Membrane Interactions

Luca Cardelli

Microsoft Research
Cambridge UK

2004-07-18 Logic and Systems Biology, Turku

www.luca.demon.co.uk

Aims

Modeling biological *systems*.

By adapting paradigms and techniques developed for modeling information-processing systems.

Because they have some similar features:

Deep layering of abstractions.
Complex composition of simpler components.
Discrete (non-linear) evolution.
Digital coding of information.
Reactive information-driven bahavior.
Very high degree of concurrency.
'Emergent behavior" (not obvious from part list).

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

Methods

Model Construction (writing things down precisely)

1st Half — Studying the notations used in systems biology.

2nd Half — Formulating process calculi, for various purposes.

Stochastic semantics. (Real Time Markov Chains)

Model Validation (using models for postdiction and prediction)

Stochastic Similation.

Now based on compositional descriptions.

"Program" Analysis

Control flow analysis
Causality analysis

Modelchecking

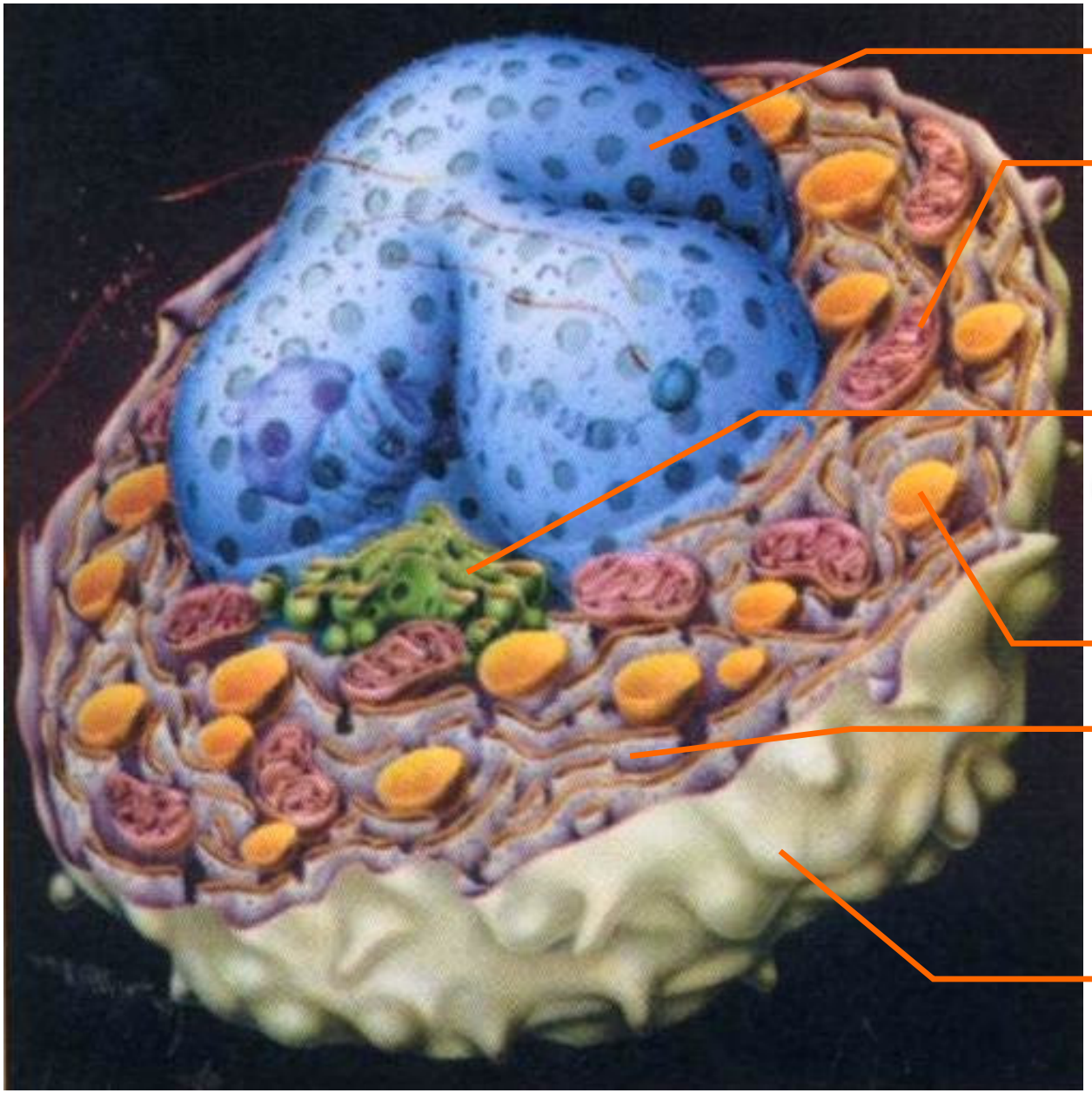
Standard, Quantitative, Probabilistic

Structural Architecture

Eukaryotic Cell

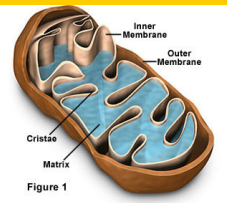
(10~100 trillion in human body)

Membranes everywhere

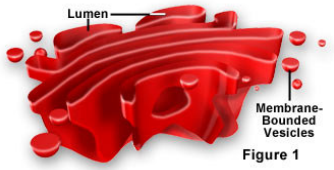


Nuclear membrane

Mitochondria

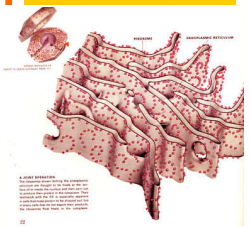


Golgi



Vesicles

E.R.



