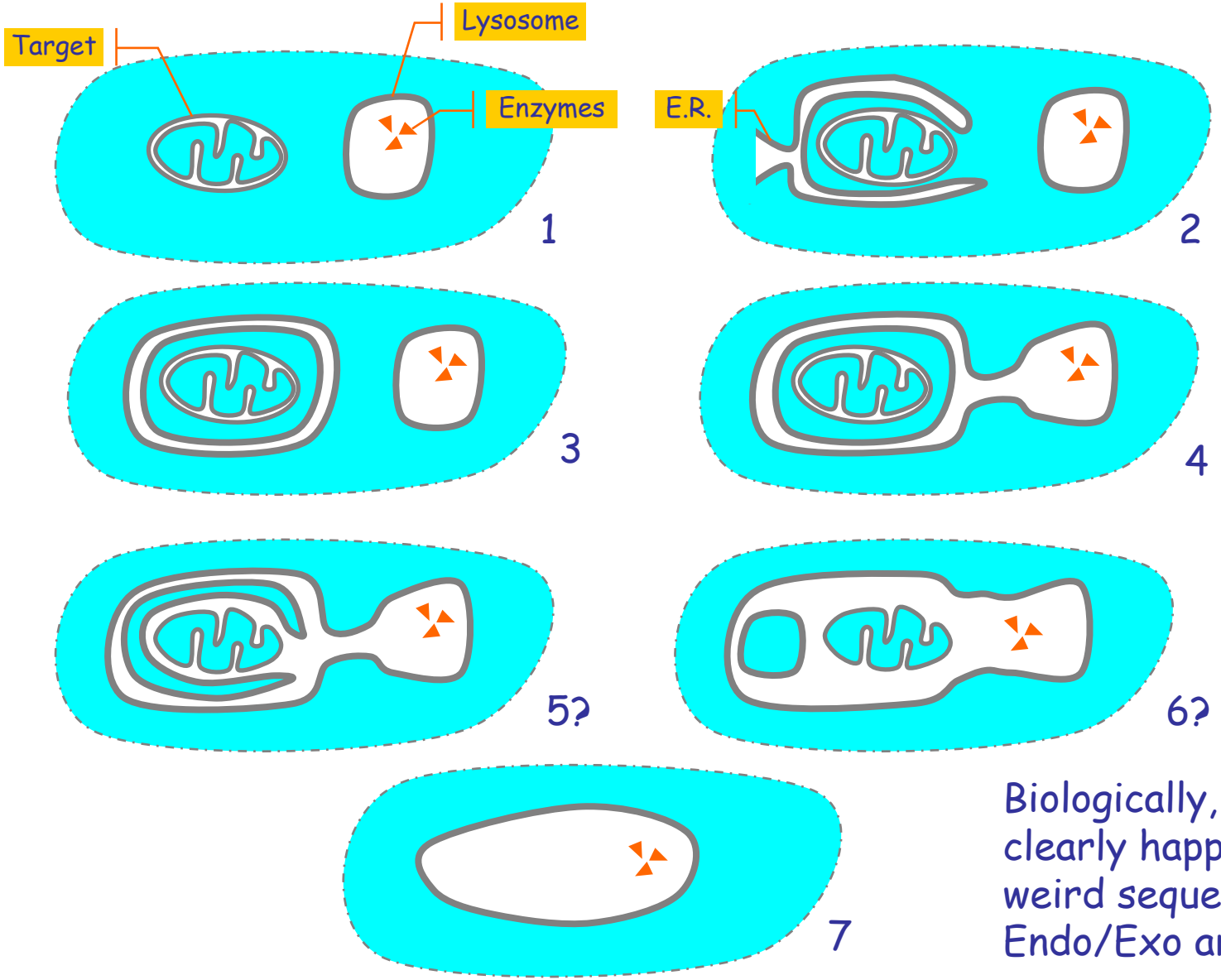
(fake) Ex: Clean Eating

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



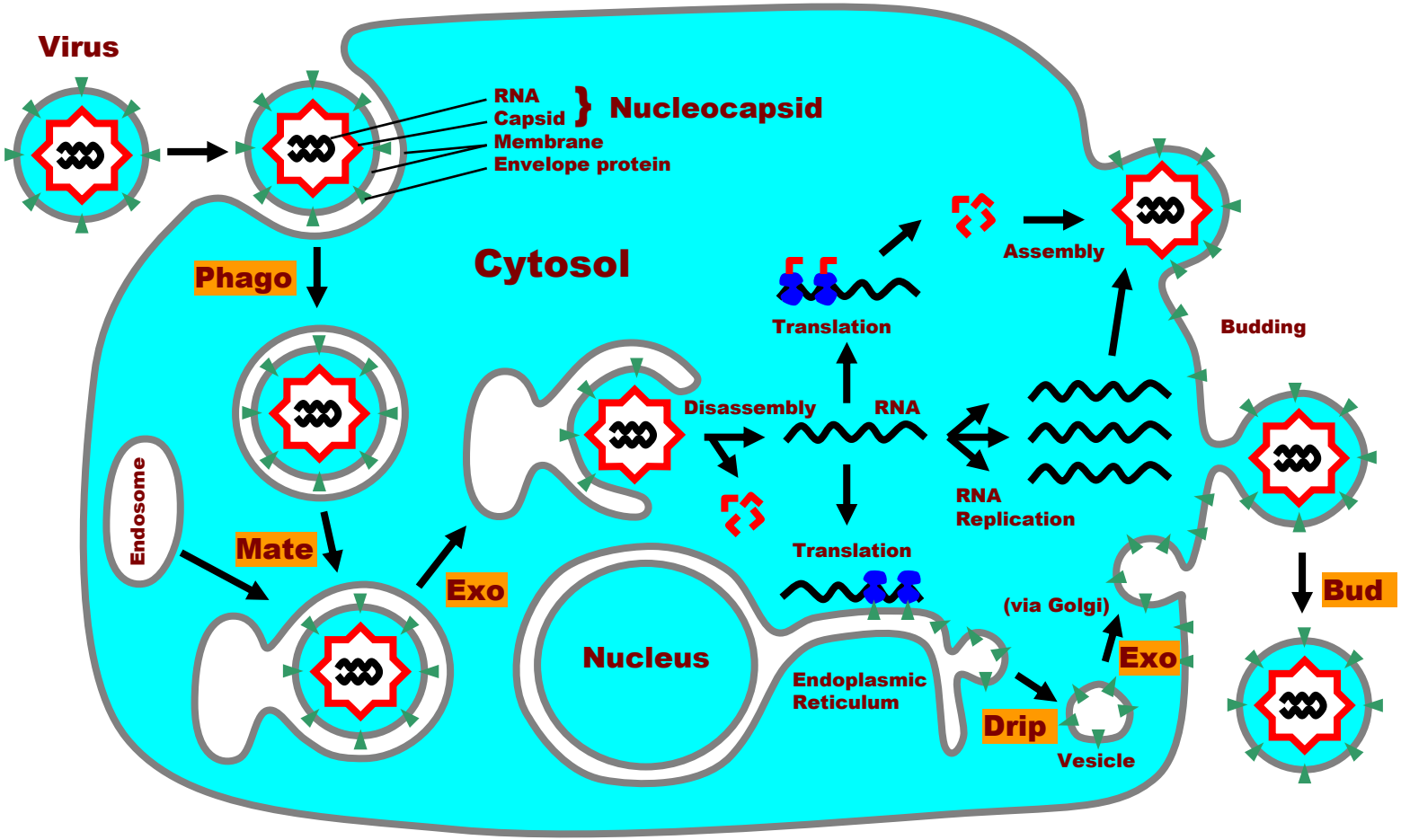
Ex: Autophagic Process

Lysosome and target don't just merge.



