Membrane Interactions

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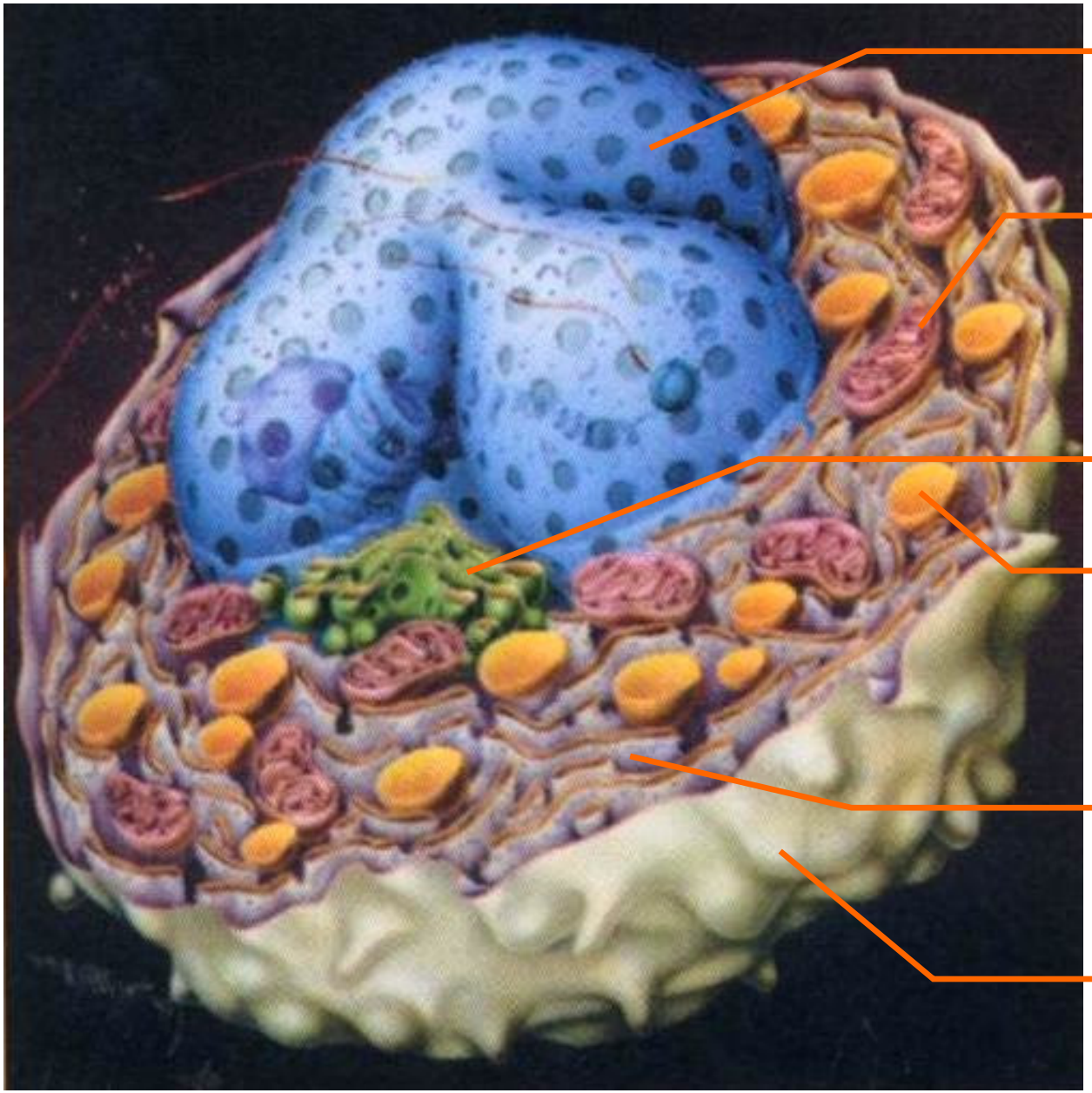
Biological *Systems*

The emerging area of *Systems Biology*: interdisciplinary study of relationships and interactions of biological components

Eukaryotic Cell

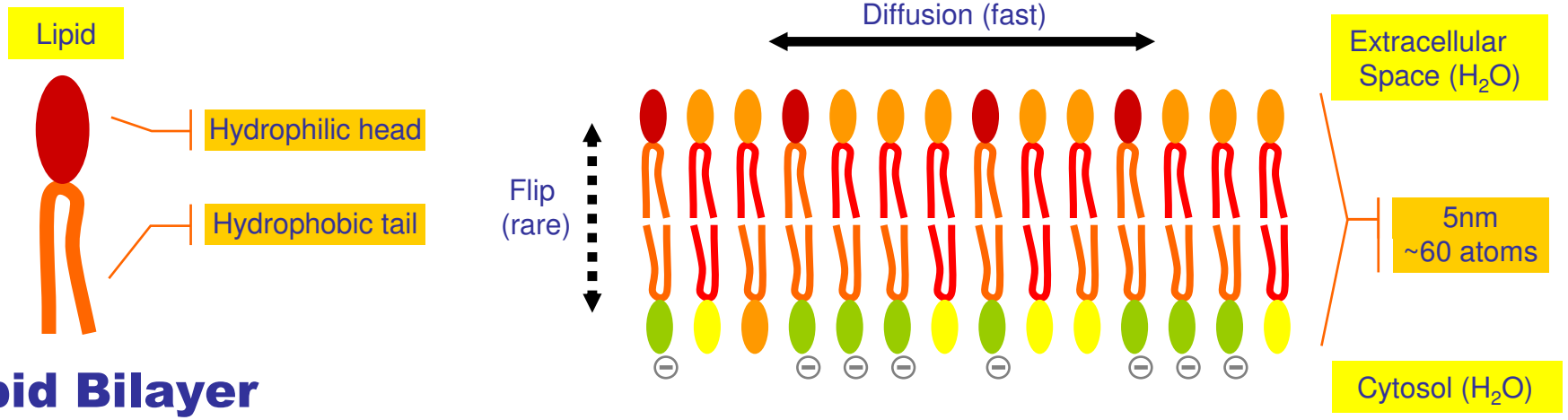
Membranes everywhere



Importance of Membranes

- 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?

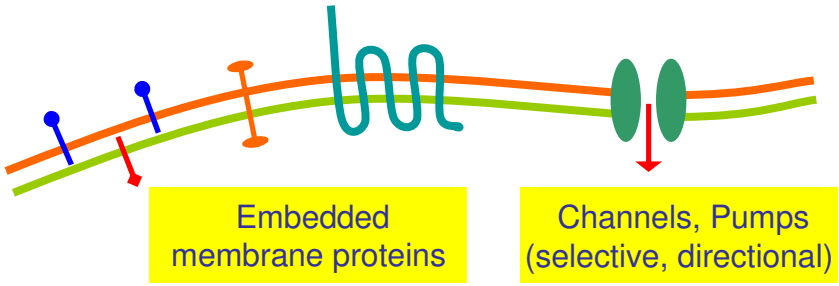
Membranes are Oriented 2D Surfaces

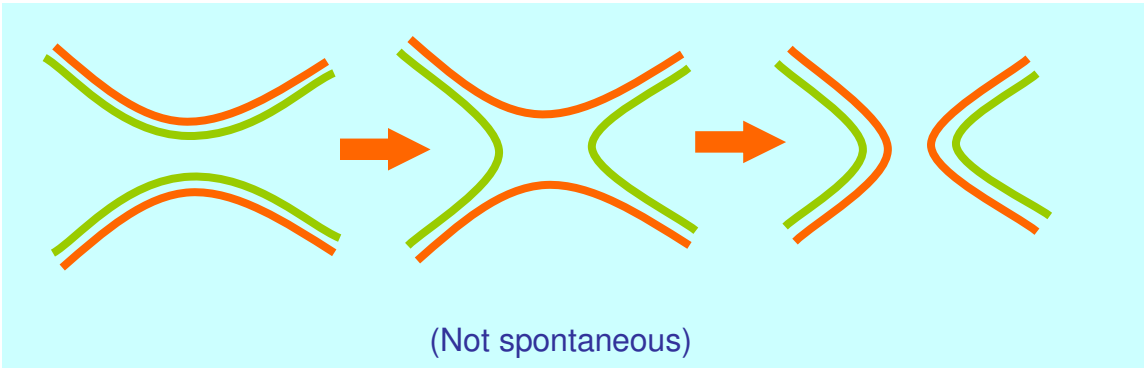


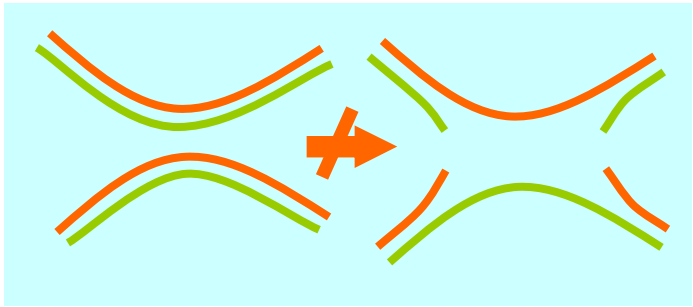
Lipid Bilayer

Self-assembling
Largely impermeable
Asymmetrical (in real cells)
With embedded proteins
From microns to meters long

A 2D fluid inside a 3D fluid!

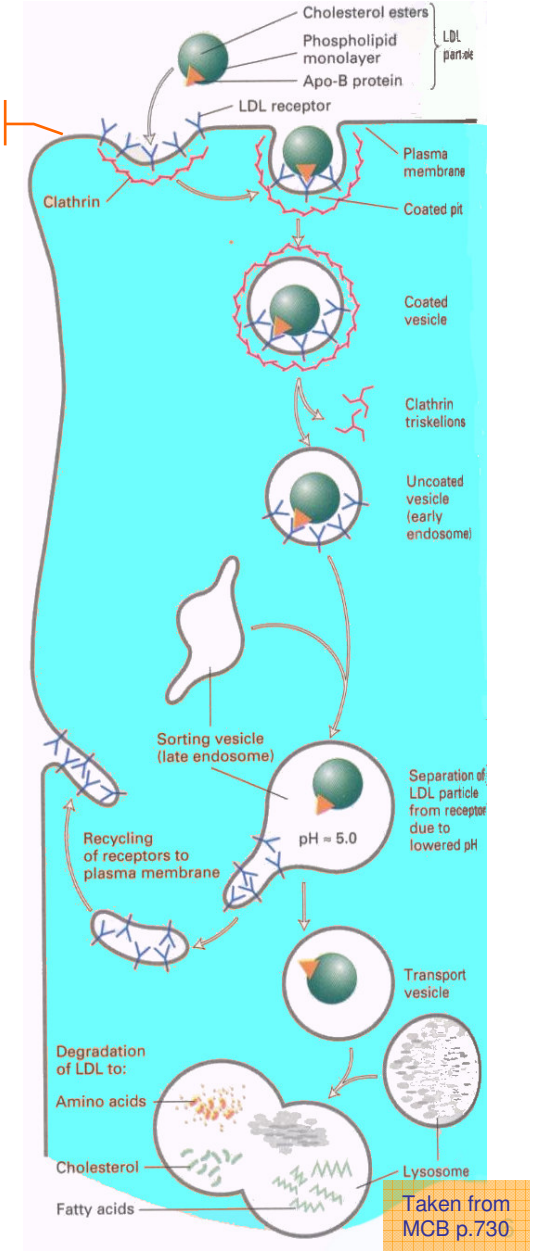




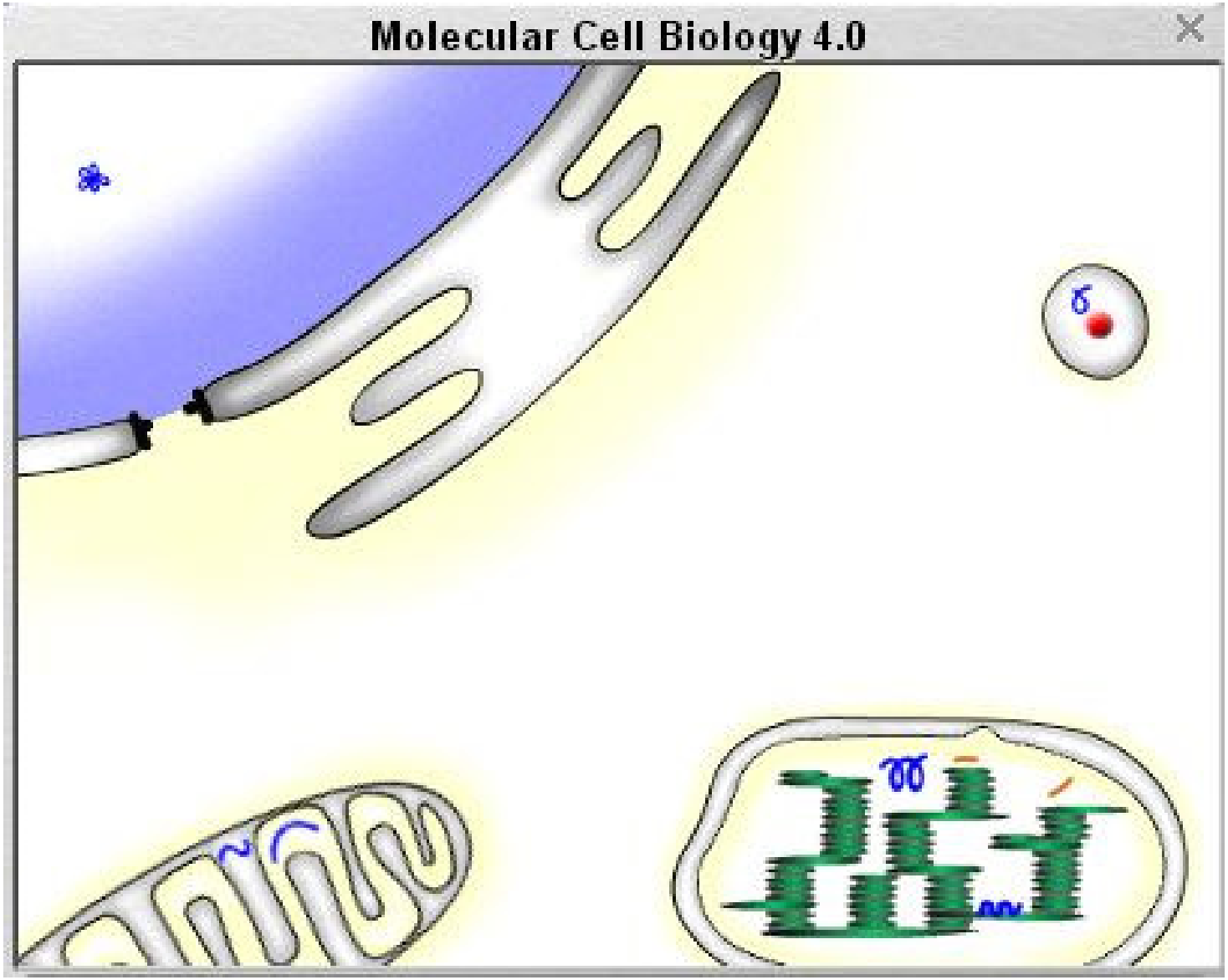


A Biological Algorithm

- 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.