Plasma membrane (<10% of all membranes)

Functional Architecture

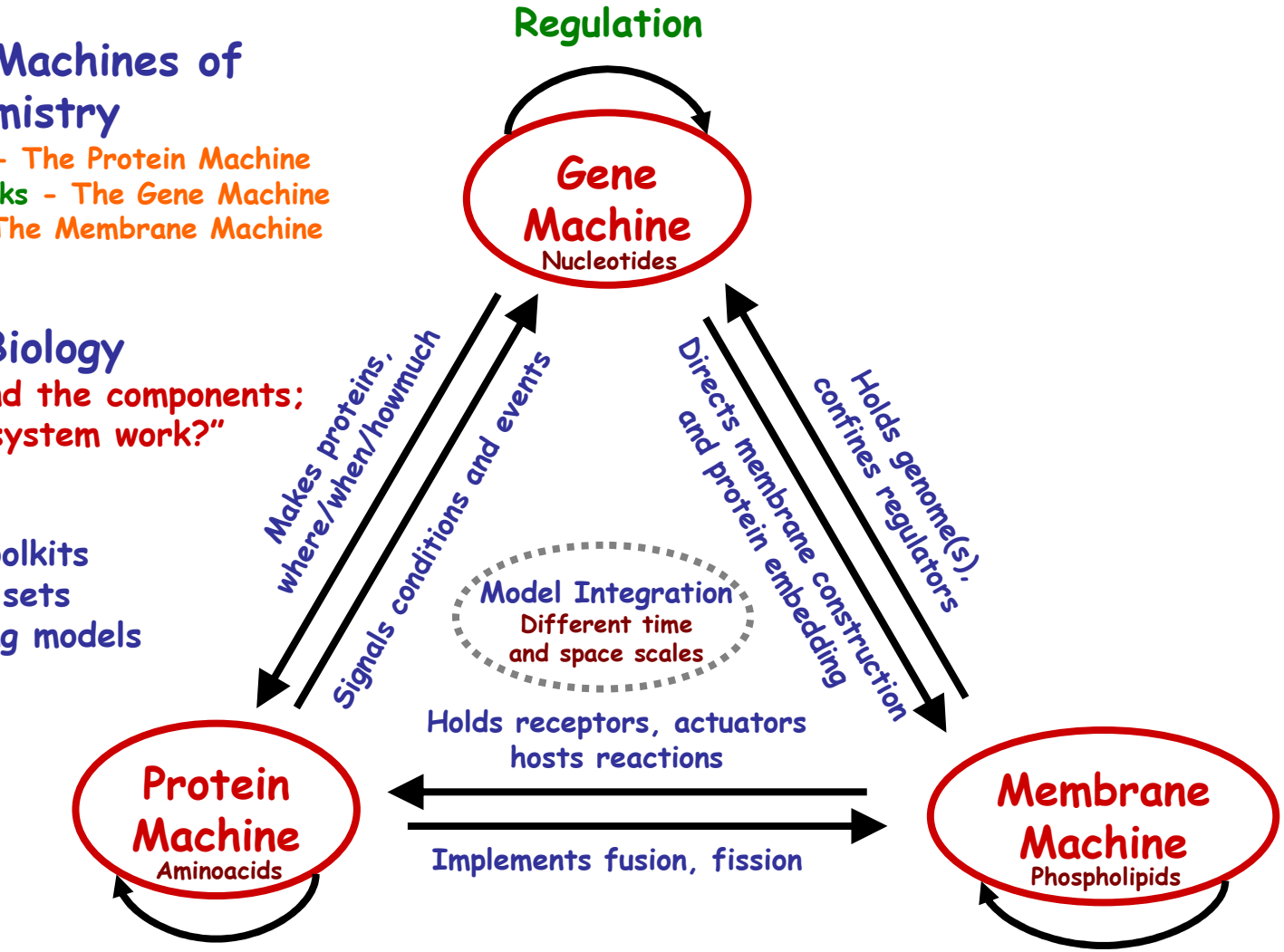
The Virtual Machines of Biochemistry

Biochemical Networks - The Protein Machine
Gene Regulatory Networks - The Gene Machine
Transport Networks - The Membrane Machine

Systems Biology

"We (kind of) understand the components; but how does the system work?"

Different chemical toolkits
Different instruction sets
Different programming models
Different notations



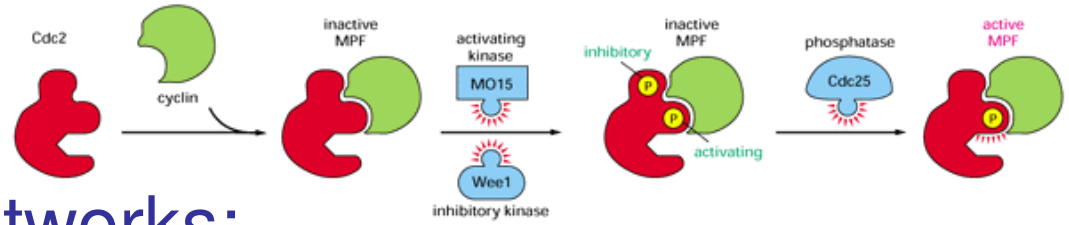
Metabolism, Propulsion
Signal Processing
Molecular Transport