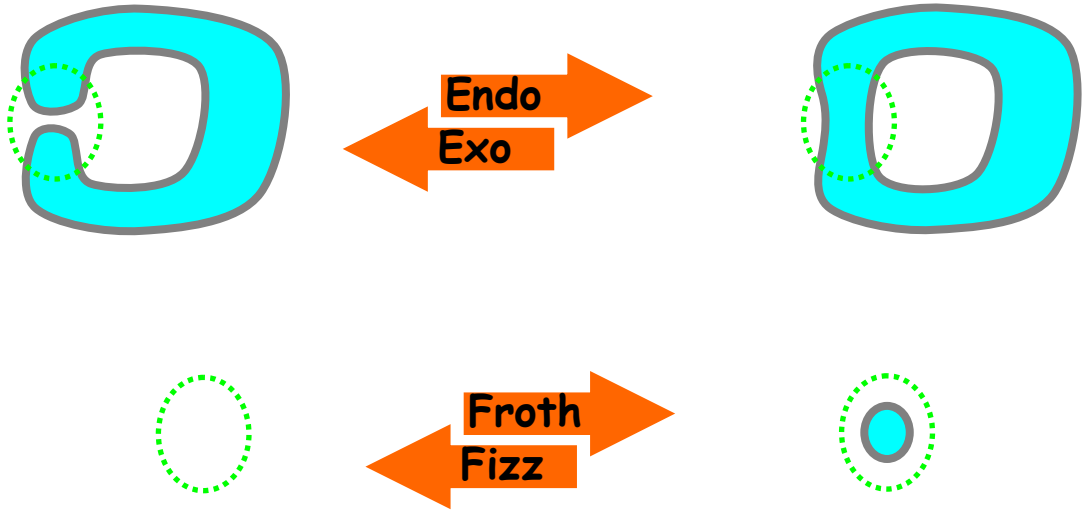
Biologically, Mito/Mate clearly happens. However, weird sequences of Endo/Exo are also common.

Ex: Viral Reproduction



[MBC p.279]
annotated

An "Instruction Set" for the Membrane Machine



Others bitonal reactions are Derivable, e.g.:

Are *all* other derivable? YES!

Characterization

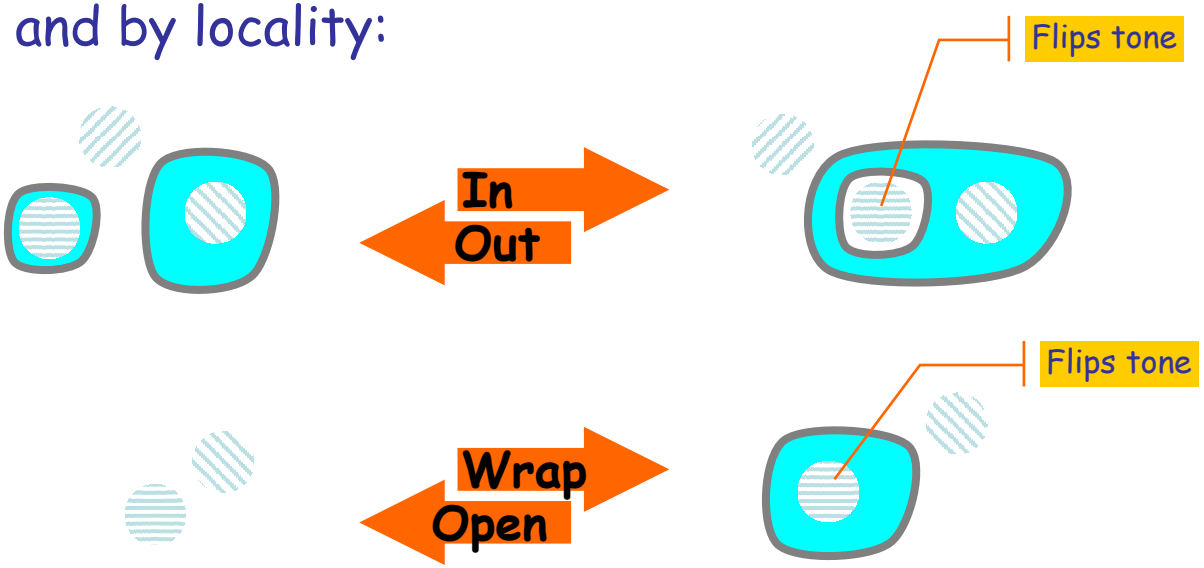
- Soundness and Completeness Theorem
  - A transformation of membrane systems:
    - **is locally realizable**
      (realizable by a sequence of switch + froth/fizz)
    - **iff it is bitonal**
      (changes tone of at most a simply-connected region at a time)
    - **iff it is fusion/fission-realizable**
      (realizable by a sequence of endo/exo + froth/fizz)
- A simple prediction:
  - Non-bitonal operations are non-local and hence should not be observed.

Any model embodies certain invariants that determine what *cannot* be expressed in the model and therefore predict what *cannot* happen.

Thus a model can be falsified, or perhaps more usefully, its range of applicability can be investigated.

Non-local Operations

Some global reactions are *ruled out* by bitonality, and by locality:



Violate bitonality.

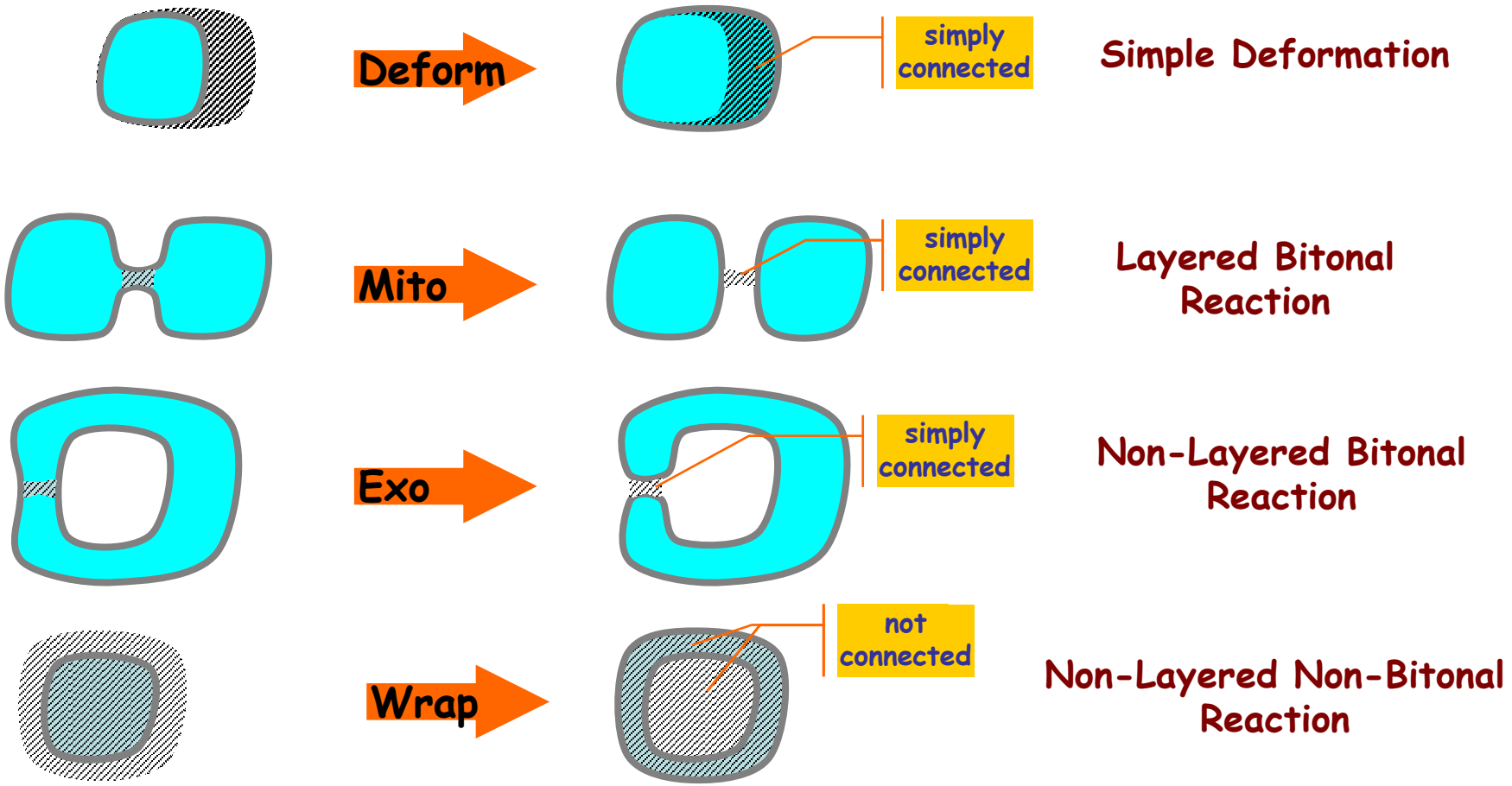
Non implementable by "local" membrane operations.