Dynamic Compartments



Taken from MCB CD

Aims

- Describing biological processes
  - More precisely than informal diagrams.
  - Writing bioalgorithms in something close to a language.
  - For precision, analysis, simulation, storage, search…
- Abstraction options
  - Start too low ⇒ get lost in a mess of details.
  - Start too high ⇒ ignore too many details.
  - But certainly need to model different abstraction levels.
- Evolving Approach
  - Molecular Reactions, using process calculi (BioSPi)
  - Molecular Reactions + Membranes (BioAmbients)
  - Reactions *on* Membranes (*Brane Calculi*)

The Architecture of Biological Cells

A lot of esoteric chemistry implementing:

Three Abstract Machines

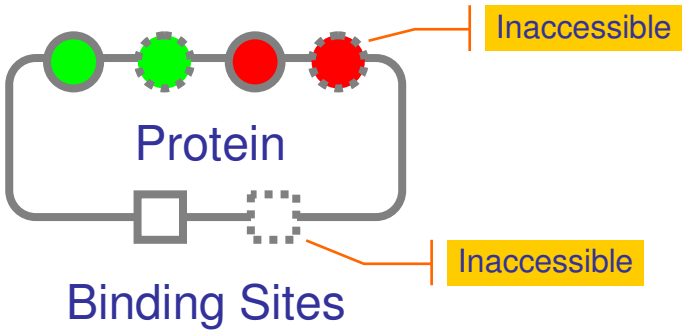
Molecular Interaction Networks - The Protein/RNA Machine
Gene Regulatory Networks - The Gene Machine
Transport Networks - The Membrane Machine

"When you want to have a predictive science, you have to be able to calculate" - Sydney Brenner,
2002 Nobel Prize in Physiology and Medicine

1. The Protein/RNA Machine

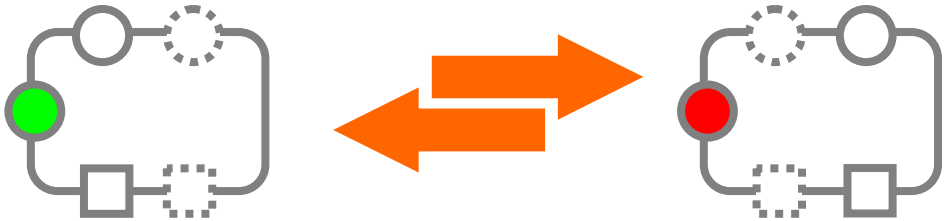
cf. BioCalculus [Kitano Nagasaki], κ-calculus [Danos Laneve]

On/Off switches

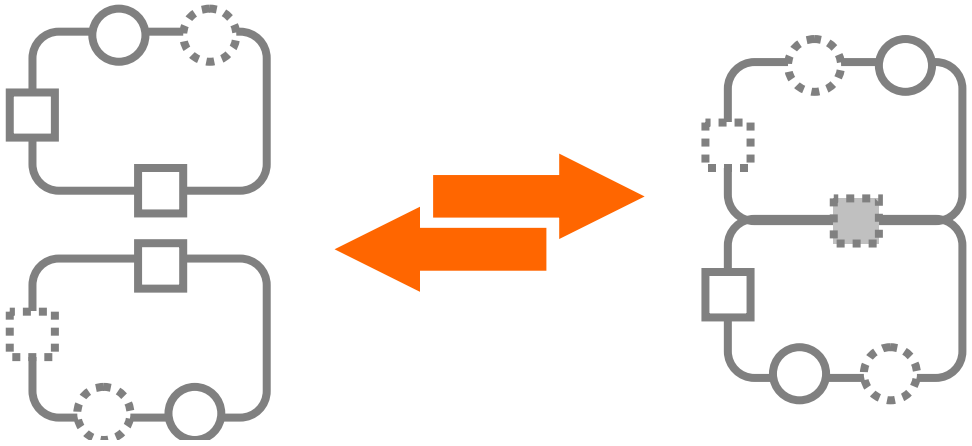


Each protein has a fixed structure of binary switches and binding sites. But not all may be always *accessible*.

No need to worry about lower levels of chemical description IF we accept ~10000 primitives!



Switching of accessible switches.
- May cause other switches and binding sites to become (in)accessible.
- May be triggered or inhibited by nearby specific proteins in specific states.

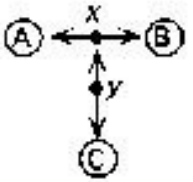


Binding on accessible sites.
- May cause other switches and binding sites to become (in)accessible.
-- May be triggered or inhibited by nearby specific proteins in specific states.

Molecular Interaction Maps (Kohn)

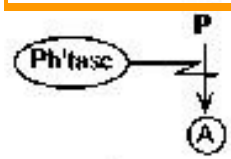
The double-arrowed line indicates that proteins **A** and **B** can bind to each other. The "node" placed on the line represents the **A:B** complex.

Asymmetric binding where protein **A** donates a peptide that binds to a receptor site or pocket on protein **B**.

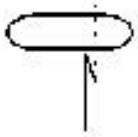


Representation of multimolecular complexes: x is **A:B**; y is **(A:B):C**. This notation is extensible to any number of components in a complex.

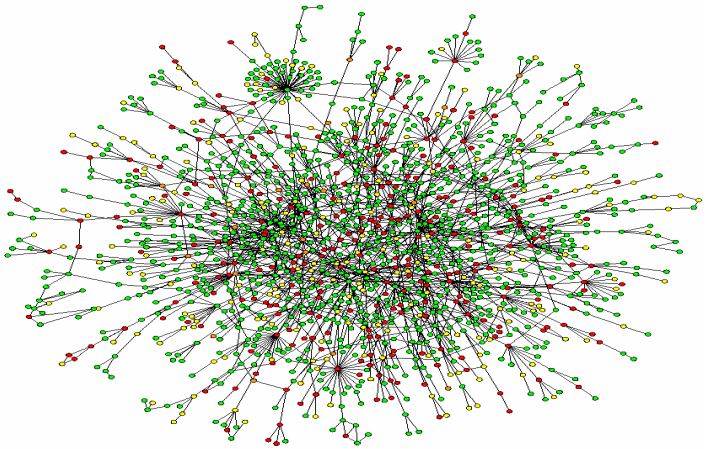
Covalent modification of protein **A**. The single-arrowed line indicates that **A** can exist in a phosphorylated state. The node represents the phosphorylated species.



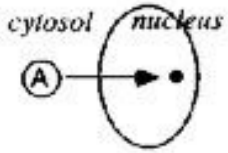
Cleavage of a covalent bond: dephosphorylation of **A** by a phosphatase.



Proteolytic cleavage at a specific site within a protein.

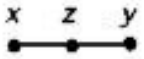


Stoichiometric conversion of **A** into **B**.



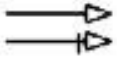
Transport of **A** from cytosol to nucleus. The node represents **A** after it has been transported into the nucleus.

Formation of a homodimer. Filled circle on the right represents another copy of **A**. The node on the line represents the homodimer **A:A**.



z is the combination of states defined by x and y.

Enzymatic stimulation of a reaction.



General symbol for stimulation.
A bar behind the arrowhead signifies necessity.

General symbol for inhibition.

Shorthand symbol for transcriptional activation.

Shorthand symbol for transcriptional inhibition.

Degradation products

Taken from Kurt W. Kohn

An actual molecular interaction network.
(Nodes are distinct protein kinds,
arcs mean that two kinds of proteins interact.)

The p53-Mdm2 and DNA Repair Regulatory Network

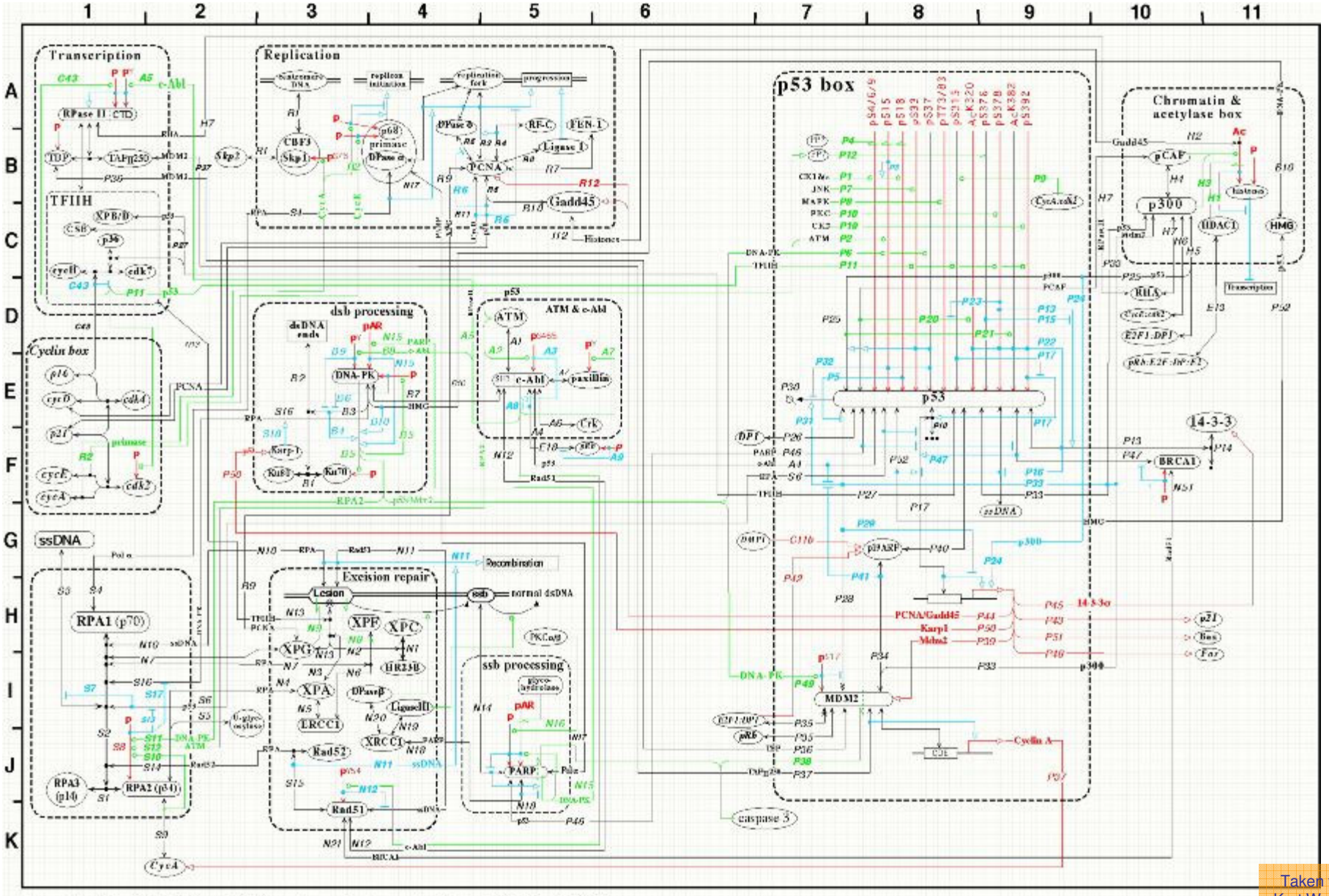


Figure 6B: The p53-Mdm2 and DNA repair regulatory network (version 2p - May 19, 1999)

Taken from Kurt W. Kohn

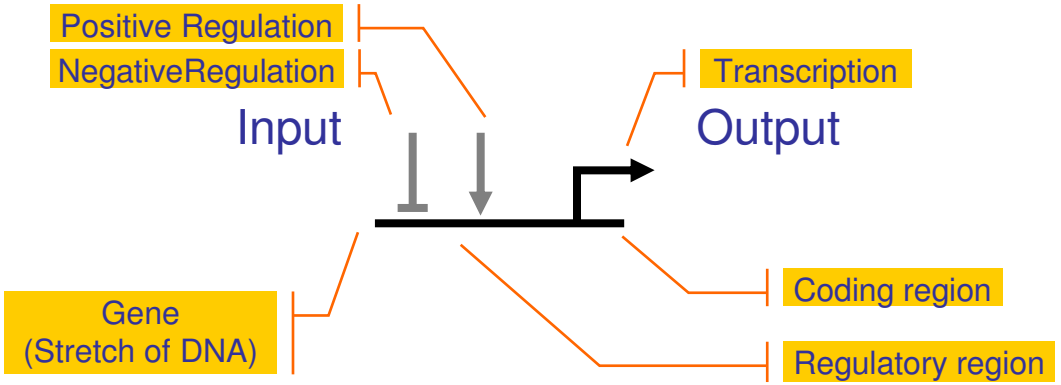
SBML

- Systems Biology Markup Language
  - Kitano's revised Molecular Interaction Maps
    - Better description for molecular interactions
    - Still graphically-oriented, semi-static
  - XML dialect with:
    - Compartments (statically nested)
    - Reagents with concentrations
    - Reactions with various rate equations
  - Read and written by many tools
    - Graph editors
    - Simulators (including simulation servers)
    - Databases

Formalization of the Protein Machine

- BioSPi
  - Regev-Shapiro-Silverman propose modeling chemical interactions (exchange of electrons and small molecules) as “communication”.
  - Standard stochastic simulation algorithms (Gillespie) can be used to run in-silico experiments.
  - Complex formation is encoded via π-restriction.
- Stochastic π-Calculus
  - Priami formalizes a stochastic version of π-calculus where channels have communication *rates*.
- κ-calculus
  - Danos and Laneve (following Kitano’s BioCalculus) define a calculus where complex formation is primitive.
- Bio State Charts
  - Harel uses State Charts to model biological interactions via a semi-graphical FSM notation.
- Pathway Logic
  - Talcott-Eker-Knapp-Lincoln use term-rewriting.

2. The Gene Machine



Think Petri Nets
with inhibitor arcs…

Regulation of a gene (positive and negative) influences transcription. The regulatory region has precise DNA sequences, but not meant for coding molecules: meant for binding regulators.

Transcription produces molecules (RNA or, through RNA, proteins) that bind to regulatory region of other genes (or that are end-products).