Confinement
Storage
Bulk Transport

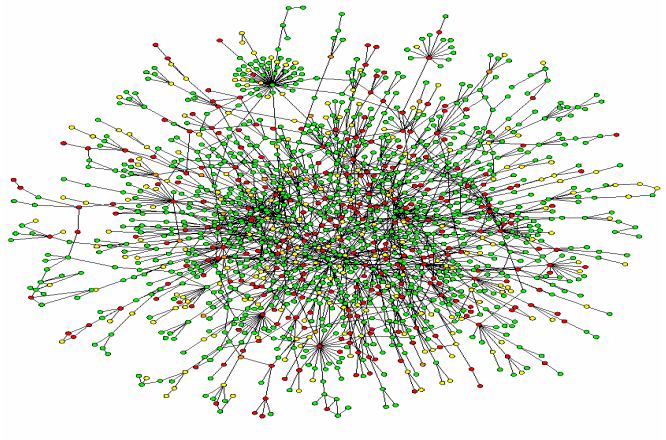
1. The Protein Machine

Very close to the atoms.

- Complex folded-up shapes that:
  - Fit together, dock, undock.
  - Excite/unexcite, warp each other.
  - Bring together, catalyze, transform materials.
  - Form complex aggregates and networks.



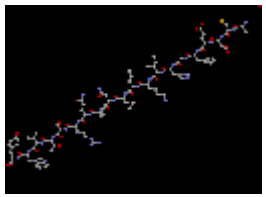
- Mapping out such networks:
  - In principle, it's "just" a very large set of chemical equations.
  - Notations have been developed to summarize and abstract.