Not observed (except gradual Open during "digestion" or "lysis").

Happen to be the Ambient Calculus operations :-(

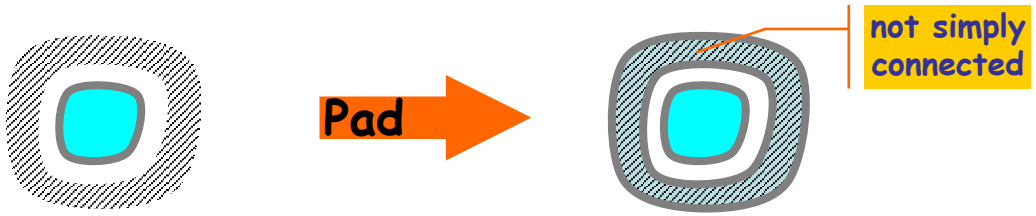
Further Details Bitonal Reactions

- 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).

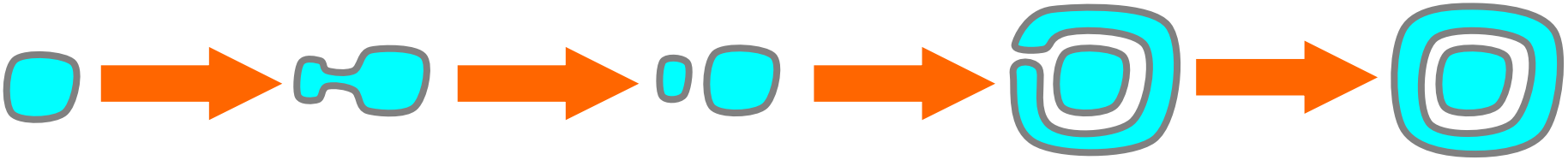


Bitonal Transformations

- *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:



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



- Some transformations are inherently non-bitonal.

Brane Calculi

What makes Endo happen?

- Membrane transformations are usually "meant":
  - They do not happen spontaneously. They are regulated by membrane-embedded proteins.
  - We need to move down a level, to explain how/when certain membrane reactions happen.
- Formalization
  - Action/coaction interactions in process calculi.
  - Actions "on" the membranes, not "inside" them!
  - Leads to smoother modeling than previous attempts (e.g. BioAmbients).

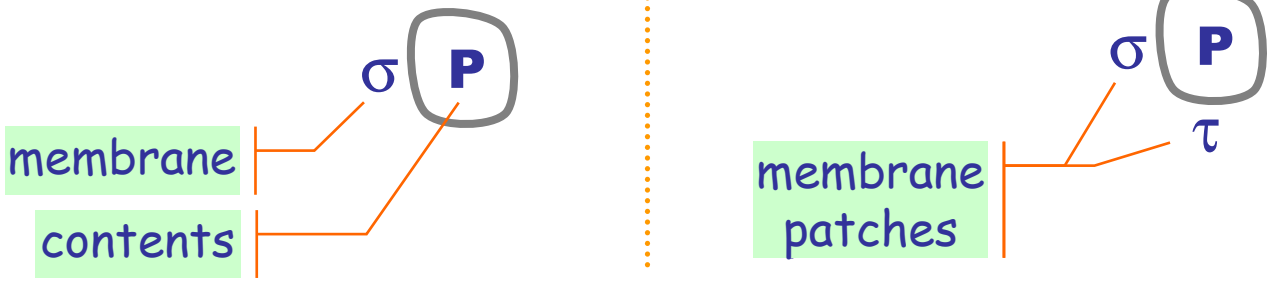
Brane Calculi

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	$a ::= 1 \mid \ldots$	(fill in as needed)

1D fluids (σ) inside a 2D fluid (P)

TWO commutative monoids instead of ONE of normal process calculi

$\sigma(\!|P|\!)$ $\quad$ $\sigma|\tau(\!|P|\!)$ $\quad$ $a.\sigma|\tau = (a.\sigma)|\tau$