Human (and mammalian) Genome Size
3Gbp (Giga base pairs) **750MB** @ 4bp/Byte (CD)
Non-repetitive: 1Gbp **250MB**
In genes: 320Mbp **80MB**
Coding: 160Mbp **40MB** (< Window's *registry*!)
Protein-coding genes: 30,000-40,000

M.Genitalium (smallest true organism)
580,073bp **145KB** (PPT slide deck)
E.Coli (bacteria): 4Mbp **1MB** (floppy)
Yeast (eukaria): 12Mbp **3MB** (MP3 song)
Wheat 17Gbp **4.25GB** (DVD)

A Gene Regulatory Network

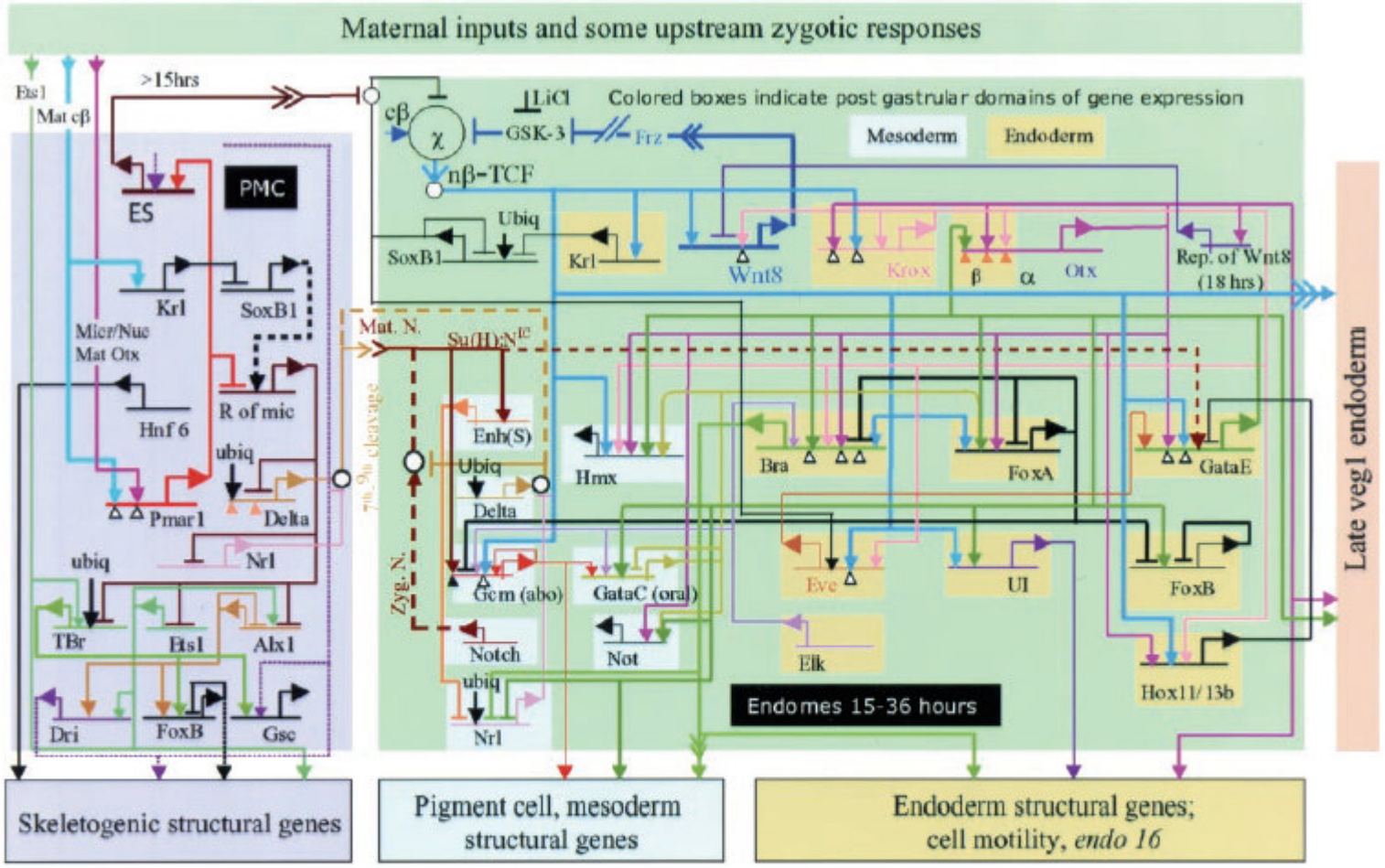
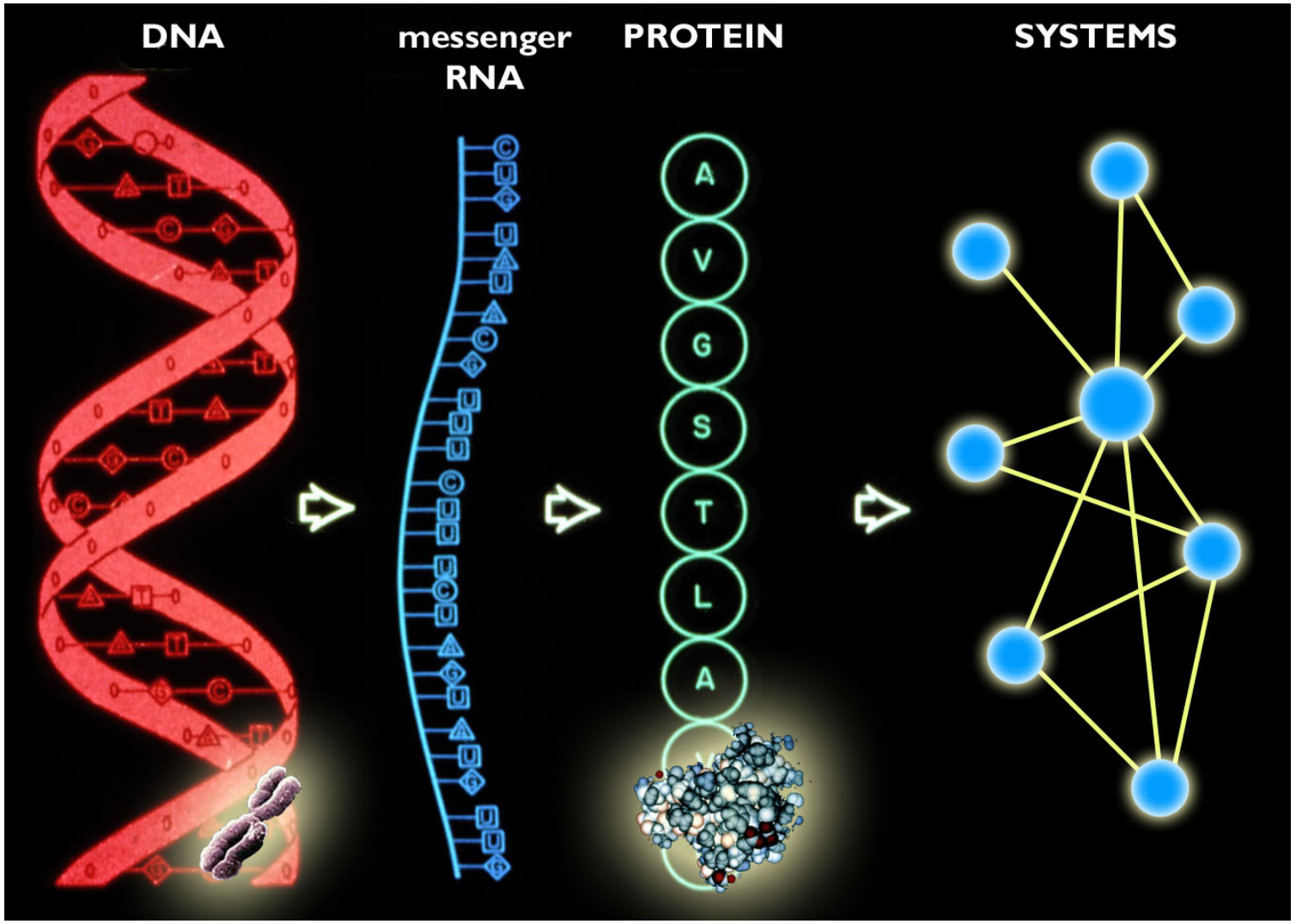


Fig. 1. Central portion of the *Strongylocentrotus purpuratus* embryo endomesoderm GRN, from fertilization to just before gastrulation. The diagram is a recent version of that initially presented in refs. 9–11. Suspected interactions at the cis-regulatory elements represented by the horizontal lines are shown, irrespective of when in the 0- to 30-h period or where in the embryo they are expected to occur [a "view from the genome" GRN (24); for interactions occurring only in given domains and at given periods see ref. 10 and www.its.caltech.edu/~mirsky/endomes.htm]. Transcriptional regulatory interactions are shown in the indicated spatial domains of the embryo: pmc domain, the skeletogenic micromere lineage; endomes domain, endomesoderm descendant from the sixth cleavage ring of eight "veg2" cells (2, 13, 24). Transcriptional inputs into the cis-regulatory elements of each named gene are indicated by arrows (activation, or permissive of activation) or bars (repression). Outputs from each gene (where known) are indicated by color-coded lines emanating from the bent arrows that symbolize transcription. For evidence see text, refs. 9–11, 15, 16, and 18, and www.its.caltech.edu/~mirsky/endomes.htm. An arrowhead inserted in an arrow tail indicates an intercellular signaling interaction; small open circles indicate cytoplasmic interactions or specific events off the DNA, e.g., that by which the Soxb1 factor interferes with nuclearization of β-catenin (26). For further details see refs. 9 and 10 and www.its.caltech.edu/~mirsky/endomes.htm.

Taken from
Eric H Davidson

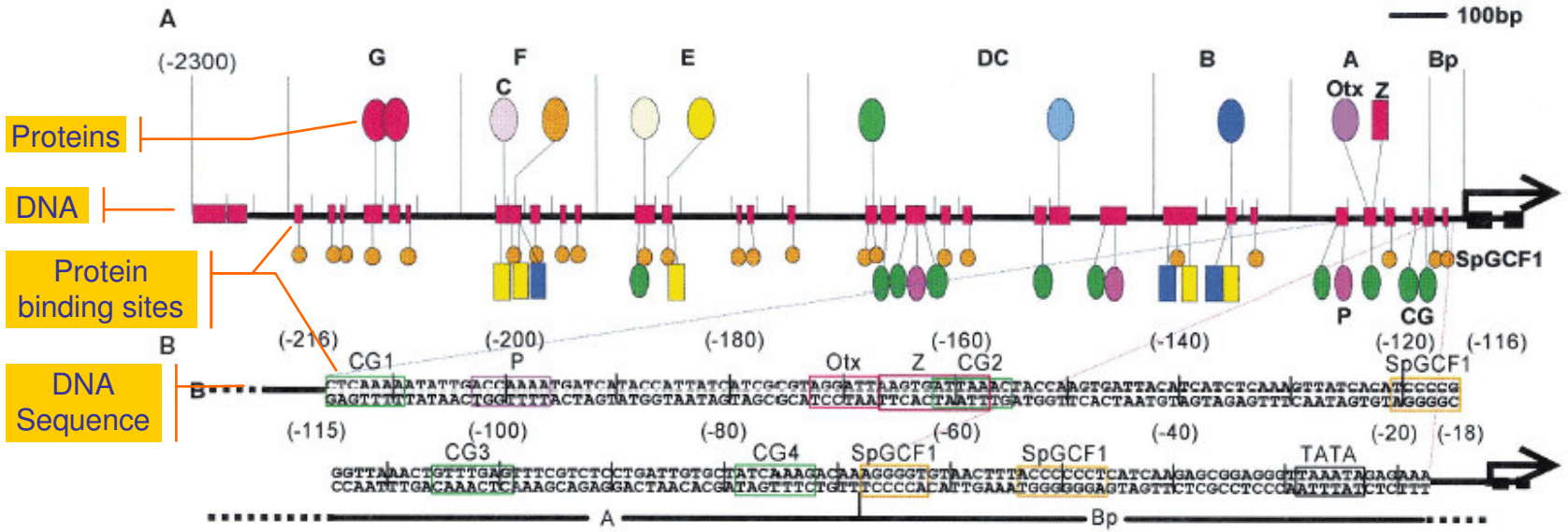
Structure of the Coding Region

- Central Dogma of Molecular Biology:



Taken from Leroy Hood

Structure of a Regulatory Region



2300bp!

> average protein

C **Module A functions:**

Vegetal plate expression in early development:

Synergism with modules B and G enhancing endoderm expression in later development:

Repression in ectoderm (modules E and F) and skeletogenic mesenchyme (module DC):

Modules E, F and DC with LiCl treatment:

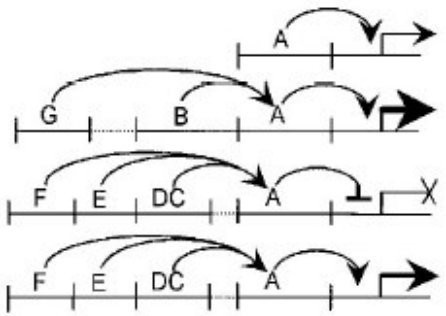
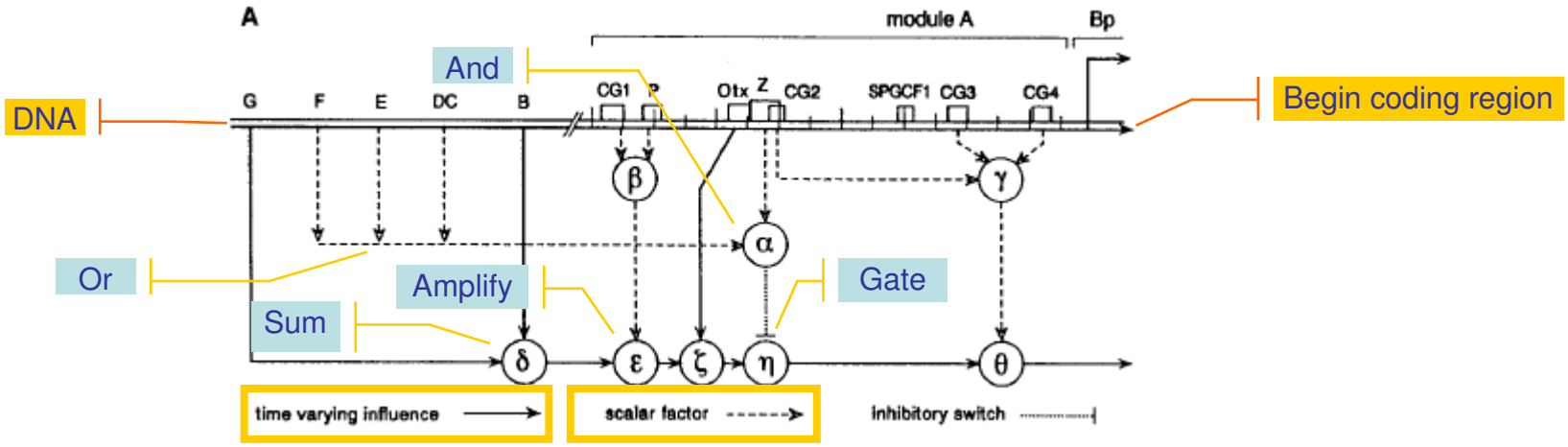


Fig. 1. *Endo16* cis-regulatory system and interactive roles of module A. (**A**) Diversity of protein binding sites and organization into modular subregions [modified from (*7*)]. Specific DNA binding sites are indicated as red blocks; modular subregions are denoted by letters G to A (Bp, basal promoter). Proteins binding at the target sites considered in this work are indicated: Otx, SpOtx-1 (*12*); SpGCF1 (*14*); the proteins CG, Z, and P, which are not yet cloned; and protein C [a CREB family protein (*18*)] in subregion F. Proteins for which sites occur in multiple regions of the DNA sequence (indicated by the black line) are shown beneath. (**B**) Sequence of module A and location of protein binding sites. Sites are indicated in the same colors as in (A). A fragment containing CG_3 and CG_4 sites as well as Bp has no endoderm-specific activity and services other upstream cis-regulatory systems promiscuously; similarly, the *Endo16* cis-regulatory system functions specifically with heterologous promoters substituted for Bp (*5, 8, 19*). Boxed sequences indicate conserved core elements of the target sites (*7, 12, 14*), not the complete target site sequences. (**C**) Integrative and interactive functions of module A (*5, 8*). Module A communicates the output of all upstream modules to the basal transcription apparatus. It also initiates endoderm expression, increases the output of modules B and G, and is required for functions of the upstream modules F, E, and DC. These functions are repression of expression in nonendodermal domains and enhancement of expression in response to LiCl.