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

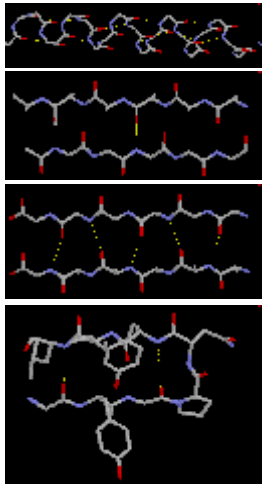
Protein Structure

Primary



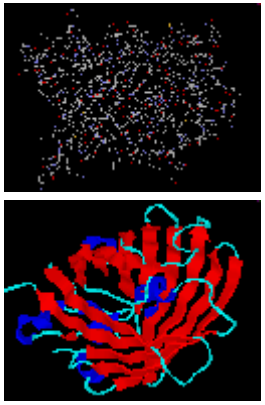
The 20 Aminoacids

Secondary



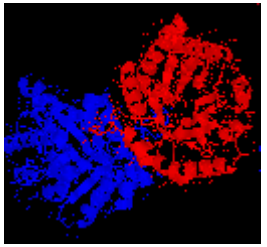
Alpha Helix, Beta Sheet

Tertiary



Green Fluorescent Protein

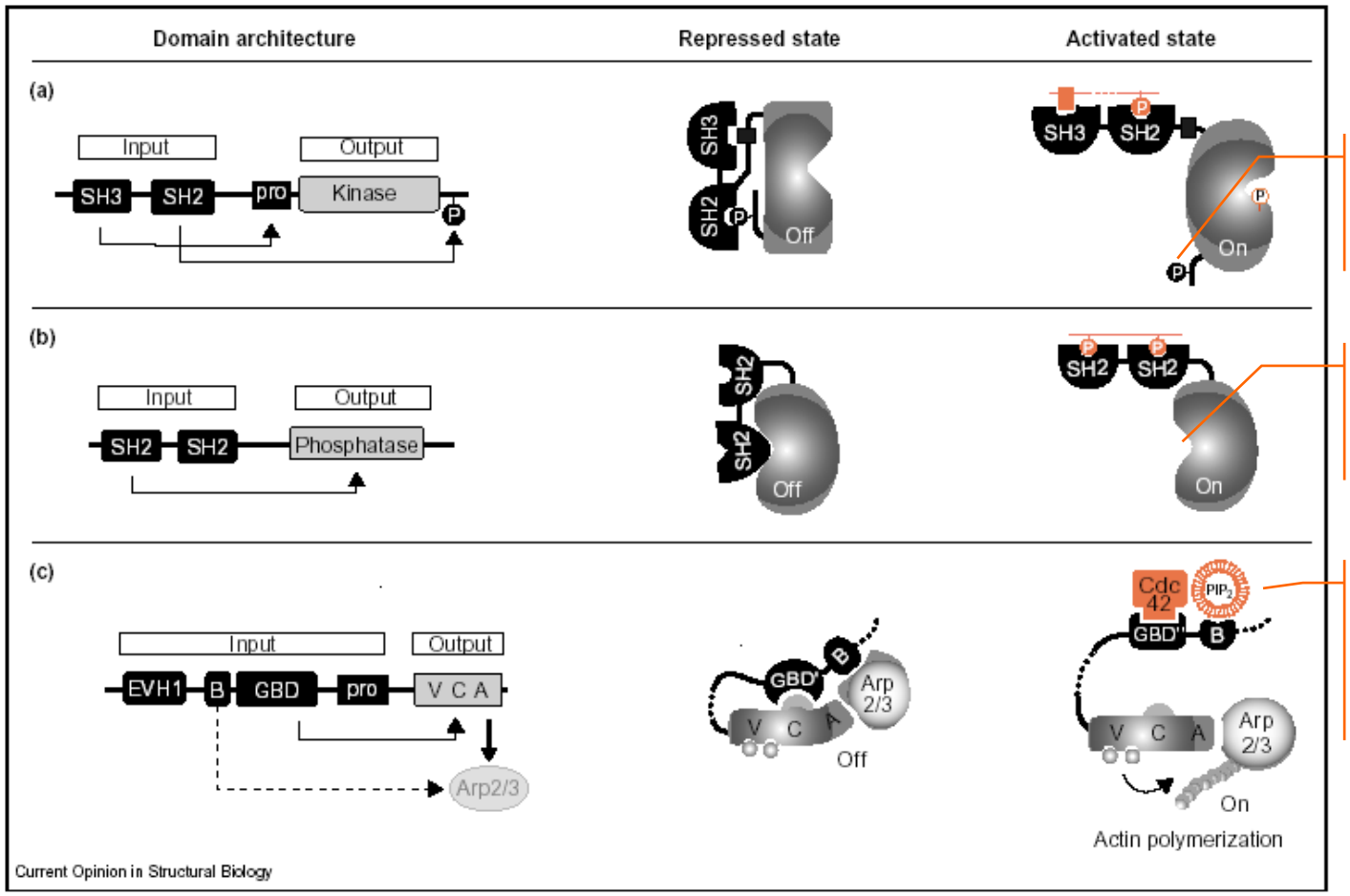
Quaternary



Triose Phosphate Isomerase

http://www.cmbi.kun.nl/gvteach/bioinformatica1/

Some Allosteric Switches



Current Opinion in Structural Biology

Domain architecture and autoinhibitory interactions in modular switch proteins. (a) Src family kinases contain N-terminal SH3 and SH2 domains, and a kinase domain flanked by intramolecular SH3-binding and SH2-binding sites (when the C-terminal motif tyrosine is phosphorylated by Csk). The crystal structures of several family members show that both intramolecular domain interactions function in concert to lock the kinase in an inactive conformation. Activating stimuli (red) include external SH2 or SH3 ligands. After initial activation, the kinase is maintained in an active state by autophosphorylation of its activation loop. (b) SHP-2 phosphatase contains two SH2 domains and a phosphatase domain. The crystal structure of the phosphatase shows that the N-terminal SH2 domain participates in an autoinhibitory interaction that directly blocks the phosphatase active site. Binding of external SH2 ligands activates by disrupting the autoinhibitory interaction. (c) N-WASP contains an Enabled VASP homology 1 (EVH1) domain, a B motif, a GBD, a proline-rich segment (pro) and an output region (VCA) that alone binds the Arp2/3 complex and stimulates its actin nucleation activity. The B and GBD motifs are required to repress activity and, by current models, are thought to participate in intracomplex interactions (only the structure of the GBD intramolecular complex for WASP is known). GTP-bound Cdc42 and PIP_2 synergistically activate N-WASP.

Allosteric ("other shape") reactions modify accessibility.

Kinase

= donates phosphate P
= phosphorilates other proteins

Phosphatase

= accepts phosphate P
= dephosphorilates other proteins

Logical AND

at equal concentrations of the individual input stimuli, activation is much higher if both stimuli are present

"Phosphatase Kinase Kinase" = a kinase that activates a kinase that activates a phosphatase that deactivates a protein.

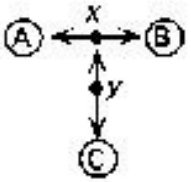
Humans have the same number of modular protein *domains* (building blocks) as worms, but twice the number of multi-domain proteins.

Taken from Wendell Lim

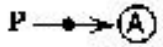
MIM: Molecular Interaction Maps (Kohn)

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.

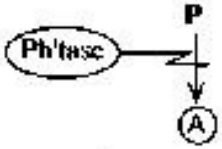
Asymmetric binding where protein **A** donates a peptide that binds to a receptor site or pocket on protein **B**.



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.



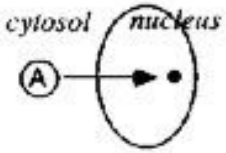
Covalent modification of protein **A**. The single-arrowed line indicates that **A** can exist in a phosphorylated state. The node represents the phosphorylated species.



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

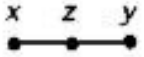
Proteolytic cleavage at a specific site within a protein.