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

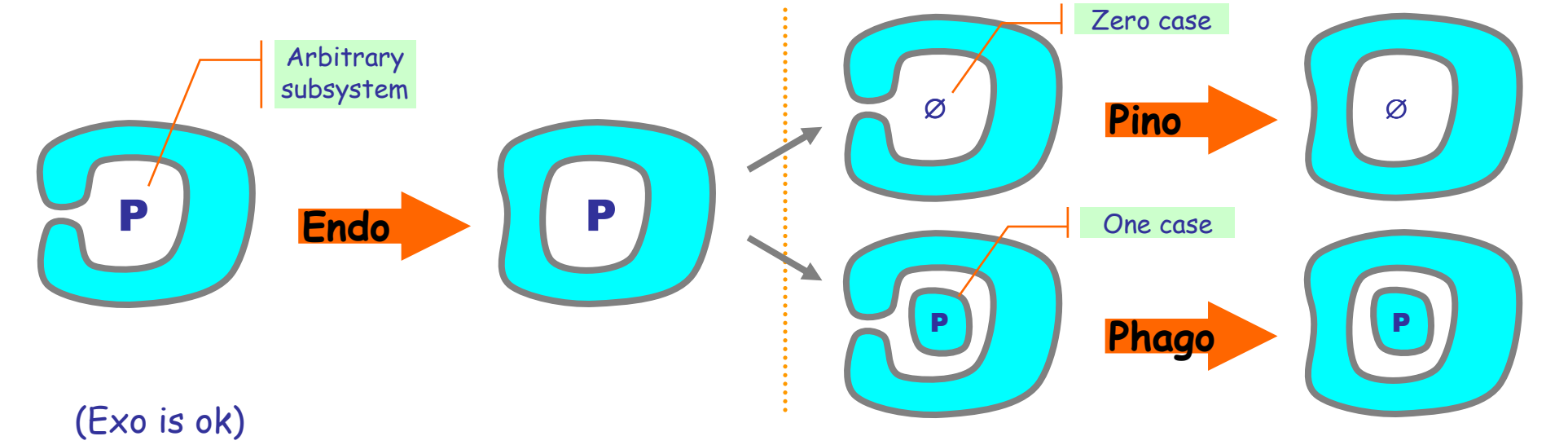
Congruence ≡ and Reaction ➡

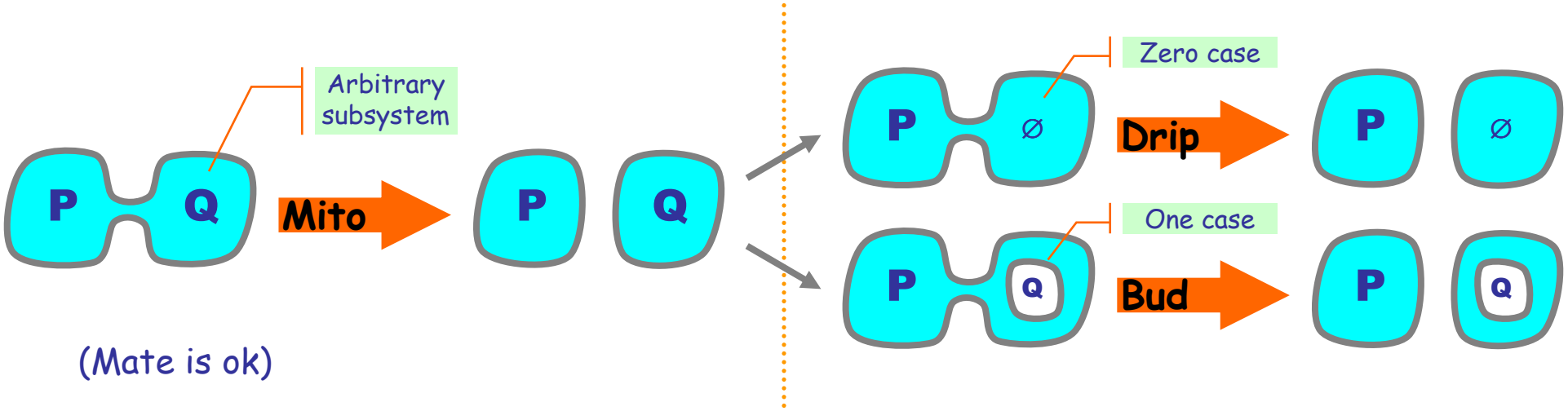
	System	Brane
Fluidity	$P \circ Q \equiv Q \circ P$ $P \circ (Q \circ R) \equiv (P \circ Q) \circ R$ $P \circ \diamond \equiv P$	$\sigma \mid \tau \equiv \tau \mid \sigma$ $\sigma \mid (\tau \mid \rho) \equiv (\sigma \mid \tau) \mid \rho$ $\sigma \mid 0 \equiv \sigma$
Plentitude	$!P \equiv P \circ !P$ etc.	$!\sigma \equiv \sigma \mid !\sigma$ etc.
Units	$0(\!(\diamond)\!) \equiv \diamond$ Froth/Fizz	$1.\sigma \equiv \sigma$ Inaction
Congruence	$P \equiv Q \Rightarrow P \circ R \equiv Q \circ R$ $P \equiv Q \Rightarrow !P \equiv !Q$ $P \equiv Q \wedge \sigma \equiv \tau \Rightarrow \sigma(\!(P)\!) \equiv \tau(\!(Q)\!)$	$\sigma \equiv \tau \Rightarrow \sigma \mid \rho \equiv \tau \mid \rho$ $\sigma \equiv \tau \Rightarrow !\sigma \equiv !\tau$ $\sigma \equiv \tau \Rightarrow a.\sigma \equiv a.\tau$

Reaction is up to congruence	$P \equiv P' \wedge P' \rightarrow Q' \wedge Q' \equiv Q \Rightarrow P \rightarrow Q$
Reactions in solution	$P \rightarrow Q \Rightarrow P \circ R \rightarrow Q \circ R$ $P \rightarrow Q \Rightarrow \sigma(\!(P)\!) \rightarrow \sigma(\!(Q)\!)$

This is the whole semantics, except for the effects of individual actions.

"Determinization"





Brane Reactions

actions

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

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

coordination tags
sometimes omitted

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

...

Phago $\mathcal{Y}_n.\sigma|\sigma'(\!|P|\!) \circ \mathcal{Y}^{\perp}_n(\rho).\tau|\tau'(\!|Q|\!) \rightarrow \tau|\tau'(\!|\rho(\!|\sigma|\sigma'(\!|P|\!)|\!)\circ Q|\!)$

Exo $\mathcal{Y}^{\perp}_n.\tau|\tau'(\!|\mathcal{Y}_n.\sigma|\sigma'(\!|P|\!)\circ Q|\!) \rightarrow P \circ \sigma|\sigma'|\tau|\tau'(\!|Q|\!)$

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

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

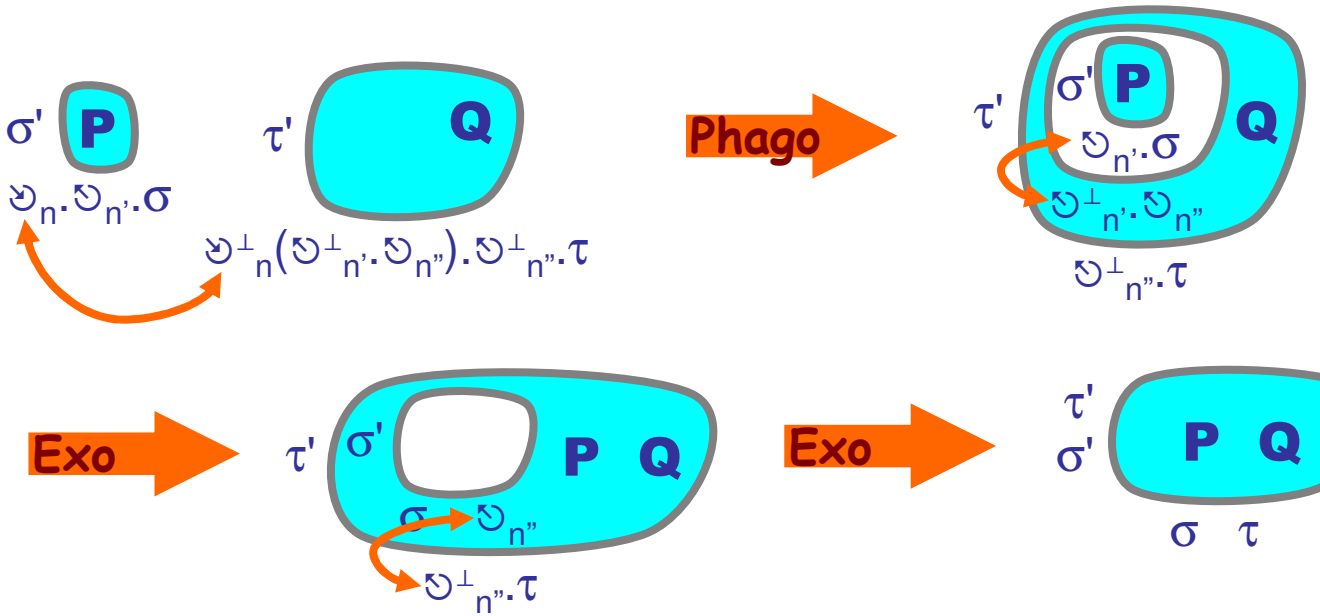
N.B.: in Phago (and Pino), one could perhaps require r to be,
conservatively, a piece of t, by a non-linear rewrite:

CPhago $\mathcal{Y}_n.\sigma|\sigma'(\!|P|\!) \circ \mathcal{Y}^{\perp}_n(\rho).\tau|\tau'|\rho(\!|Q|\!) \rightarrow \tau|\tau'(\!|\rho(\!|\sigma|\sigma'(\!|P|\!)|\!)\circ Q|\!)$