Taken from Eric H Davidson

Function of a Regulatory Region

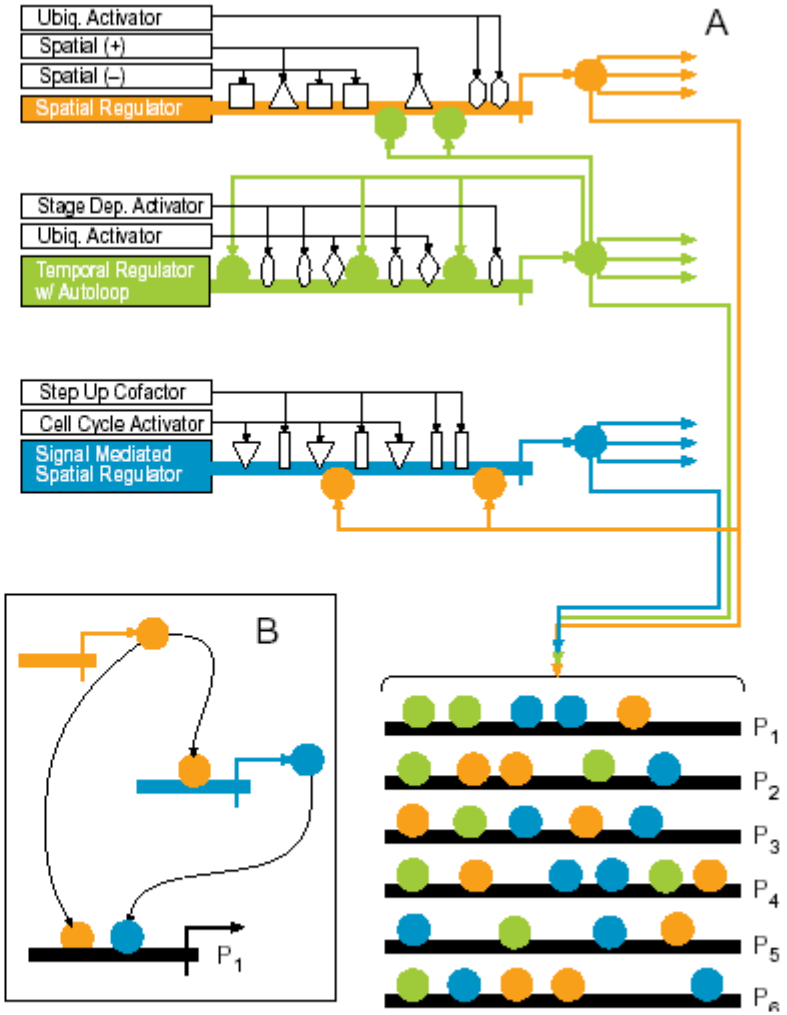


B

if (F = 1 or E = 1 or CD = 1) and (Z = 1)	Repression functions of modules F, E, and DC mediated by Z site
α = 1	
else α = 0	
if (P = 1 and CG_1 = 1)	Both P and CG_1 needed for synergistic link with module B
β = 2	
else β = 0	
if (CG_2 = 1 and CG_3 = 1 and CG_4 = 1)	Final step up of system output
γ = 2	
else γ = 1	
δ(t) = B(t) + G(t)	Positive input from modules B and G
ε(t) = β*δ(t)	Synergistic amplification of module B output by CG_1-P subsystem
if (ε(t) = 0)	Switch determining whether Otx site in module A, or upstream modules (i.e., mainly module B), will control level of activity
ξ(t) = Otx(t)	
else ξ(t) = ε(t)	
if (α = 1)	Repression function inoperative in endoderm but blocks activity elsewhere
η(t) = 0	
else η(t) = ξ(t)	
Θ(t) = γ*η(t)	Final output communicated to BTA

Taken from
Eric H Davidson

Where/When/HowMuch



3 genes encoding trascription factors

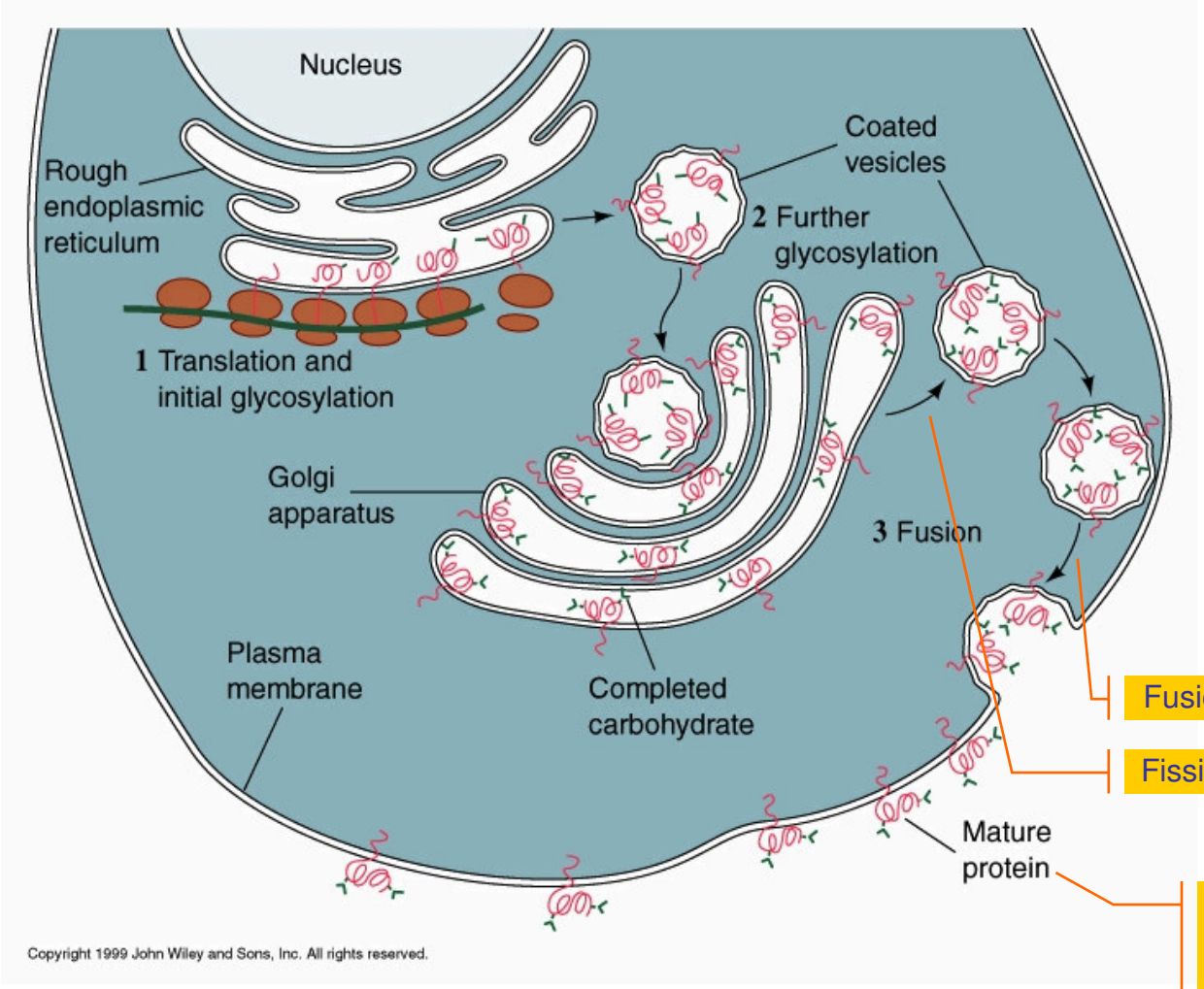
6 genes encoding proteints

Taken from Eric H Davidson

Formalization of the Gene Machine

- Hybrid Petri Nets
  - [Matsuno, Doi, Nagasaki, Miyano]
- Stochastic π-calculus
  - [?] seems natural

3. The Membrane Machine



Molecular transport and transformation through dynamic compartment fusion and fission.

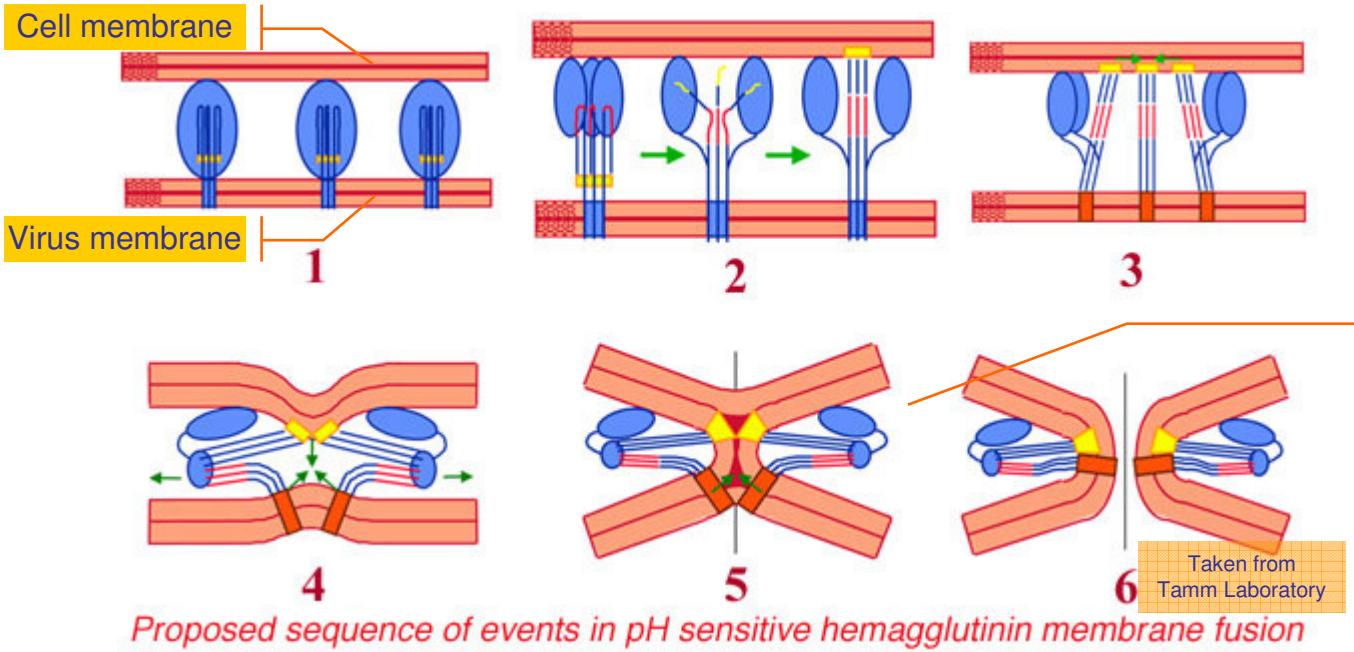
These "Life of a Saint" diagrams (all temporal stages shown at once) are popular because this is what people actually see in microscopes.

Well, what is all this for?

"Given the complicated pathways that have evolved to synthesize them, it seems likely that these [modified proteins] have important functions, but for the most part these functions are not known" [MBP p.609]

Membrane Fusion

Positive curvature to Negative curvature transition in 3D

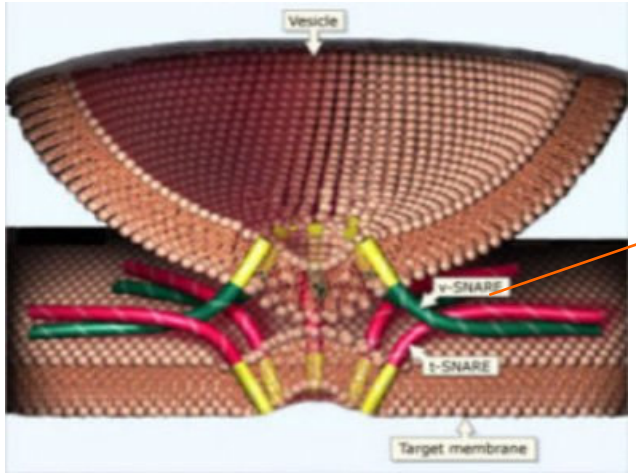


Proposed sequence of events in pH sensitive hemagglutinin membrane fusion

Taken from Tamm Laboratory

Aggressive fusion (virus)

By unknown mechanisms, the exoplasmic leaflets of the two membranes fuse" [MCB p745]

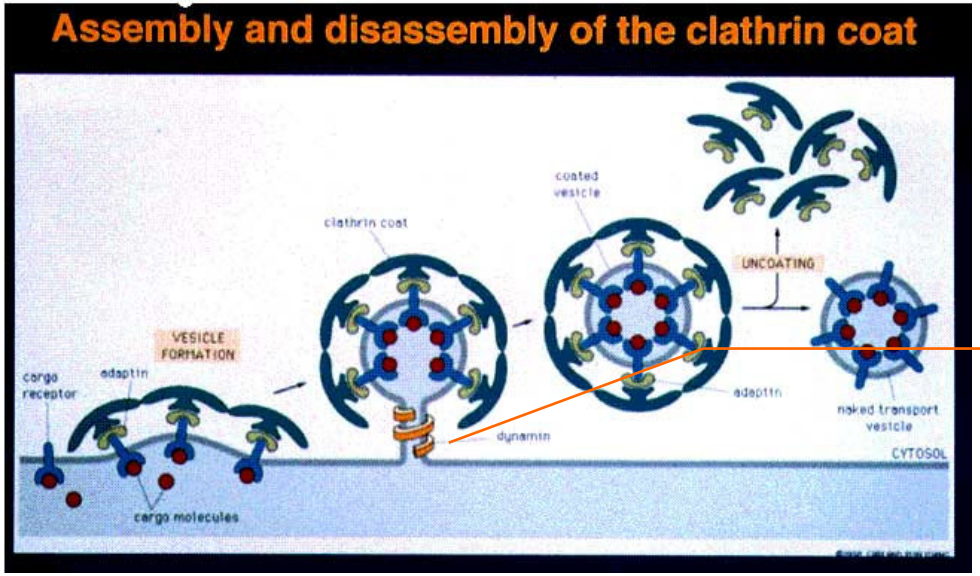


Cooperative fusion (vesicle)

"Fusion of the two membranes immediately follows prefusion, but precisely how this occurs is not known" [MCB p742]