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

Molecular Interaction Maps

http://www.cds.caltech.edu/~hsauro/index.htm

JDesigner

The p53-Mdm2 and DNA Repair Regulatory Network

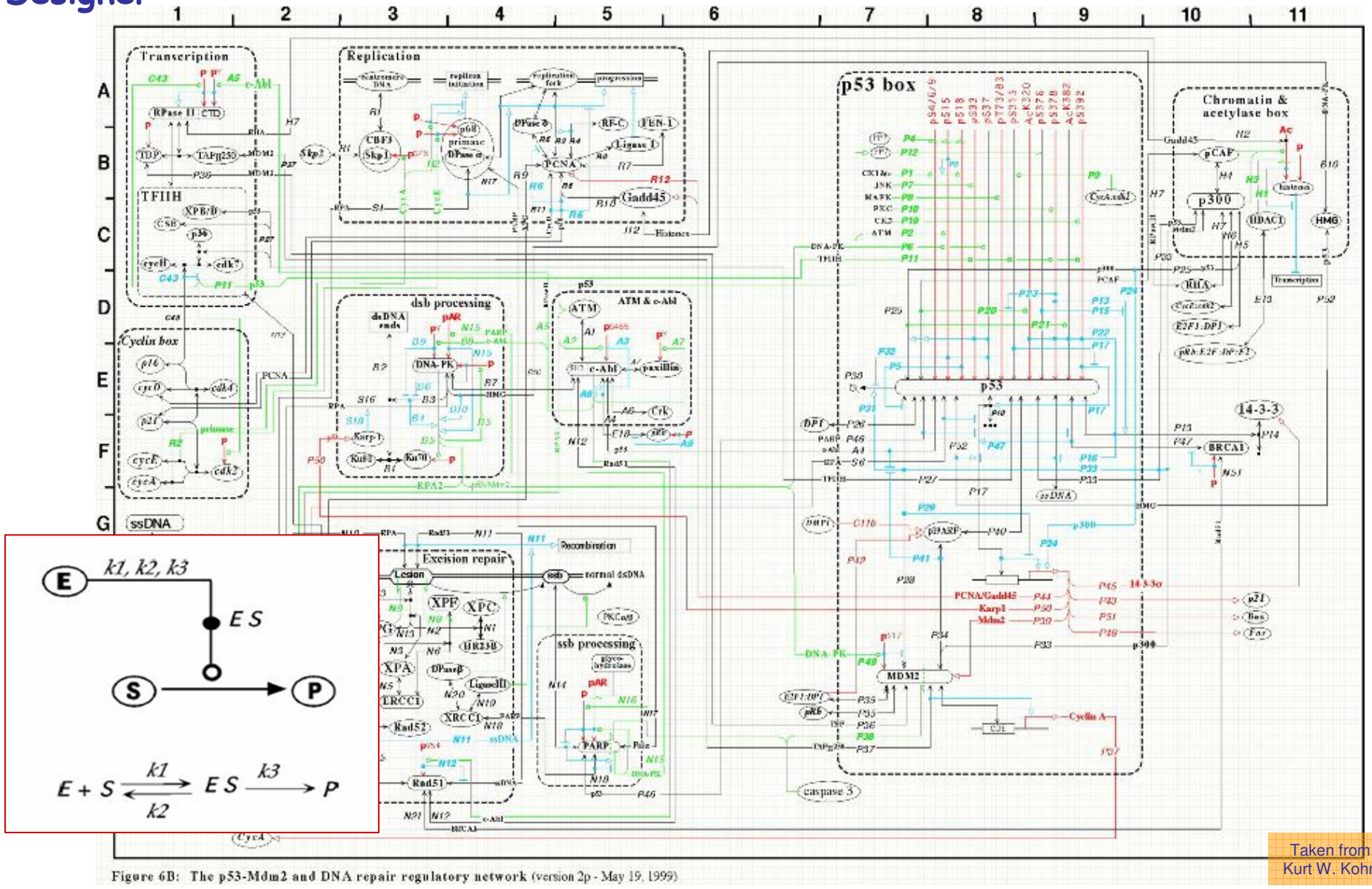


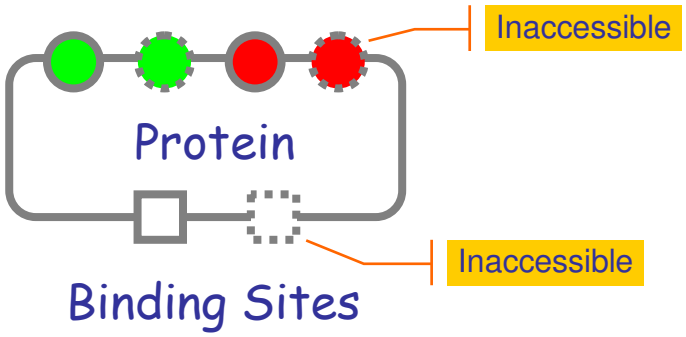
Figure 6B: The p53-Mdm2 and DNA repair regulatory network (version 2p - May 19, 1999)

Taken from Kurt W. Kohn

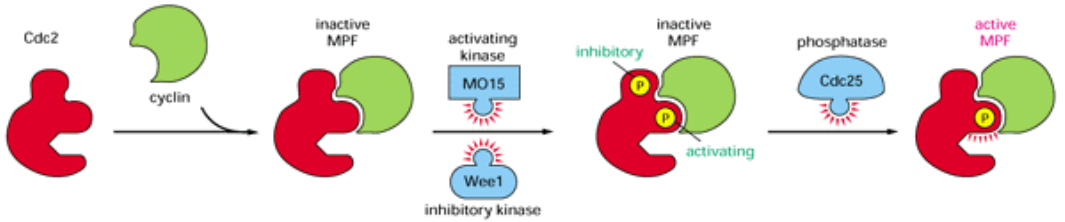
The Protein Machine "Instruction Set"

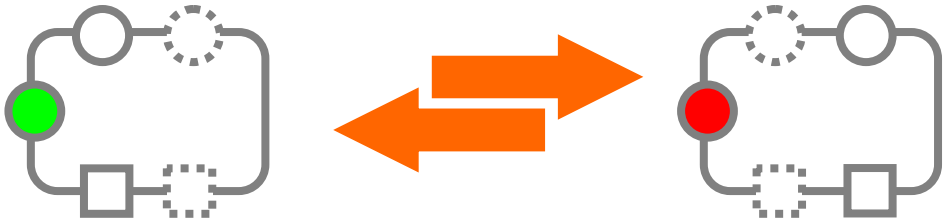
cf. BioCalculus [Kitano&Nagasaki], κ-calculus [Danos&Laneve]