Abbreviations: Mate

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

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

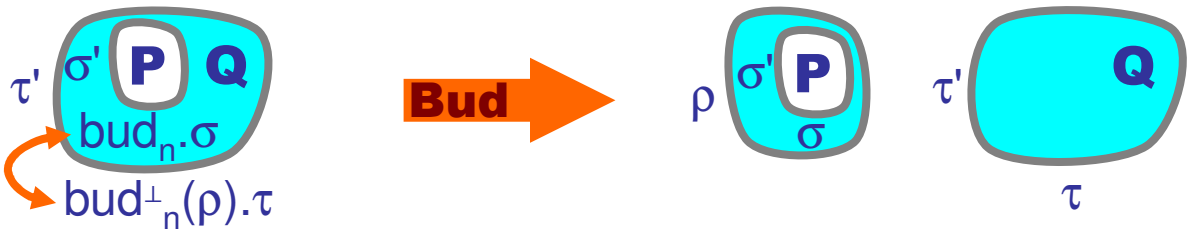


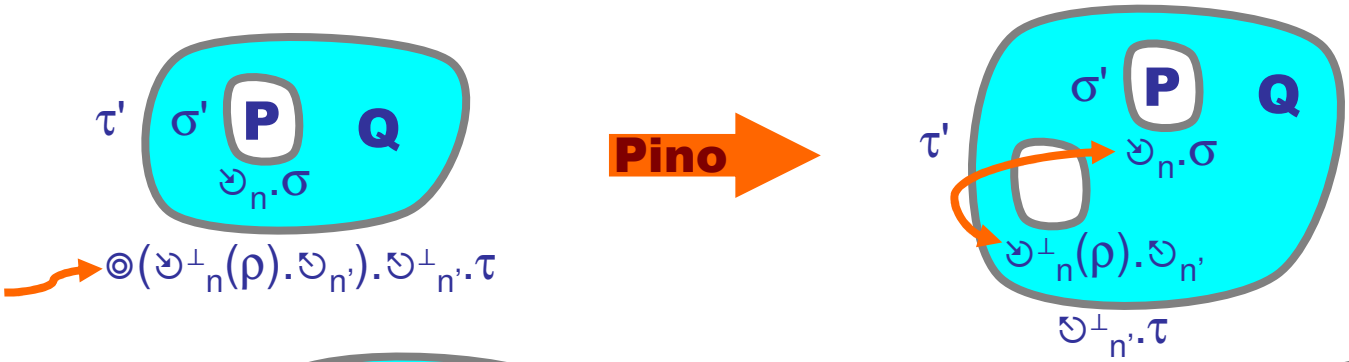
Abbreviations: Bud

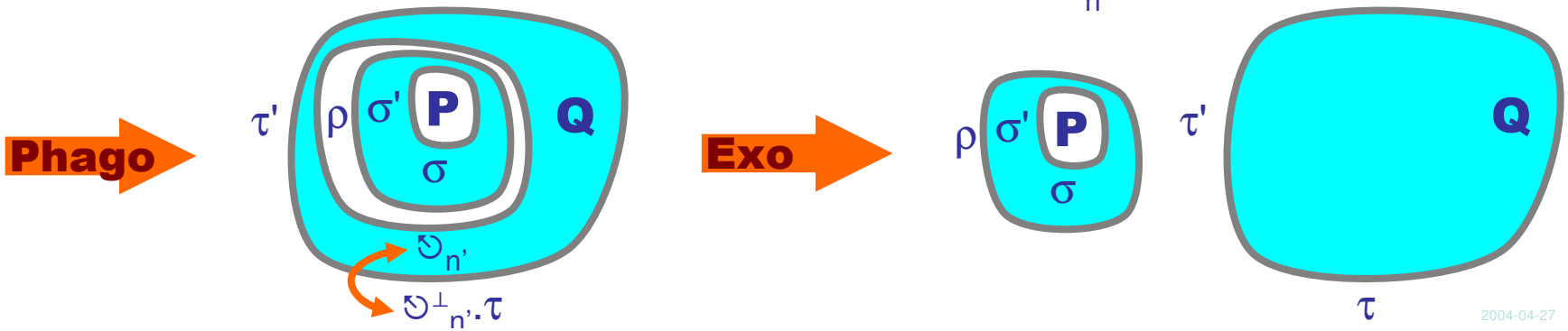
Bud $bud_n.\sigma = \circlearrowright_n.\sigma$

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

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



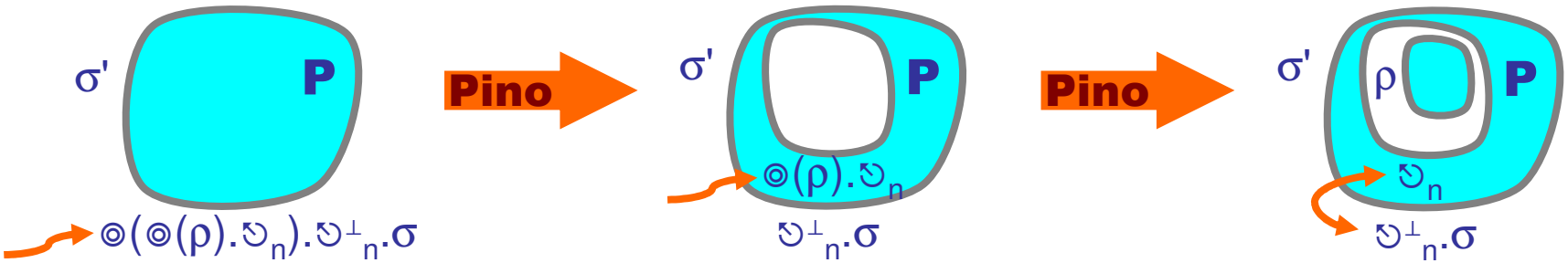


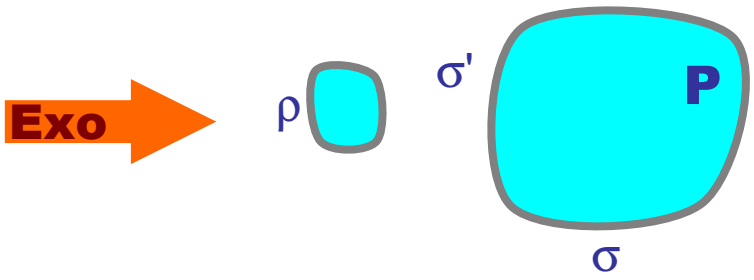


Abbreviations: Drip

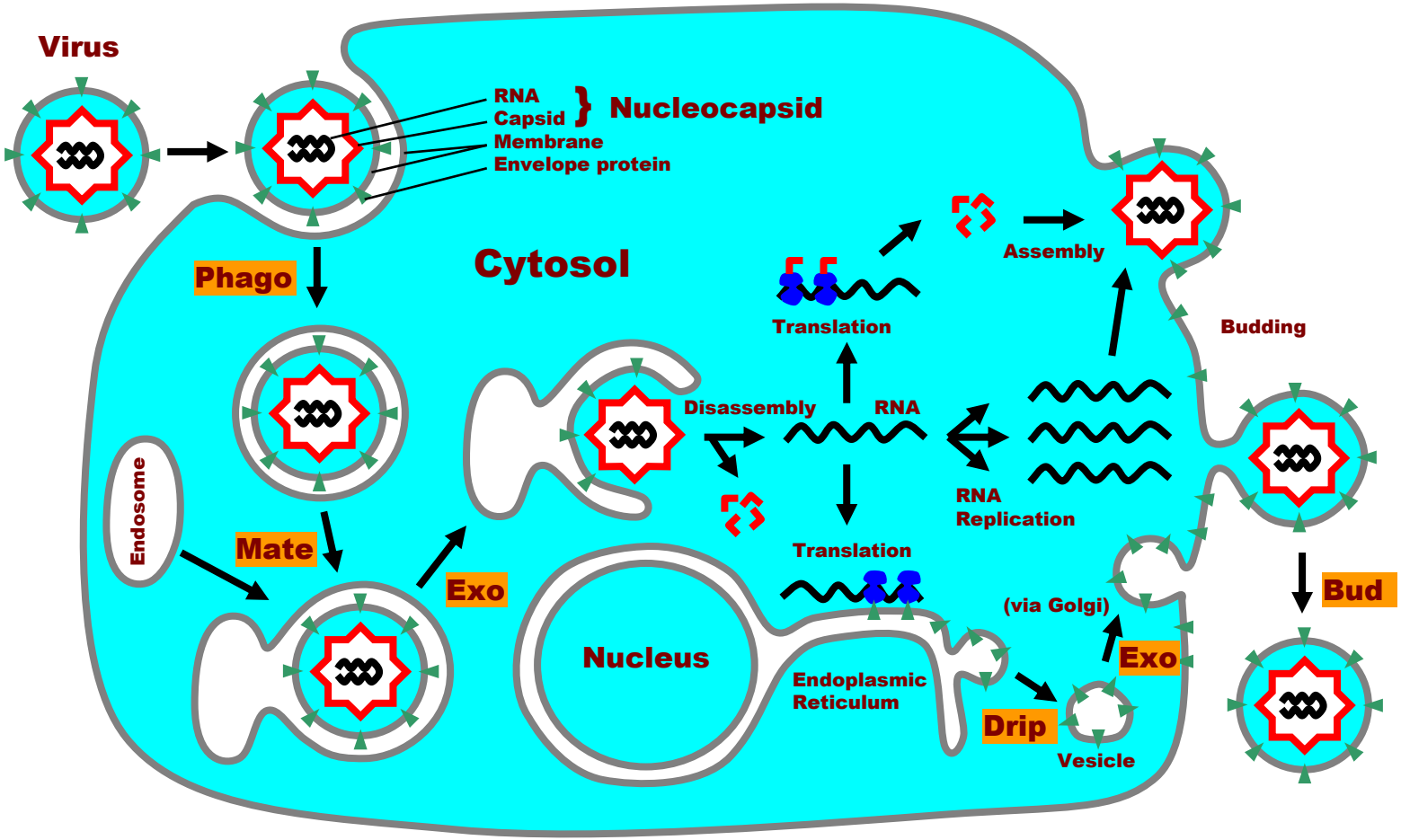
Drip $\text{drip}_n(\rho).\sigma = \circledcirc(\circledcirc(\rho).\circlearrowleft_n).\circlearrowleft^{\perp}_n.\sigma$