Membrane Fission

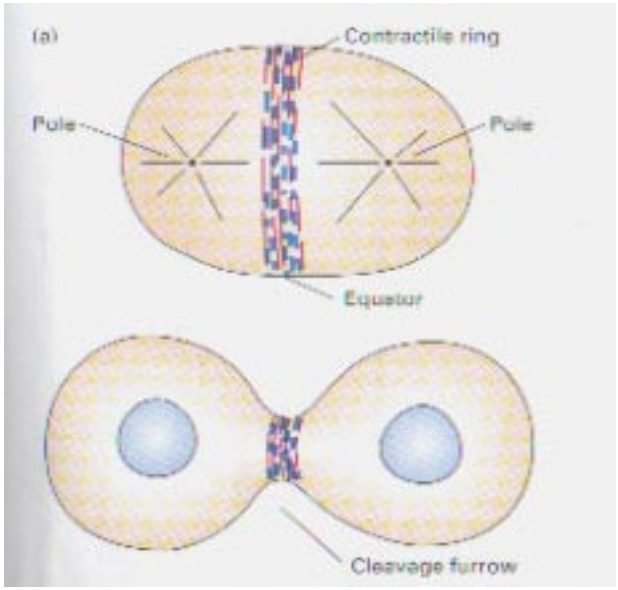
Negative curvature to Positive curvature transition in 3D



Vesicle Formation

Movie by Allison Bruce

"Nonetheless, the actual process whereby a segment of phospholipid bilayer is 'pinched off' to form a pit and eventually a new vesicle is still not understood" [MCB p.746]

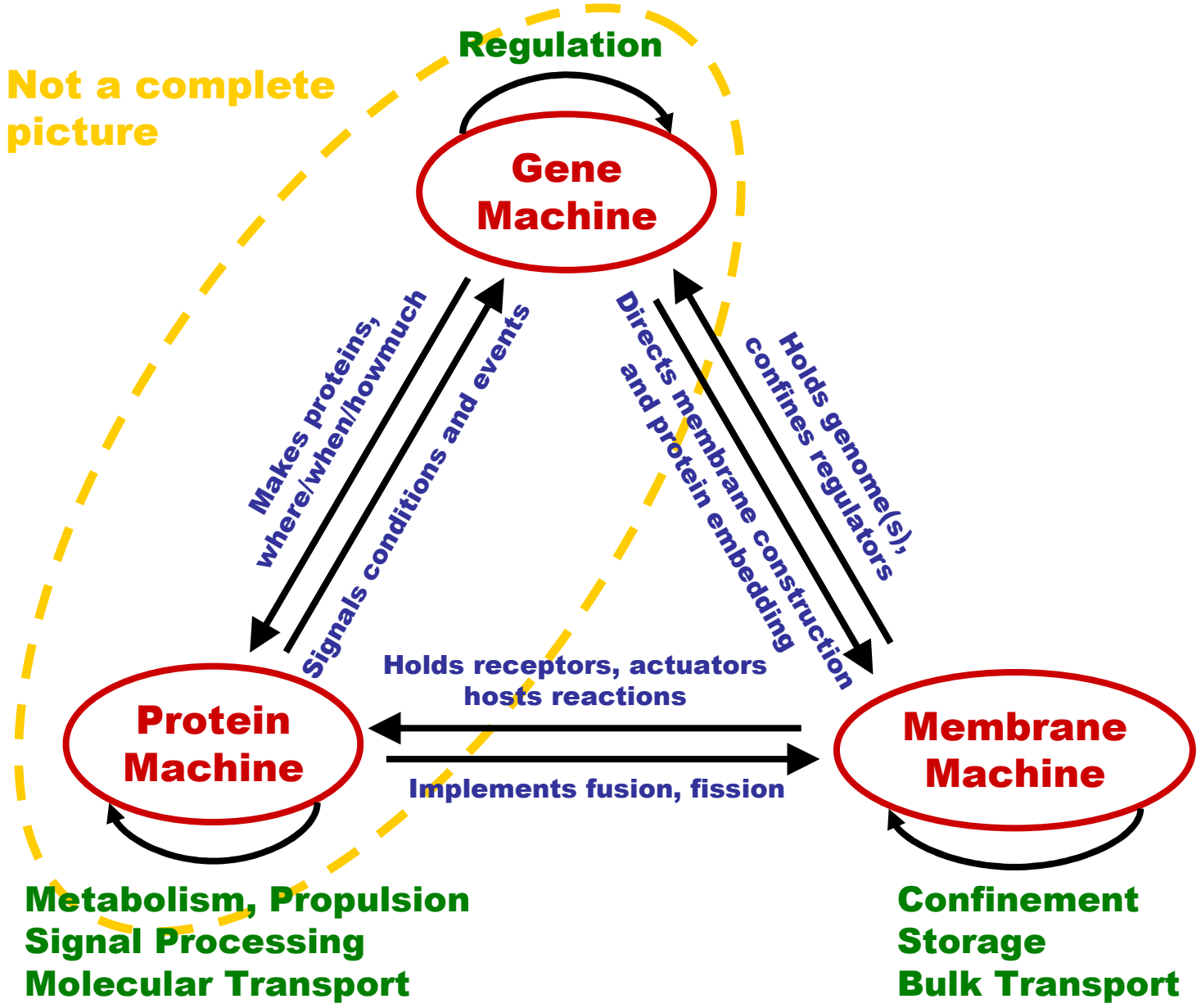


Cytokinesis (Mitosis)

Formalization of the Membrane Machine

- P-Systems
  - G.Paun (beginning ~10 years ago) uses ideas from the theory of grammars and formal languages to model “Membrane Computing”.
  - Some aspects not a good match (notions of termination, lock-step execution, only static compartments studied in depth).
- BioAmbients
  - An extension of BioSPi along Ambient Calculus lines (with more bio-relevant mobility primitives) to model dynamic compartments.
- Brane Calculi
  - Computation *on* the membrane…

4. Summary

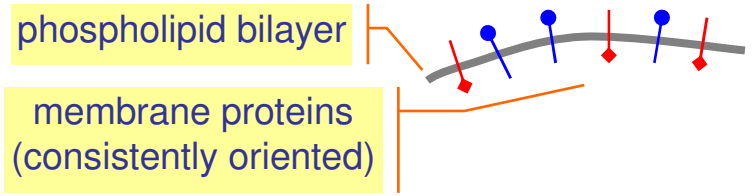

Regulation
Not a complete picture
Gene Machine
Makes proteins, where/when/howmuch
Signals conditions and events
Directs membrane construction and protein embedding
Holds genome(s), confines regulators
Holds receptors, actuators hosts reactions
Protein Machine
Membrane Machine
Implements fusion, fission
Metabolism, Propulsion
Signal Processing
Molecular Transport
Confinement
Storage
Bulk Transport

Bitonal Membrane Systems

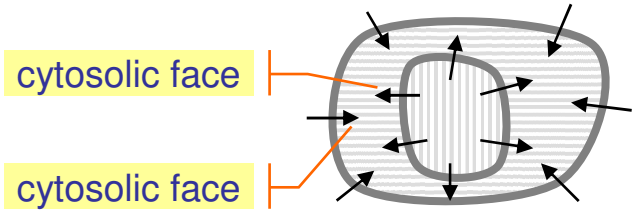
A high-level descriptive view
of basic membrane properties
but with very little “mechanism”

Systems of Oriented Membranes

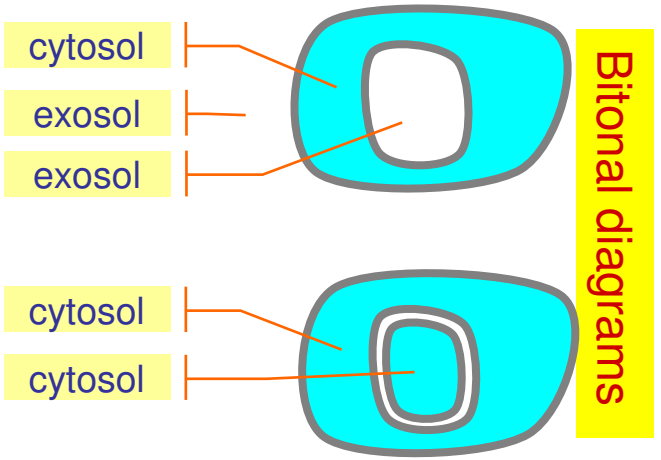
Membranes are closed non-intersecting curves, with an orientation[1].



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.)



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 Structure

Bitonality

Blue and white areas alternate.

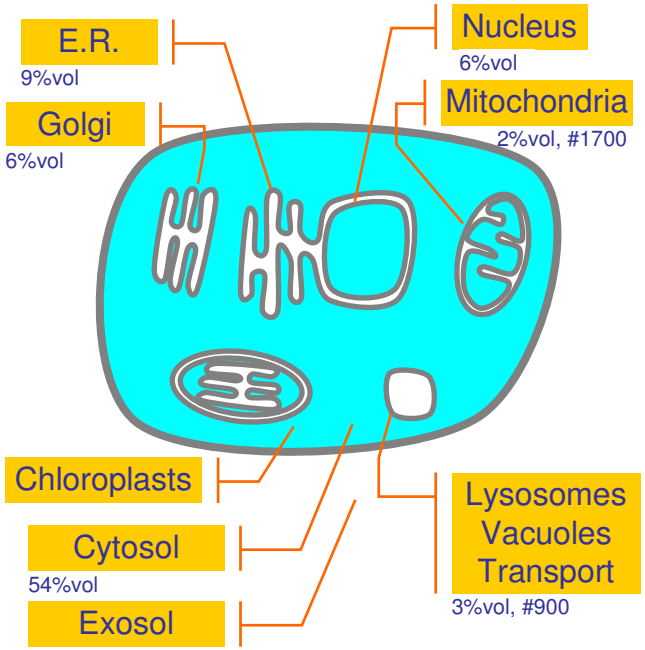
Bitonal Invariant

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

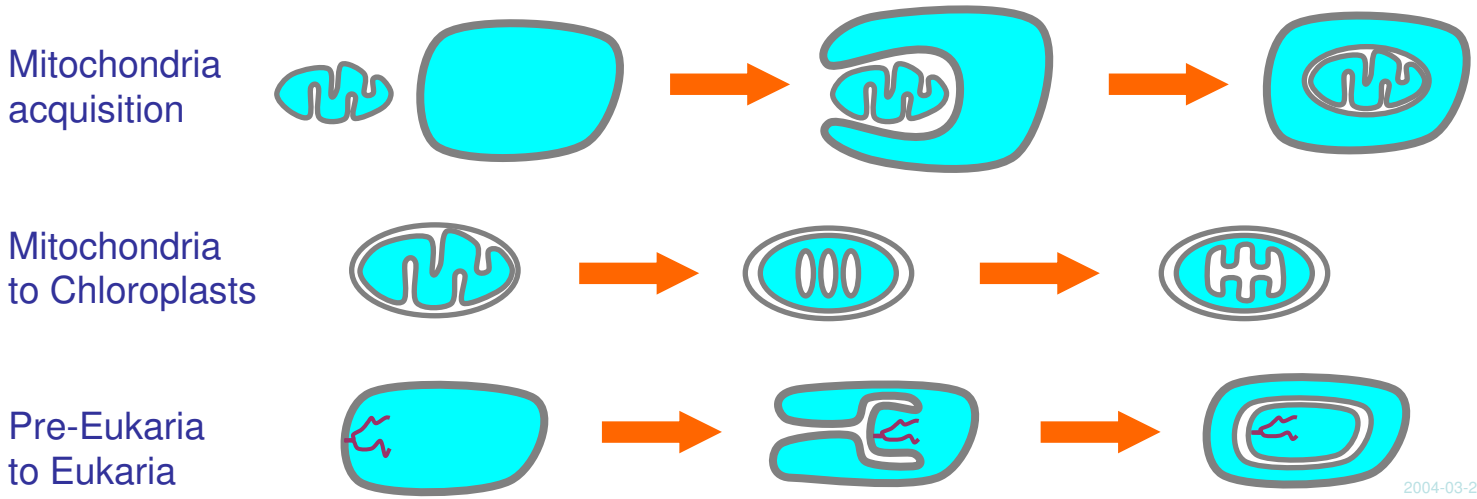
Bitonal Duality

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.

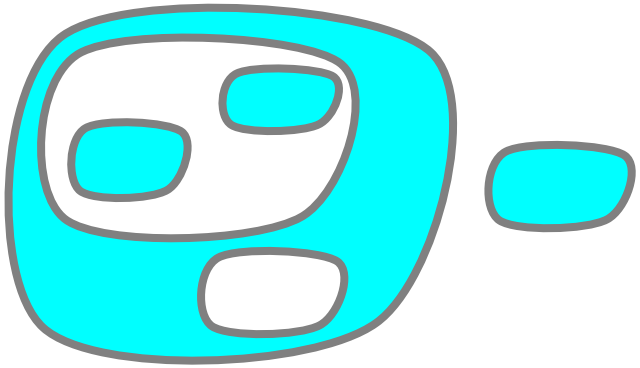


Evolutionary explanations of bitonal structure



Membrane Reactions

Membrane System



Local (Patch) Reactions

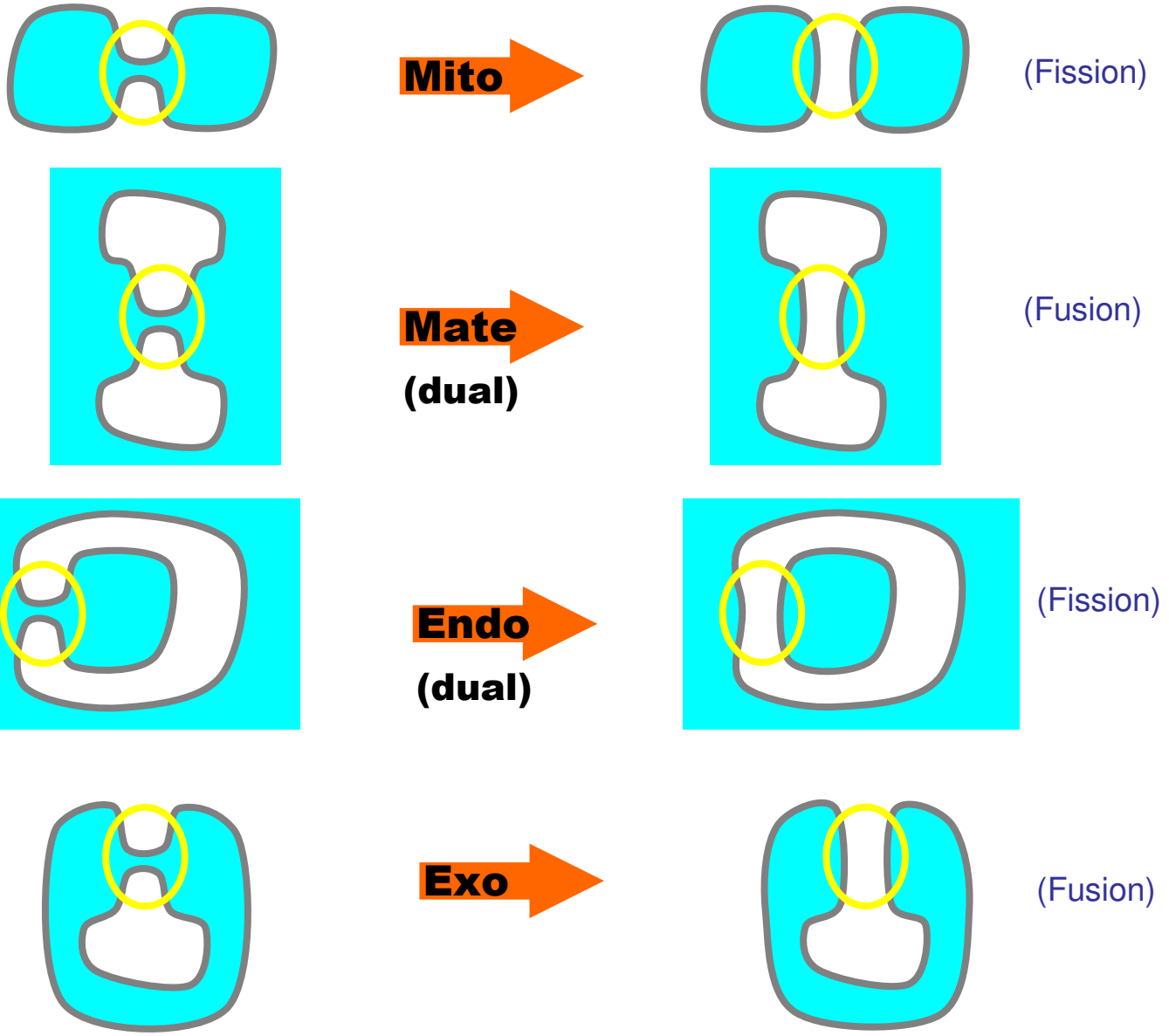
Reactions that "make sense" from a local, molecular viewpoint

(Symmetric by 90° rotation.)