On/Off switches



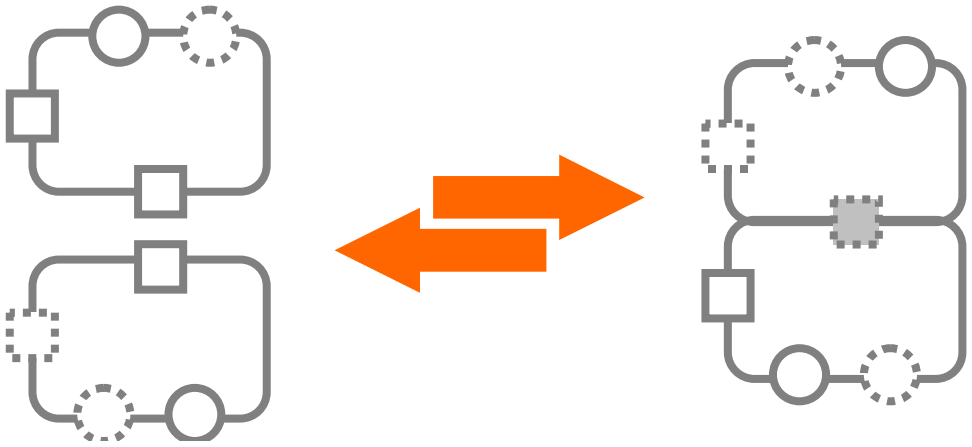
Each protein has a structure
of binary switches and binding sites.
But not all may be always *accessible*.





Switching of accessible switches.

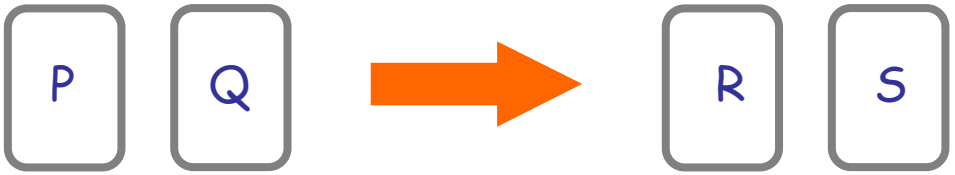
- May cause other switches and
binding sites to become (in)accessible.
- May be triggered or inhibited by nearby specific
proteins in specific states.



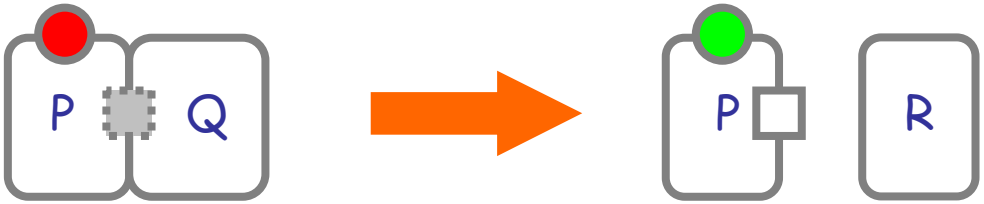
Binding on accessible sites.

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

...