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



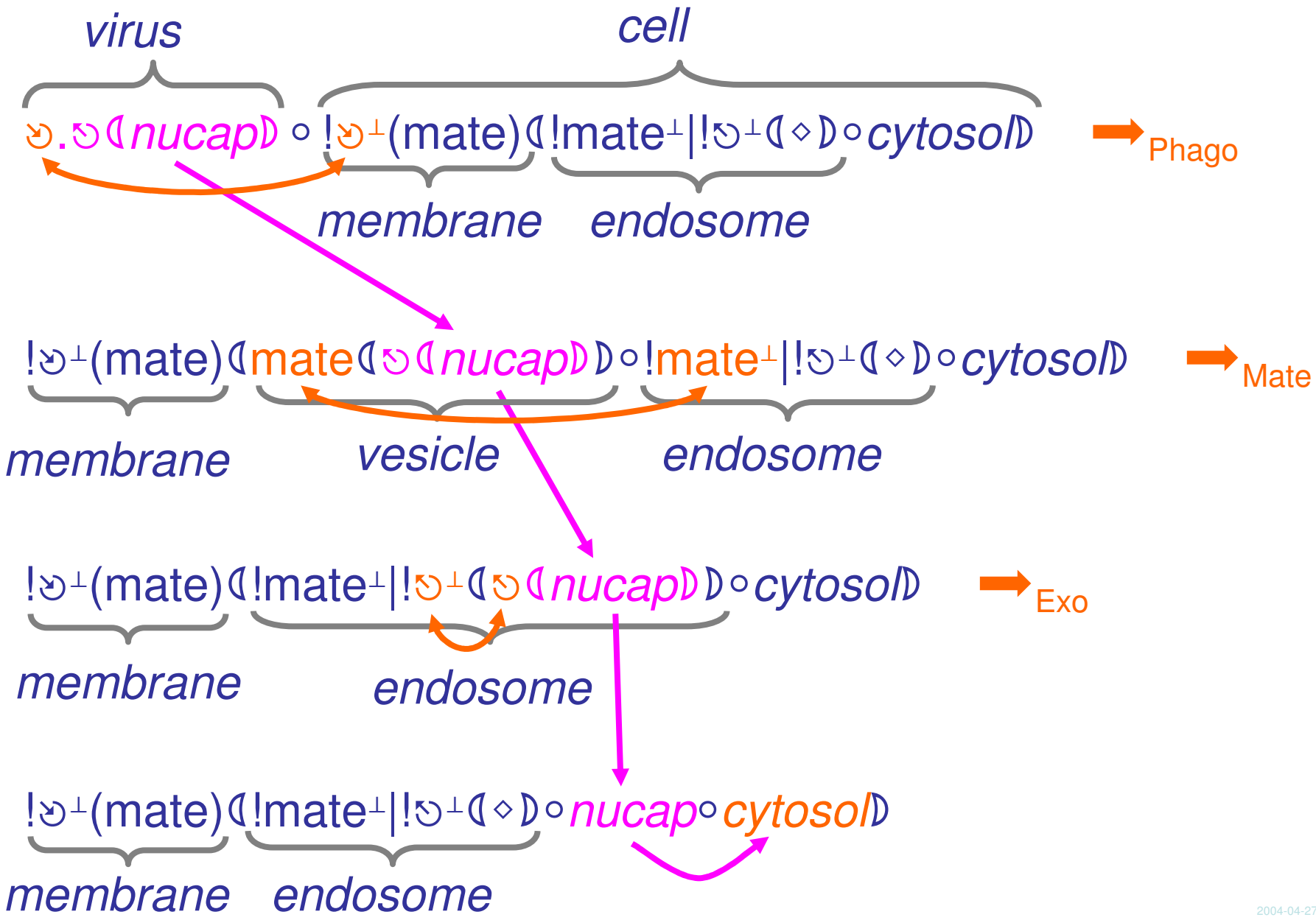


Ex: Viral Reproduction



[MBC p.279]
annotated

Ex: Viral Infection



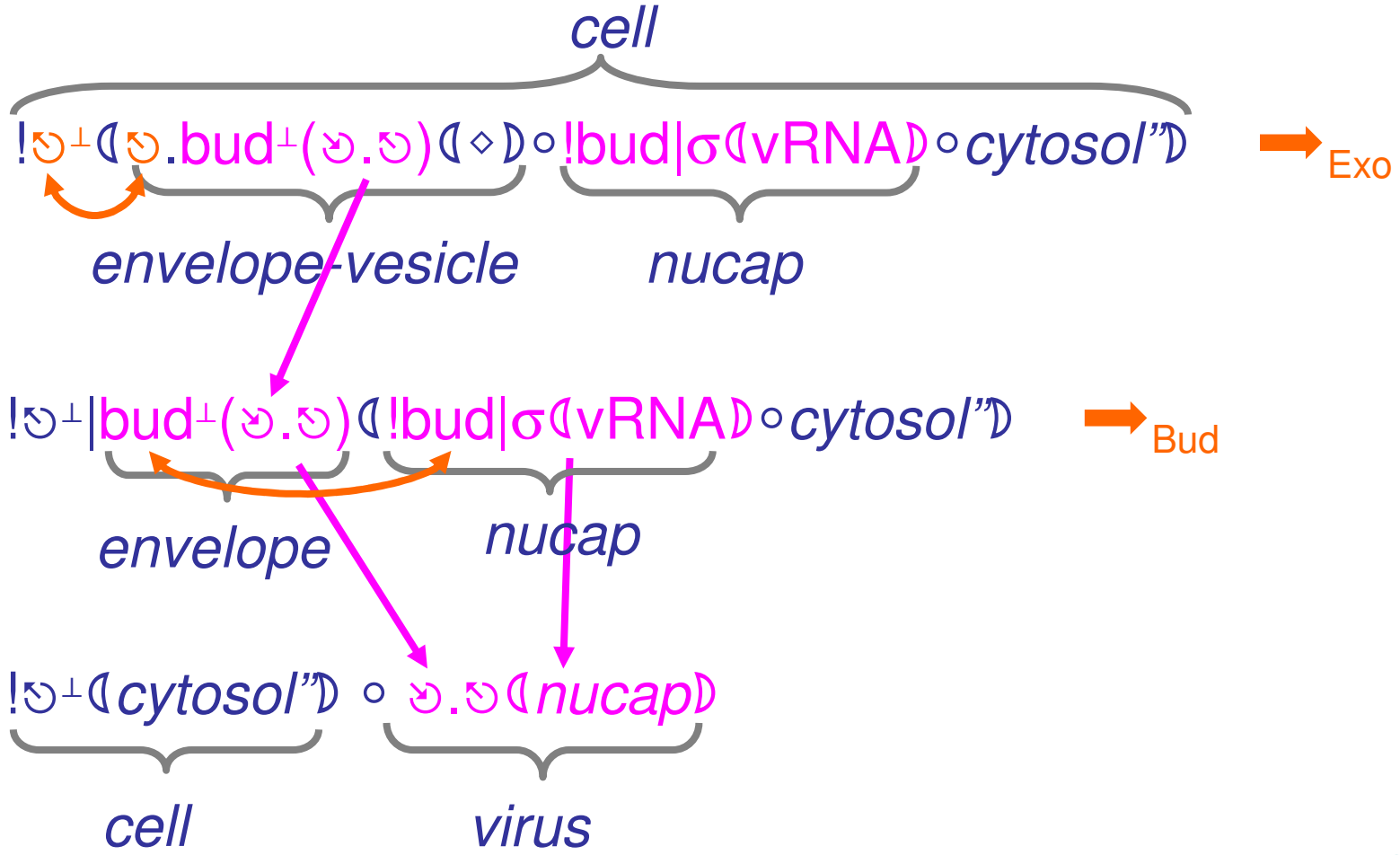
Ex: Viral Progeny

Assume:

nucap ∘ *cytosol* ➡➡ *nucap*^{n} ∘ *envelope-vesicle*^{m} ∘ *cytosol'*

by available cellular machinery

Then:

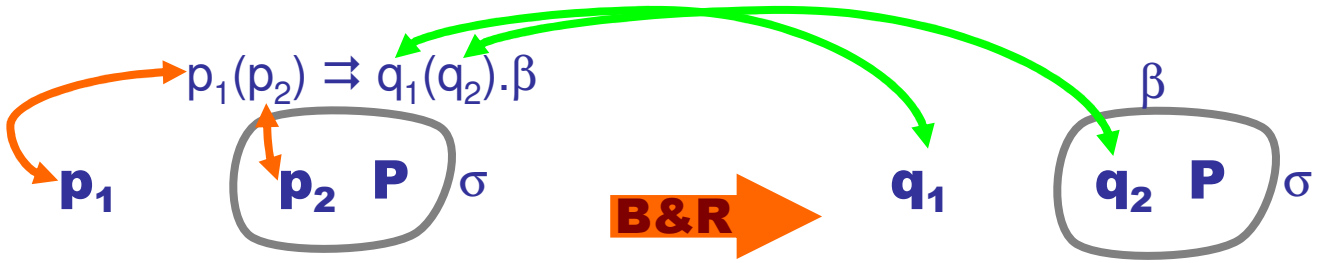


Handling Molecules

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



This single operation can essentially account for the whole Protein Machine, including its interactions with membranes. Except that, one must add some form of protein complexation, either as in BioSPi by adding restriction, or as in κ-calculus by adding complex molecules.

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

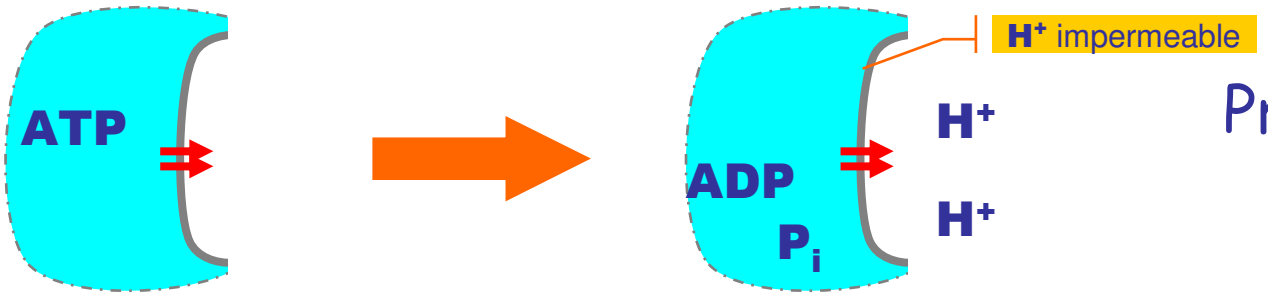
(multiset rewriting, inside and outside membranes)

Simple bindings and releases - "$\diamond(\diamond)$" is omitted:

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

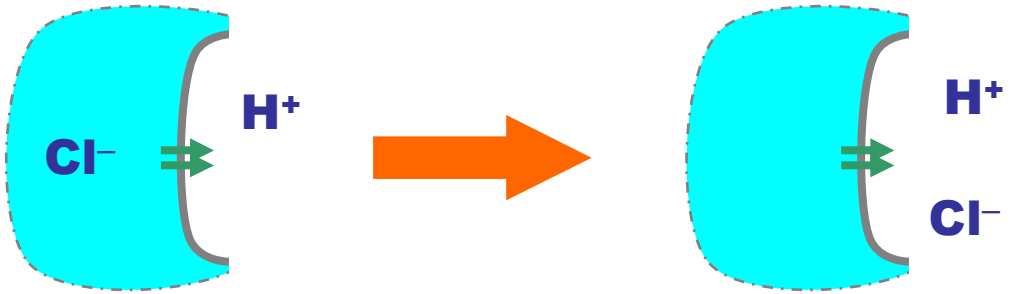
Ex: Molecular Pumps and Channels

E.g. plant vacuole (white).

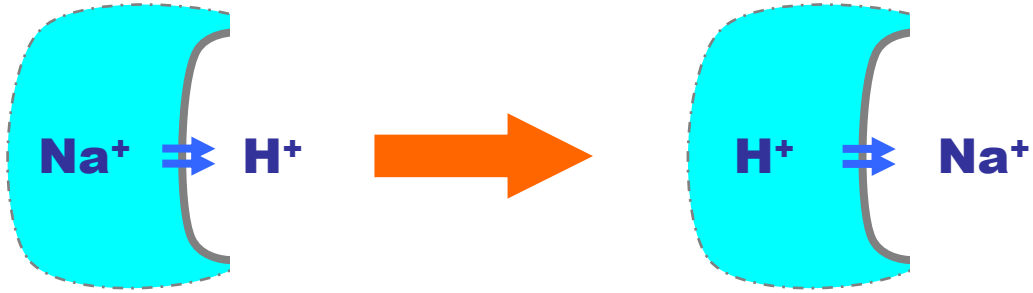


Proton Pump

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



Ion Channel



Proton Antiporter

A plant vacuole membrane has all those things on it.

...

$$\text{ProtonPump} = !\ \text{ATP}(\diamond) \rightrightarrows \text{ADP} \circ \text{P}_{\text{i}}(\text{H}^{+} \circ \text{H}^{+})$$

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

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

$$\text{PlantVacuole} = \text{ProtonPump} \mid \text{IonChannel} \mid \text{ProtonAntiporter}\ (\diamond)$$

Hence this reaction notation, $\rightrightarrows$, is "like" chemical reaction notation, $\rightarrow$, but talking about both sides on a membrane at once.

(N.B. no built-in conservation of mass in either case.)