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

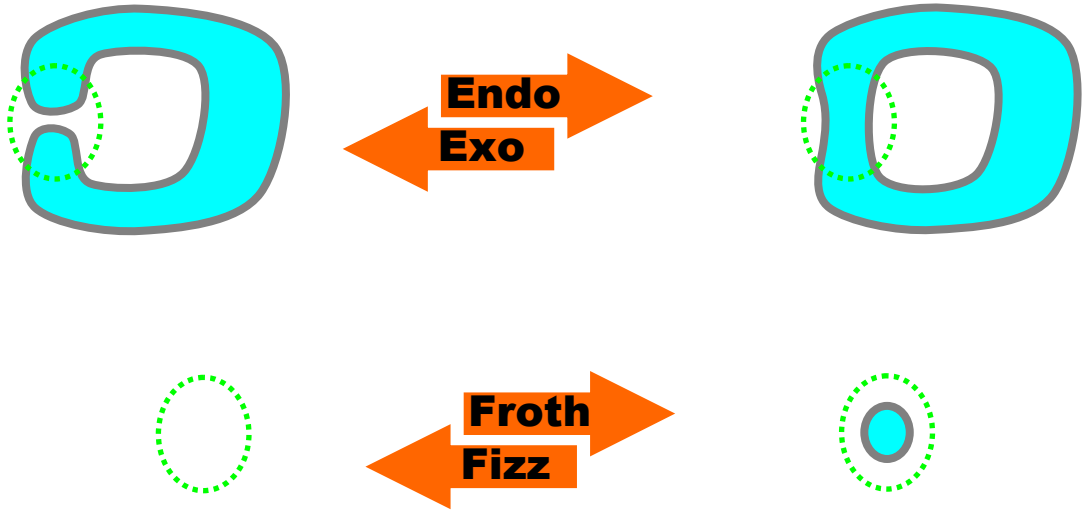
Global Reactions

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



Same Local View!

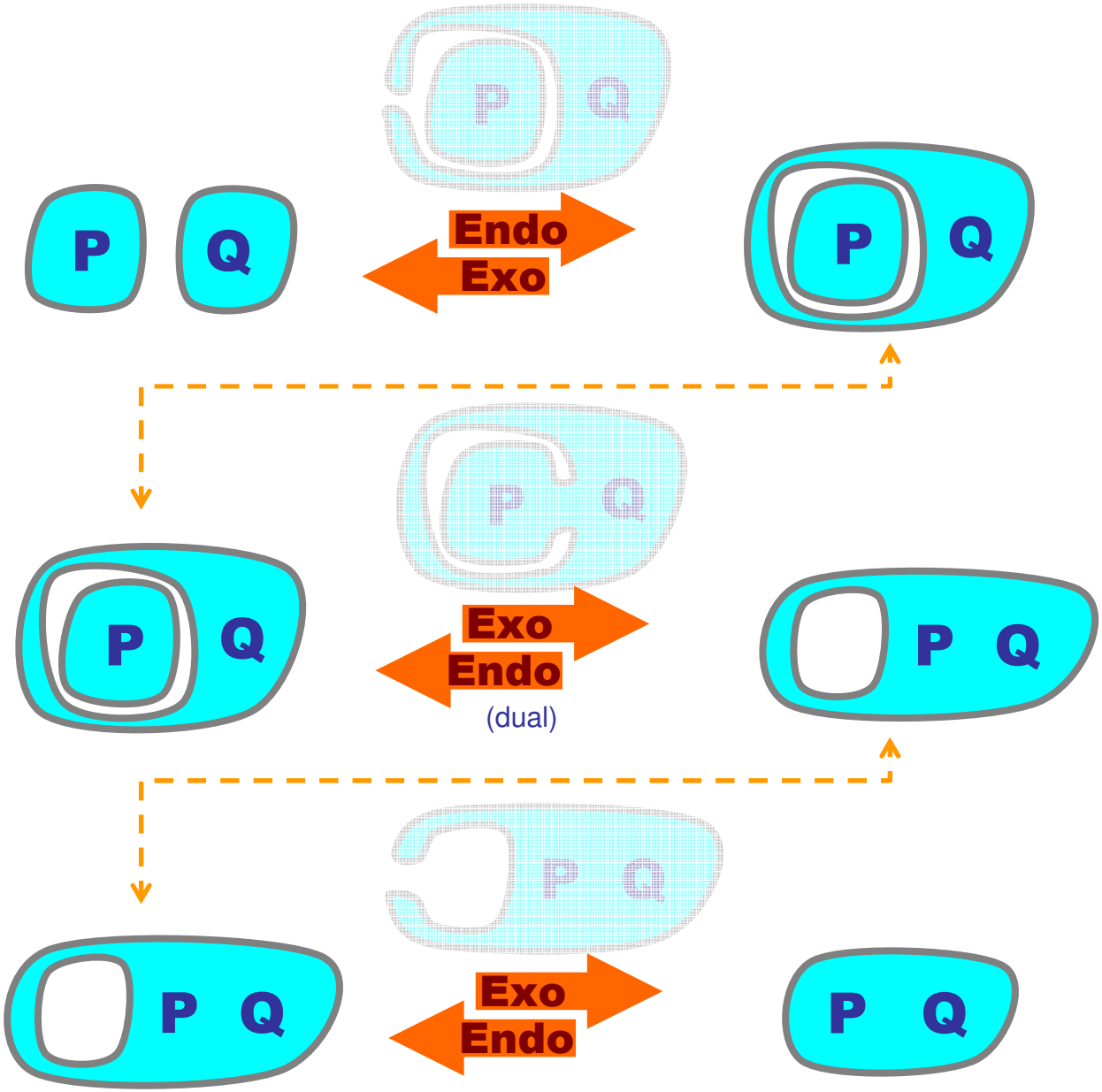
A Set of Primitives



These membrane operations are sound and complete w.r.t. patch operations.

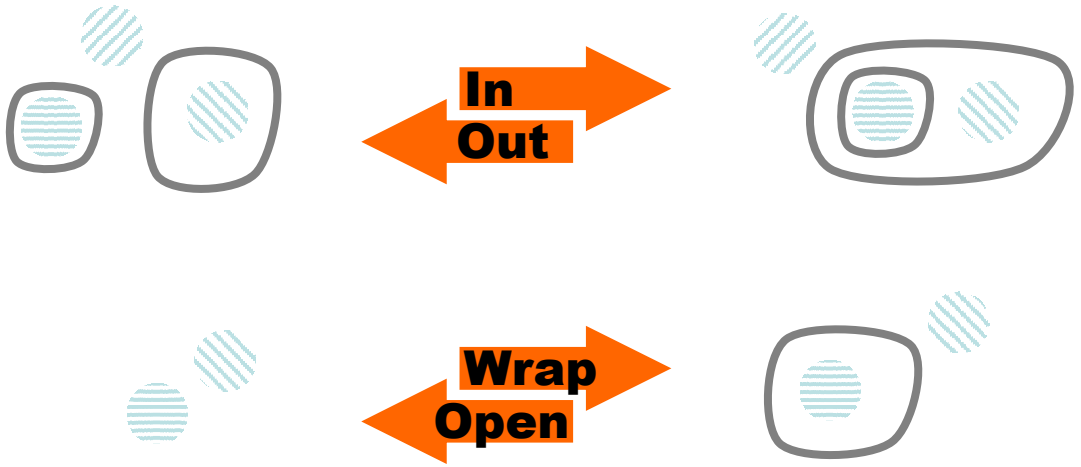
Derivable:

Mito/Mate by 3 Endo/Exo



Non-local Operations

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



Violate bitonality.

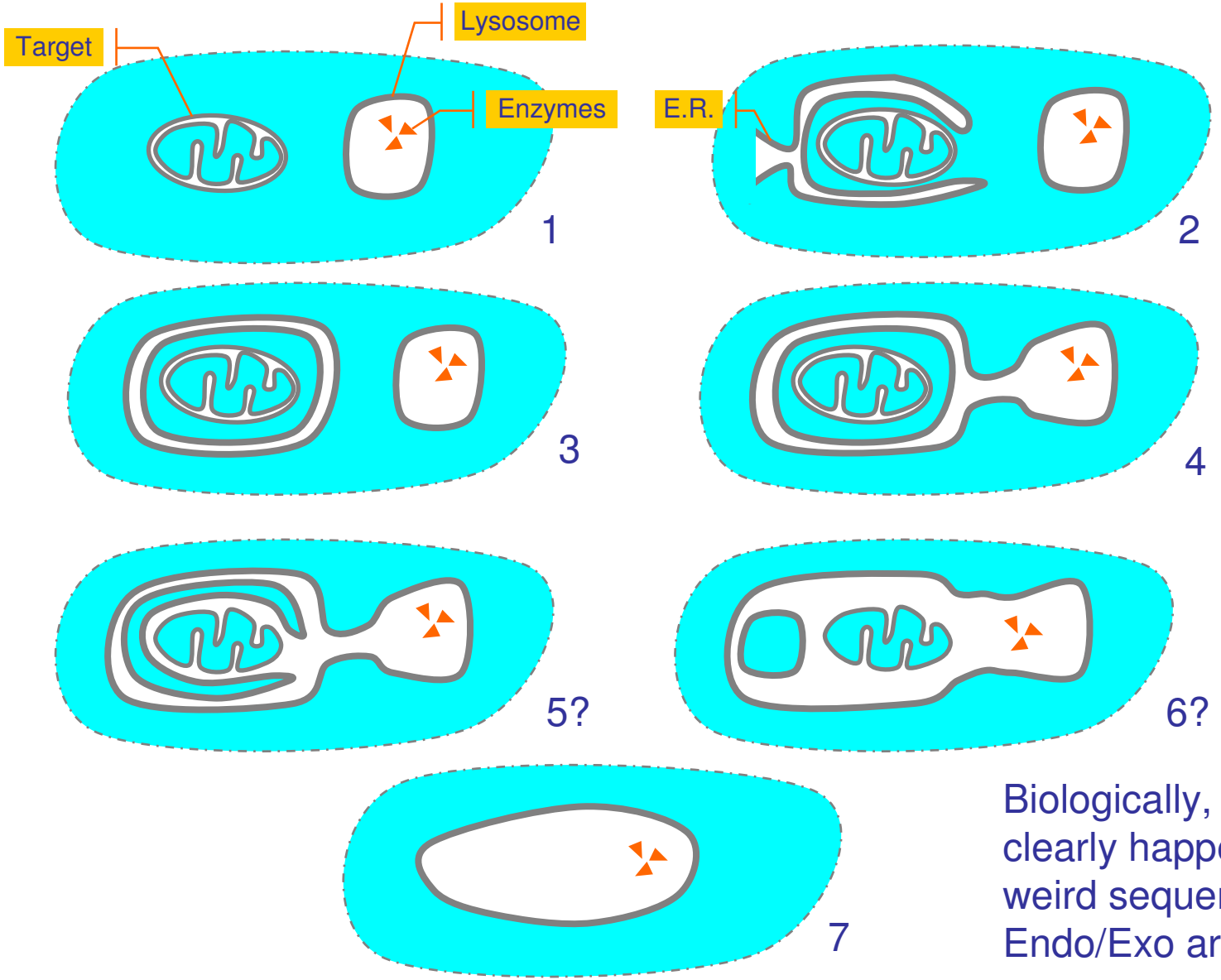
Non implementable by "local" membrane operations.

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

Happen to be the Ambient Calculus operations!!

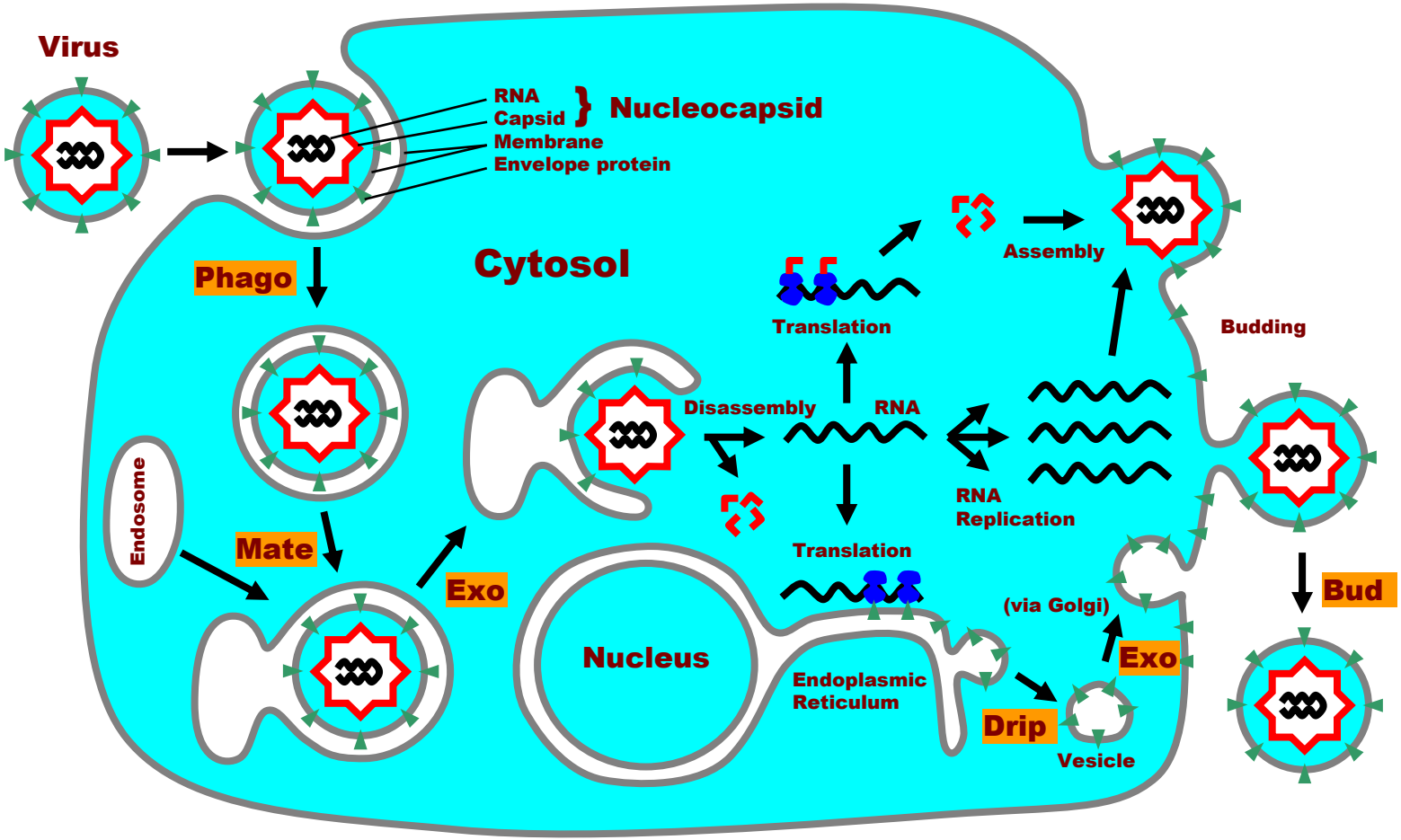
Ex: Autophagic Process

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

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!
  - Smoother modeling than previous attempts (e.g. BioAmbients).