Ordinary Chemical Reactions



Any combination of the above

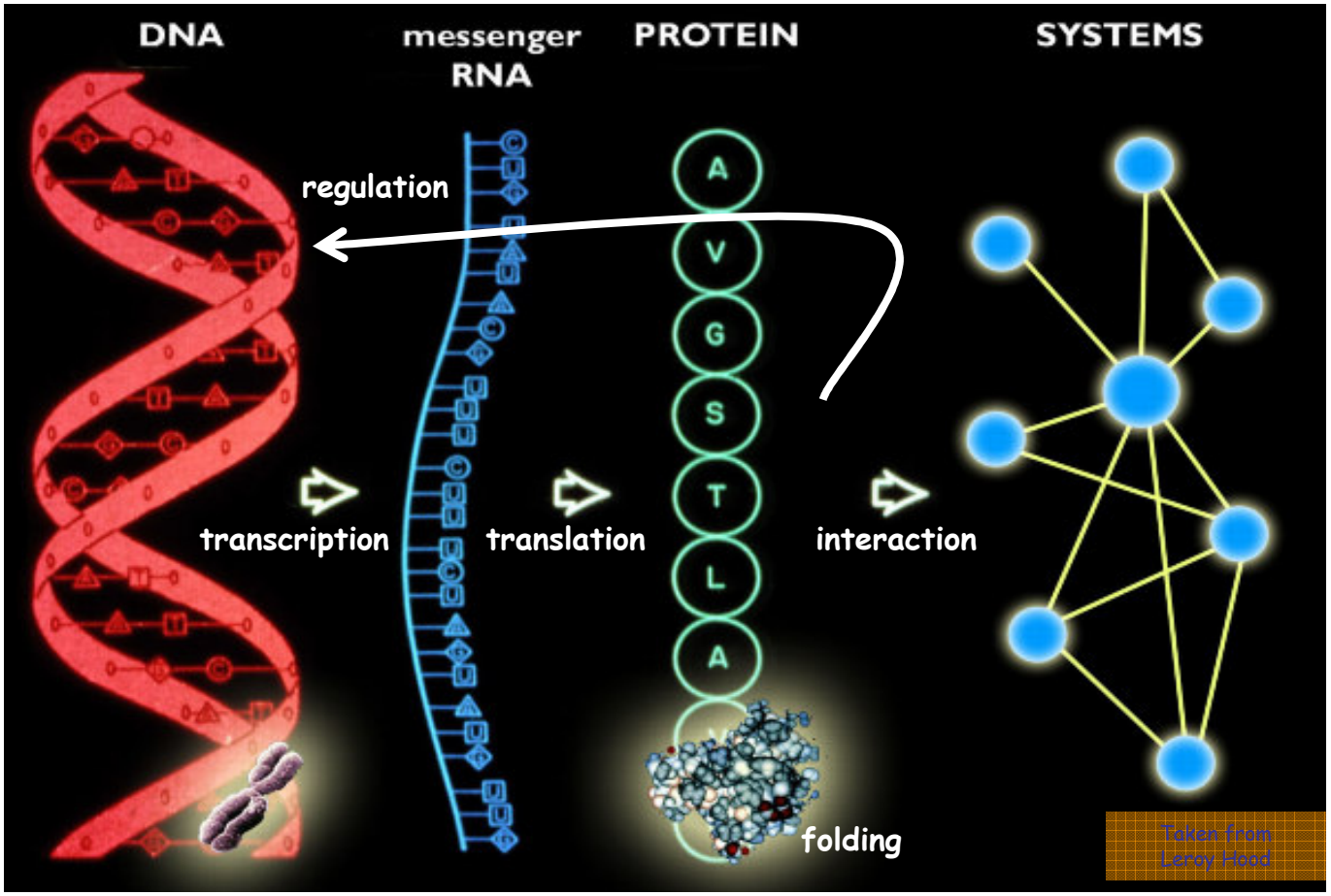
Notations for the Protein Machine

- Stochastic π-Calculus
  - Priami (following Hillston's PEPA) formalizes a stochastic version of π-calculus where channels have communication *rates*.
- 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.
- PEPA
  - Calder Gilmore and Hillston model the ERK pathway.
- k-calculus
  - Danos and Laneve (following Kitano's BioCalculus) define a calculus where complex formation is primitive.
- (Stochastic) Petri Nets
  - S.Reddy'94 modeling pathways.
  - Srivastava Perterson and Bentley analyze and simulate E.coli stress response circuit.
- 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.
- BioCham
  - ChabrierRivier-Fages-Soliman use term-rewriting and CLT modelchecking.
- Kohn Diagrams, Kitano Diagrams
- SBML (Systems Biology Markup Language)
  - XML dialect for MIM's:
    - Compartments (statically nested)
    - Reagents with concentrations
    - Reactions with various rate laws
  - Read and written by many tools via the Systems Biology Workbench protocol
    - Graph editors
    - Simulators (including simulation web services)
    - Databases

2. The Gene Machine

Pretty far from the atoms.

The "Central Dogma" of Molecular Biology



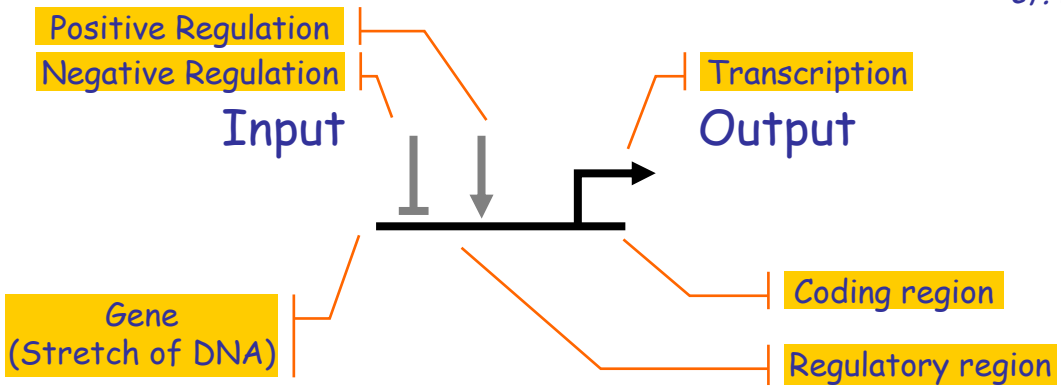
4-letter digital code

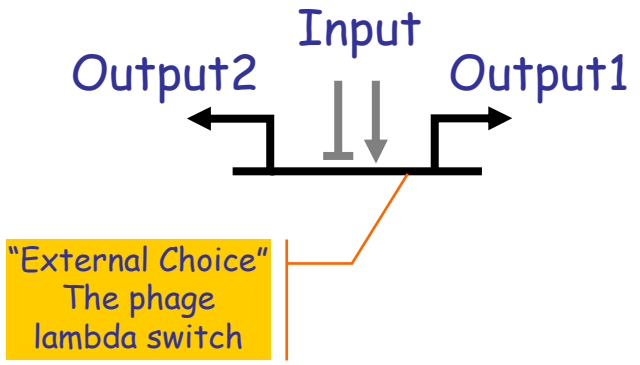
4-letter digital code

20-letter digital code

The Gene Machine "Instruction Set"

cf. Hybrid Petri Nets [Matsuno, Doi, Nagasaki, Miyano]





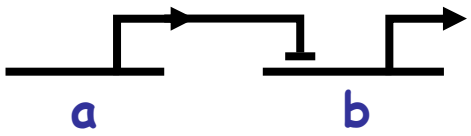
Regulation of a gene (positive and negative) influences transcription. The regulatory region has precise DNA sequences, but not meant for coding proteins: meant for binding regulators.