Special Cases of B&R

Chemical reaction catalysis (inside a compartment)

$p \longrightarrow q \triangleq\ !\, p(\diamond) \rightrightarrows q(\diamond)\text{⦇}\text{⦈}$

$p \Longleftrightarrow q \triangleq\ p \longrightarrow q \circ q \longrightarrow p$

E.g. peptide bond between two aminoacids R^1 R^2:

$R^1\text{-}COOH \circ H_2N\text{-}R^2 \longrightarrow R^1\text{-}CO\text{-}HN\text{-}R^2 \circ H_2O$

Compartment conditions (on the brane of a compartment)

$p \dot{\rightarrow} q \triangleq\ !\, \diamond(p) \rightrightarrows \diamond(q)$

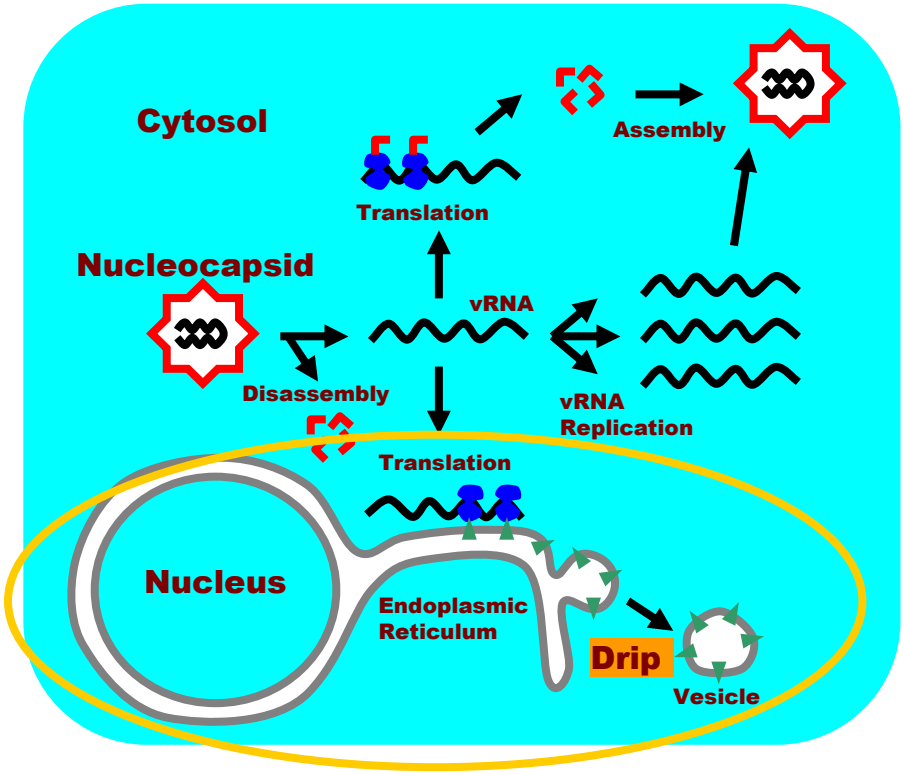
$p \dot{\rightarrow} q|\sigma\text{⦇}P\text{⦈}$ Condition affecting P

E.g. a condition-driven reaction:

$p \dot{\rightarrow} q|\sigma\text{⦇}p\text{⦈} \Rightarrow p \dot{\rightarrow} q|\sigma\text{⦇}q\text{⦈}$

Ex: Virus Replication

nucap ∘ *cytosol* ➡➡ *nucap*^{n} ∘ *envelope-vesicle*^{m} ∘ *cytosol'*



ER ≜ !vRNA(⋄)⇉vRNA(⋄). drip(↻.bud$^{\perp}$(↻.↻))《*Nucleus*》

when triggered by vRNA

exo to cell membrane

nucap budding receptor

virus membrane

envelope-vesicle

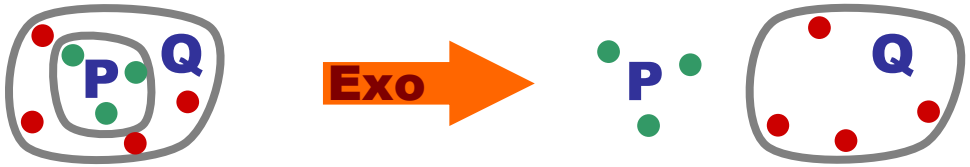
(See paper for the other two vRNA pathways)

Summary of Instruction Set So Far

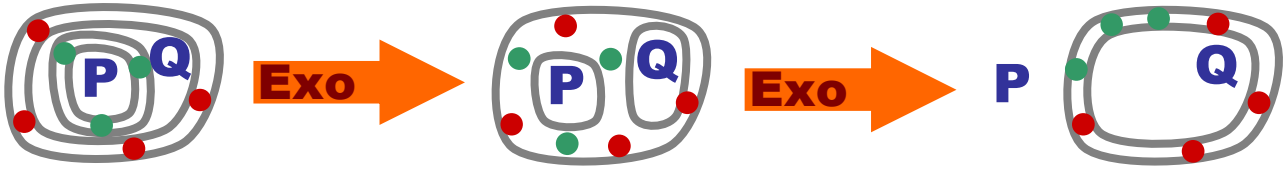
- Phago-exo-pino for the Membrane Machine
  - Plus mate-bud-drip, in principle definable.
- Bind&Release for the Protein Machine
  - Still could add κ-calculus complexation
    - Helps remove another need for π-restriction, which makes almost any analysis easier.
    - Helps avoid unrealistic uses of membranes for complexation.
- What about the Gene Machine?
  - Need some extra detailed mechanism for the regulatory regions?
  - Or conversely some simplifying abstraction for gene cascades?

Why do we need Brane Calculi, again?

Original "on brane" Exo of Brane Calculus



"In brane" encoding (e.g. in BioAmbients or SMBL) goes wrong



"Ball bearing" encoding; best we can do "in brane"

Awkward encoding. And all kinds of things can go wrong in the intermediate state.

- One cannot easily represent the Exo reaction in BioAmbients or any such compartment-based calculus, nor can one easily add it as a new primitive!
- But we can add BioAmbients-like In/Out out to Brane Calculi if we want to.

Adding Frills to the Framework

- So far, purely combinatorial:
  - No name binding, channel creation, communication…
  - Closer to combinatorial flavor of protein interactions
  - Goes a long way.
- But one can easily add all that, and more:
  - CCS-style communication
    - Diffusion of molecules on cellular membrane
  - BioAmbients-style communication
    - Diffusion of molecules across cellular membrane
  - BioAmbients-like mobility
    - Non-bitonal
  - π-style restriction
- We have a framework where we can plug&play a rich set of interactions, while supporting compartments.

Conclusions

- What's different about "bio"-compartment calculi?
  - Orientability and bitonality invariants inspire new, more bio-realistic, operators (as part of an ongoing process).
  - Fluids inside fluids: two commutative monoids.
  - Computing *on* the membrane, not *inside* of it.

- What's needed to model "the whole cell thing"?
  - A single language/calculus for protein interaction networks, gene regulatory networks, and transport networks?
  - Extensible to multicellular organisms too?
  - Oh, my!

> *"The problem of biology is not to stand aghast at the complexity but to conquer it."* - Sydney Brenner

> *"Although the road ahead is long and winding, it leads to a future where biology and medicine are transformed into precision engineering."* - Hiroaki Kitano.

References

[MCB] Molecular Cell Biology, Freeman.

[MBC] Molecular Biology of the Cell, Garland.

[Ptashne] A Genetic Switch.

[Davidson] Genomic Regulatory Systems.

[Milner] Communicating and Mobile Systems: the π-calculus.

Papers

Bitonal Systems

membrane reactions and their connections to "local" patch reactions.

Brane Calculi

process calculi with computation "on" the membranes, not inside them.

BioAmbients

a stochastic calculus with compartments.

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

Interdisciplinary Culture Shock

When meddling in somebody else's science, one can do very silly things.

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

A programmer's approach to understanding bacteria
1) Write a formal high-level spec: (eat; split)*
2) Code a 100,000 lines simulator in C++; ignore spec.
3) Use keyboard lights as only output device.
4) Take frequent core dumps, store them in database.
5) Use 7 different C++ compilers, plot the differences.
6) Remove random lines of code until it stops.
7) Memo: do *not* put PDA in centrifuge.