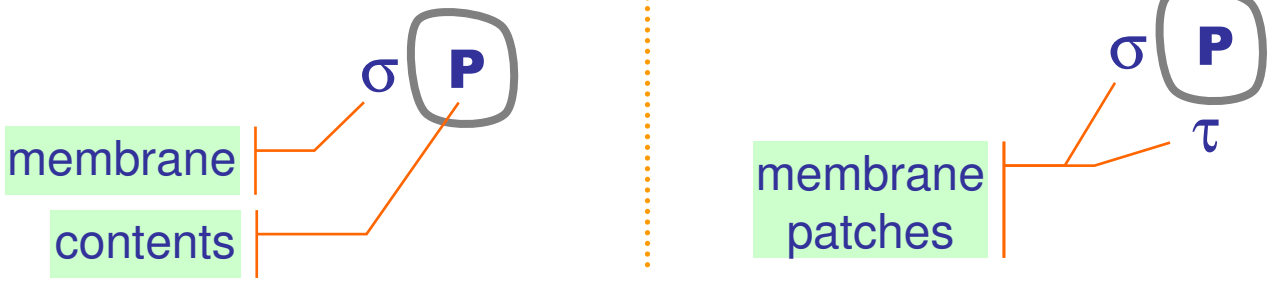
Brane Calculi

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	$a ::= 1 \mid \ldots$	(a great variety of possibilities)

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.

Structural Congruences

Fluidity

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

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

$P \circ \diamond \equiv P$

Repetition

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

Units

$0(\!|\diamond|\!) \equiv \diamond$ **Froth/Fizz**

Congruence

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

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

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

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

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

$\sigma | 0 \equiv \sigma$

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

$1.\sigma \equiv \sigma$ **Inaction**

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

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

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

Reduction up to congruence

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

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.

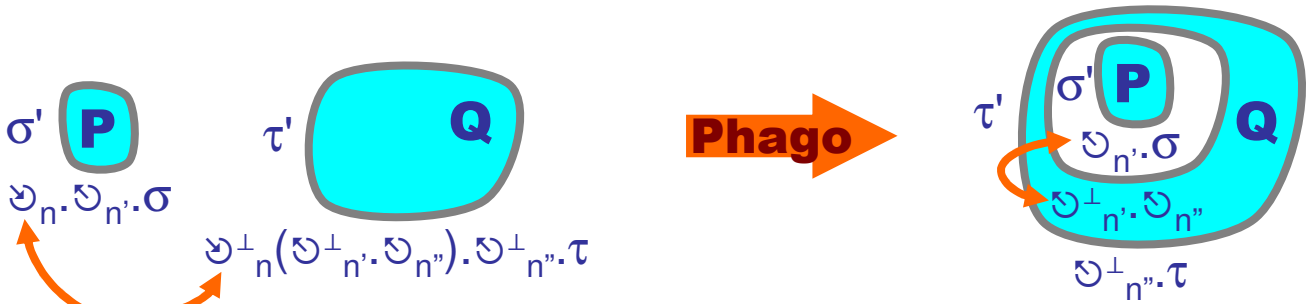
N.B.: in Phago (and Pino), one could perhaps require ρ to be, conservatively, a piece of τ, by a non-linear rewrite:

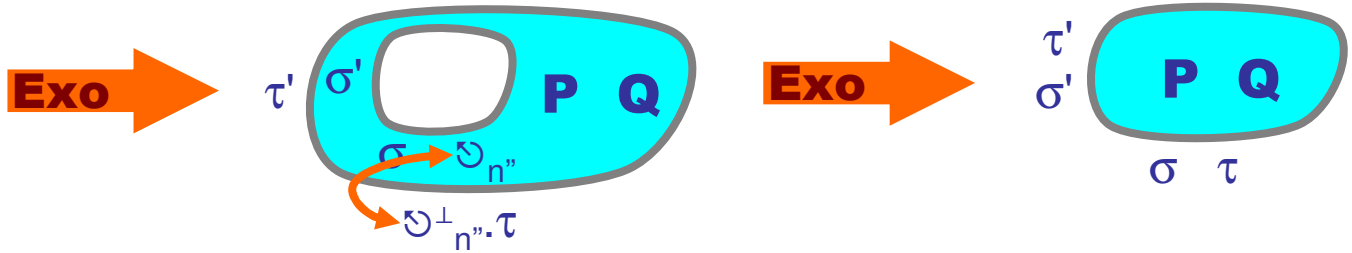
CPhago $\mathcal{Y}_n.\sigma|\sigma'(\!|P|\!) \circ \mathcal{Y}^{\perp}_n(\rho).\tau|\tau'|\rho(\!|Q|\!) \rightarrow \tau|\tau'(\!|\rho(\!|\sigma|\sigma'(\!|P|\!)|\!)\circ Q|\!)$

Abbreviations: Mate

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

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



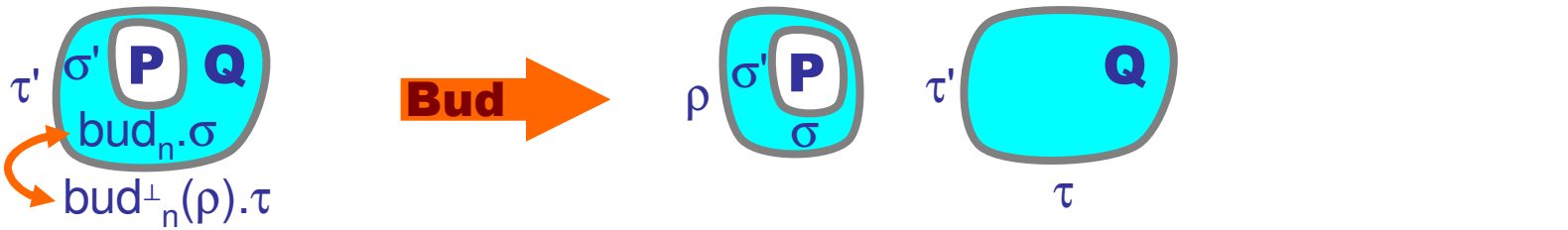


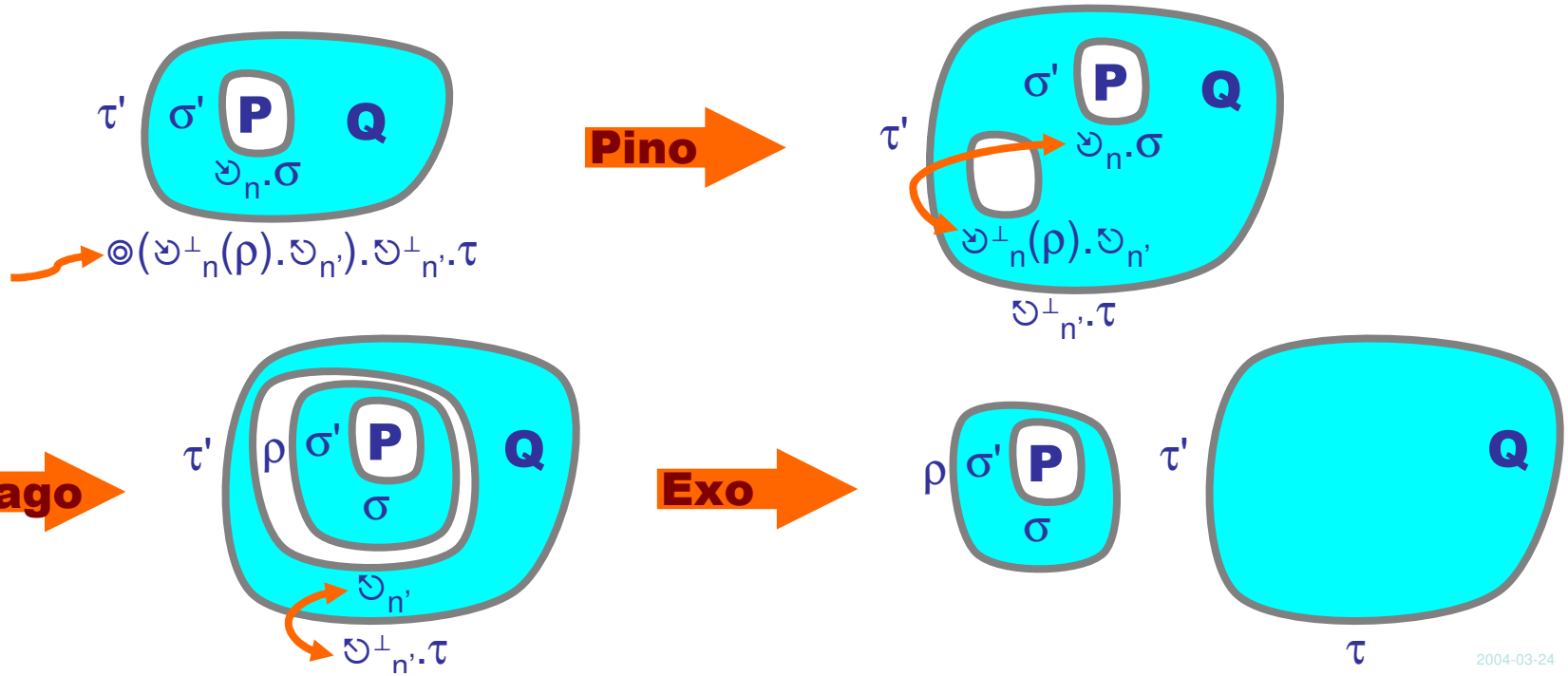
Abbreviations: Bud

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.

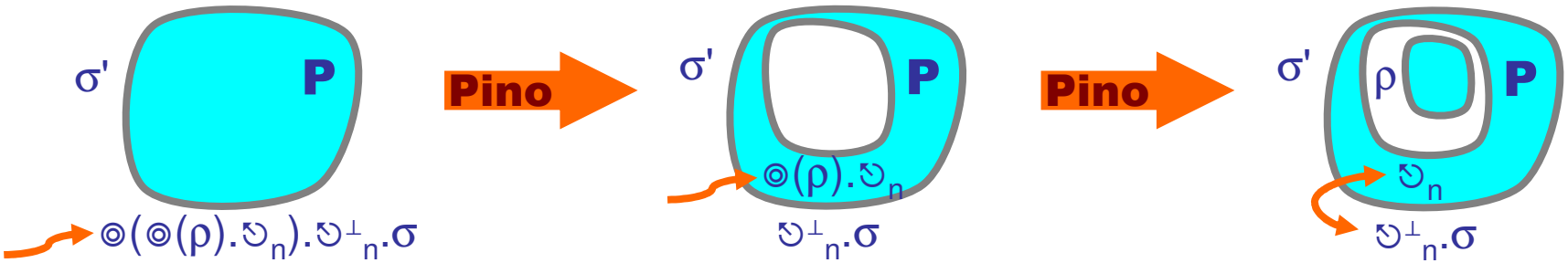


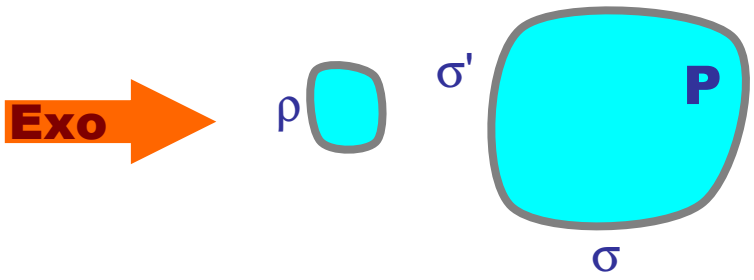


Abbreviations: Drip

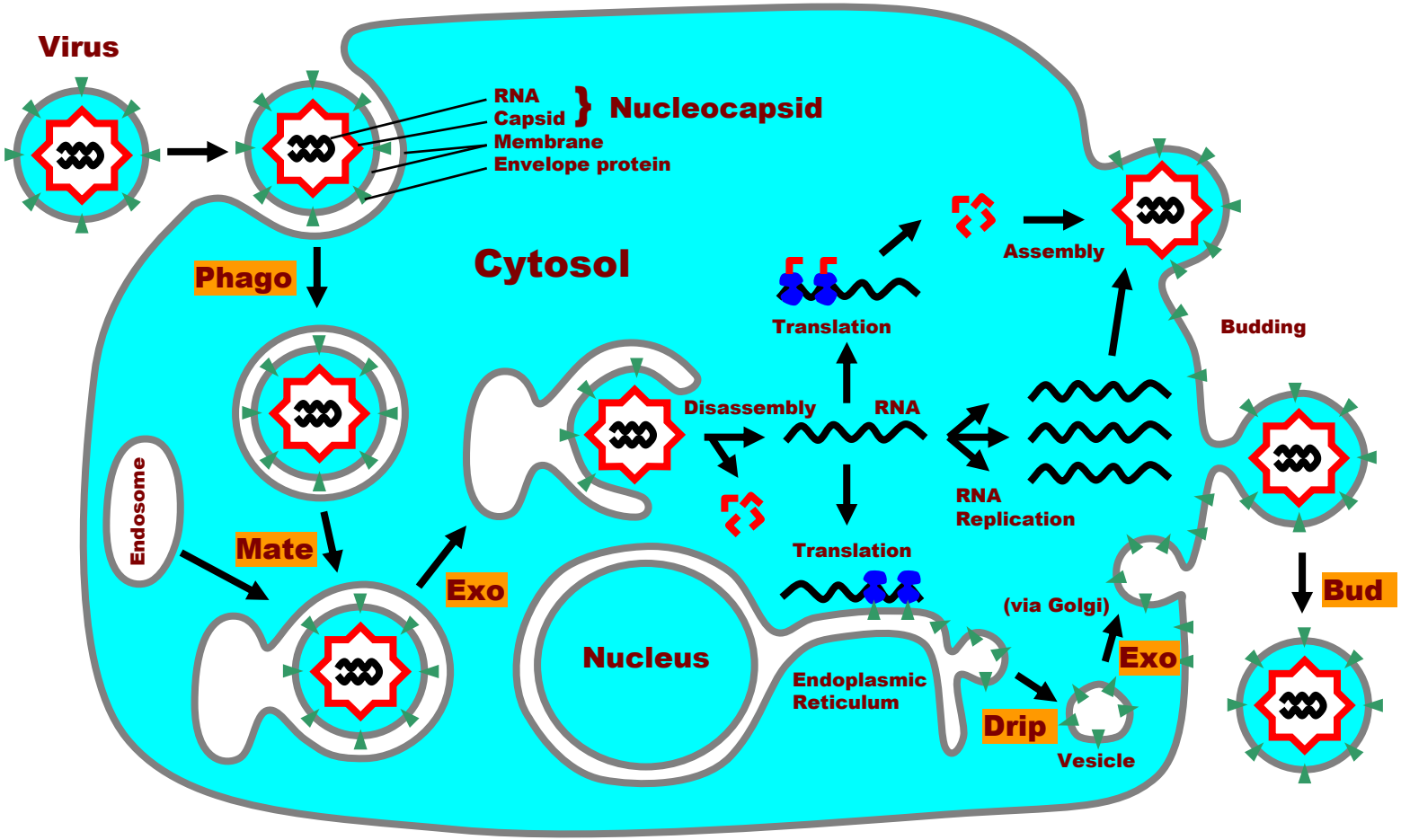
Drip $\text{drip}_n(\rho).\sigma = \circledcirc(\circledcirc(\rho).\circlearrowleft_n).\circlearrowleft^{\perp}_n.\sigma$

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



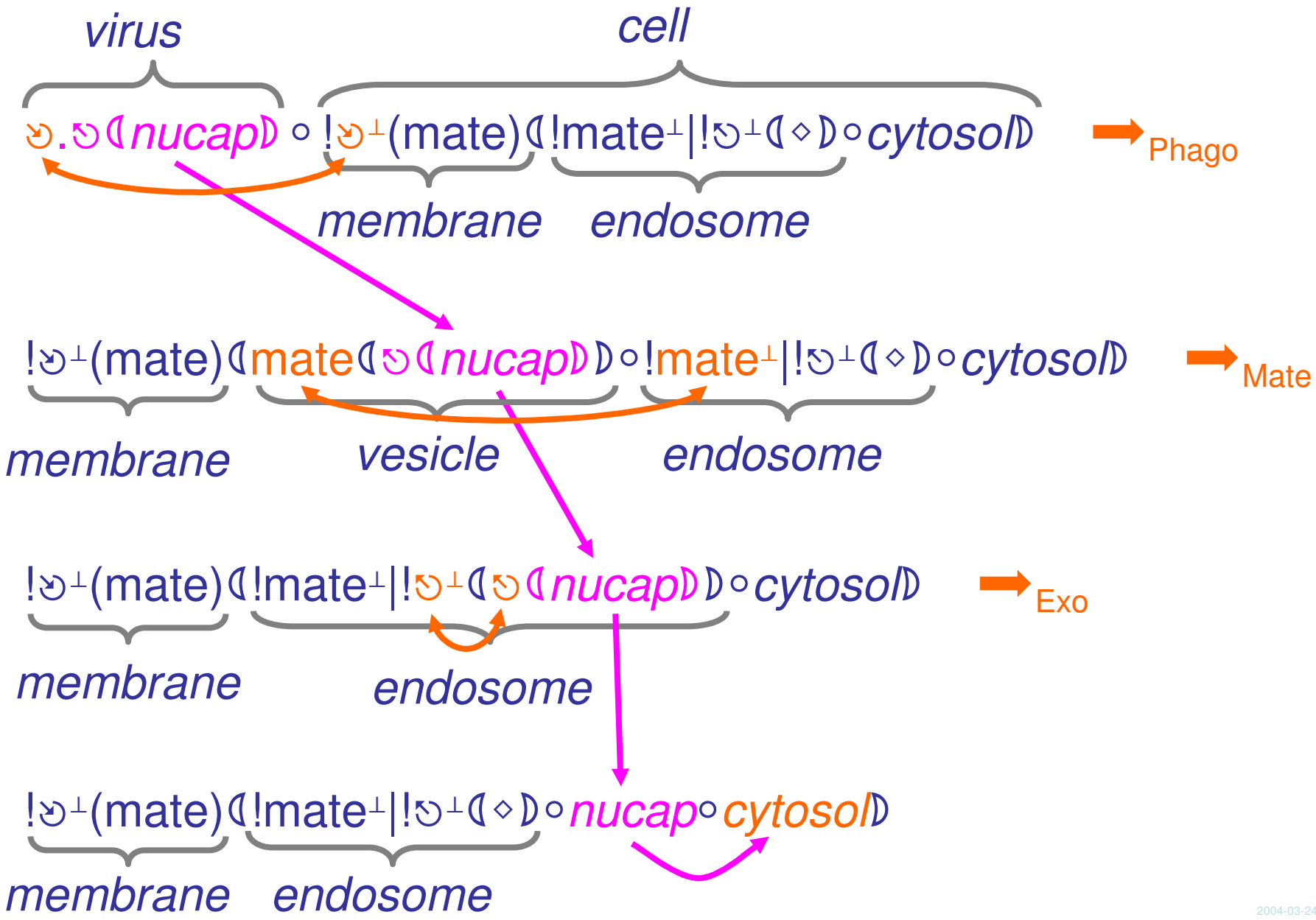


Ex: Viral Reproduction



[MBC p.279]
annotated

Ex: Viral Infection



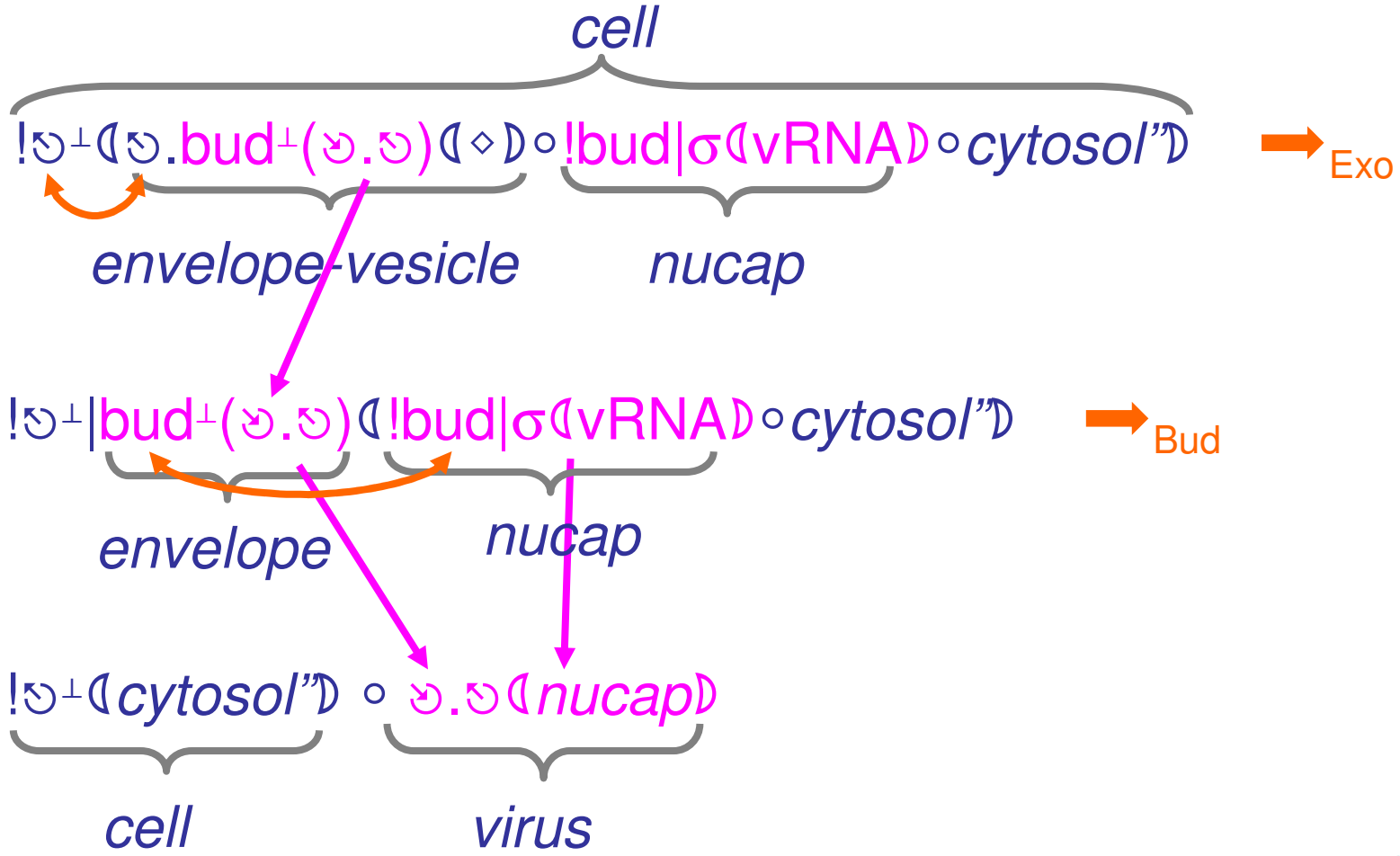
Ex: Viral Progeny

Assume:

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

by available cellular machinery

Then:

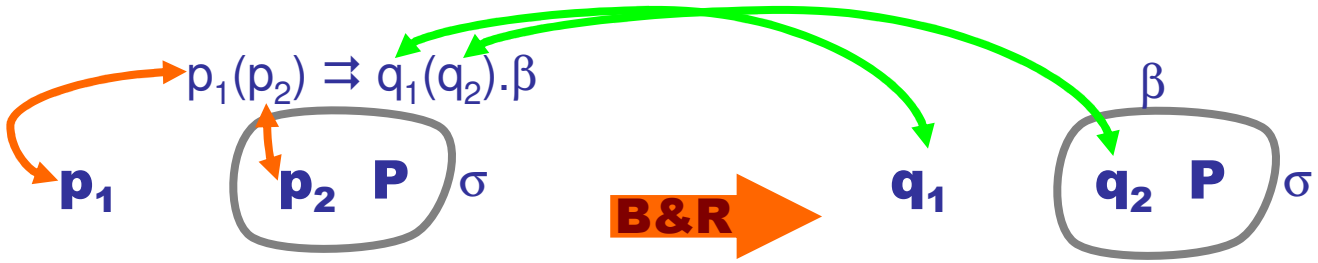


Molecular Actions

systems $P,Q ::= \ldots \mid m \qquad m \in M$ 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 binding, either as in BioSPi by adding restriction, or better 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

Special Cases of B&R

Chemical reaction catalysis (inside a compartment):

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

$p \rightleftharpoons q \triangleq\ p \longrightarrow q \circ q \longrightarrow p$

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):

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

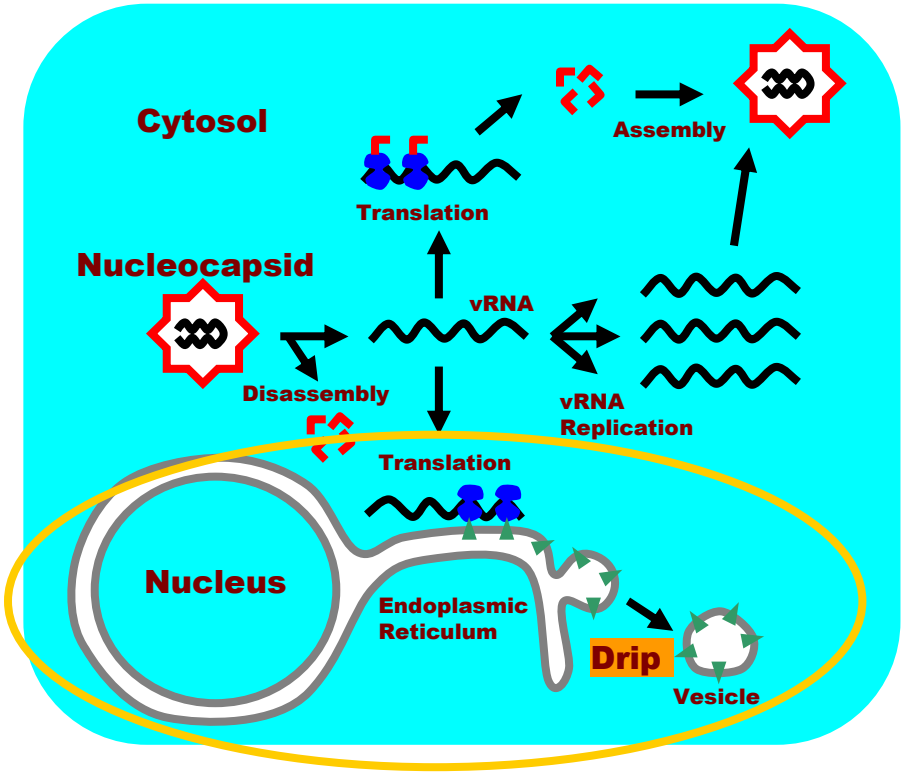
$p \dot{\rightarrow} q|\sigma\text{⦇}P\text{⦈}$ Condition affecting P

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*◗

exo to cell membrane

nucap budding receptor

virus membrane

envelope-vesicle

(See paper for the other two vRNA pathways)

Other Extensions

- Additional Actions
  - CCS-style communication
    - Diffusion of molecules on cellular membrane
  - BioAmbients-style communication
    - Diffusion of molecules across cellular membrane
  - BioAmbients-like mobility
    - Non-bitonal
- Additional Molecule Structure
  - Protein binding and unbinding
- Restriction

Conclusions

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

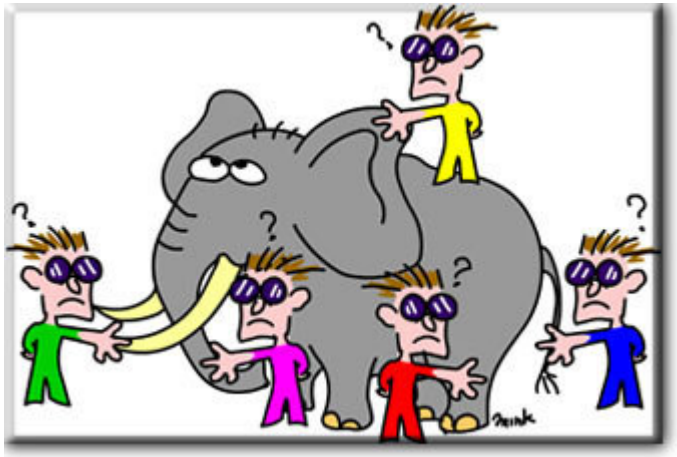
- What's needed to model "the whole thing"?
  - A single language/calculus for protein interaction networks, gene regulatory networks, and transport networks?
  - Extensible to multicellular organisms too?
  - Oh, my!

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

References

[MCB] Molecular Cell Biology, Freeman.

[MBC] Molecular Biology of the Cell, Garland.



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