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

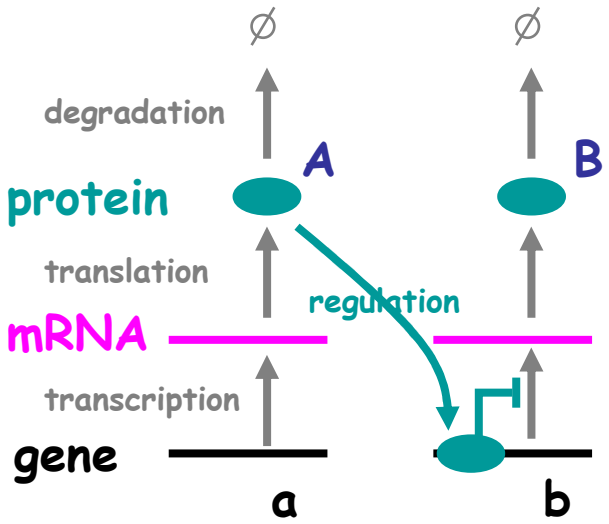
Human (and mammalian) Genome Size
3Gbp (Giga base pairs) 750MB @ 4bp/Byte (CD)
Non-repetitive: 1Gbp 250MB
In genes: 320Mbp 80MB
Coding: 160Mbp 40MB
Protein-coding genes: 30,000-40,000

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

Gene Composition



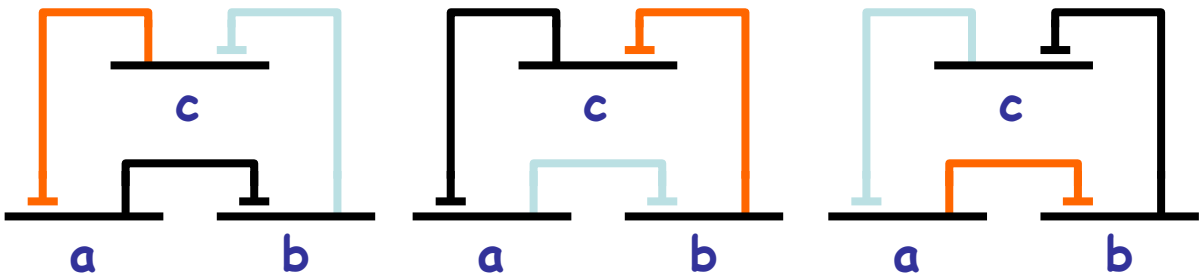
Is a shorthand for:



Under the assumptions [Kim & Tidor]
1) The solution is well-stirred
   (no spatial dependence on concentrations or rates).
2) There is no regulation cross-talk.
3) Control of expression is at transcription level only
   (no RNA-RNA or RNA-protein effects)
4) Transcriptions and translation rates monotonically
   affect mRNA and protein concentrations resp.

Ex: Bistable Switch

Ex: Oscillator

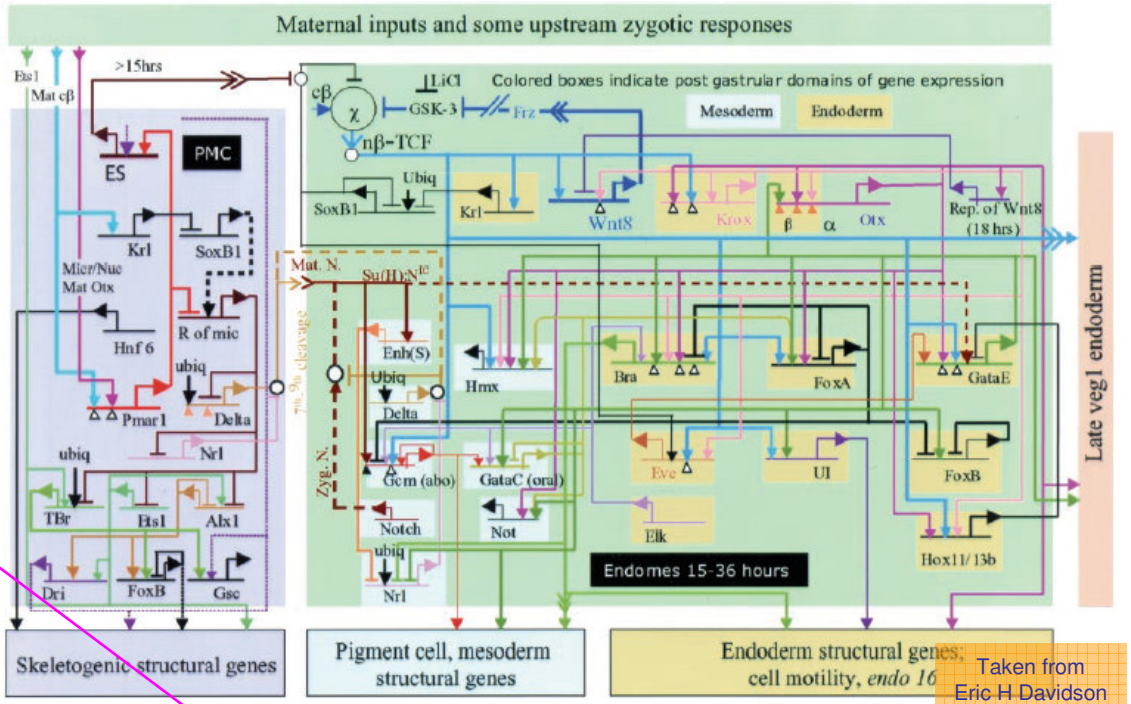


Expressed
Repressed
Expressing

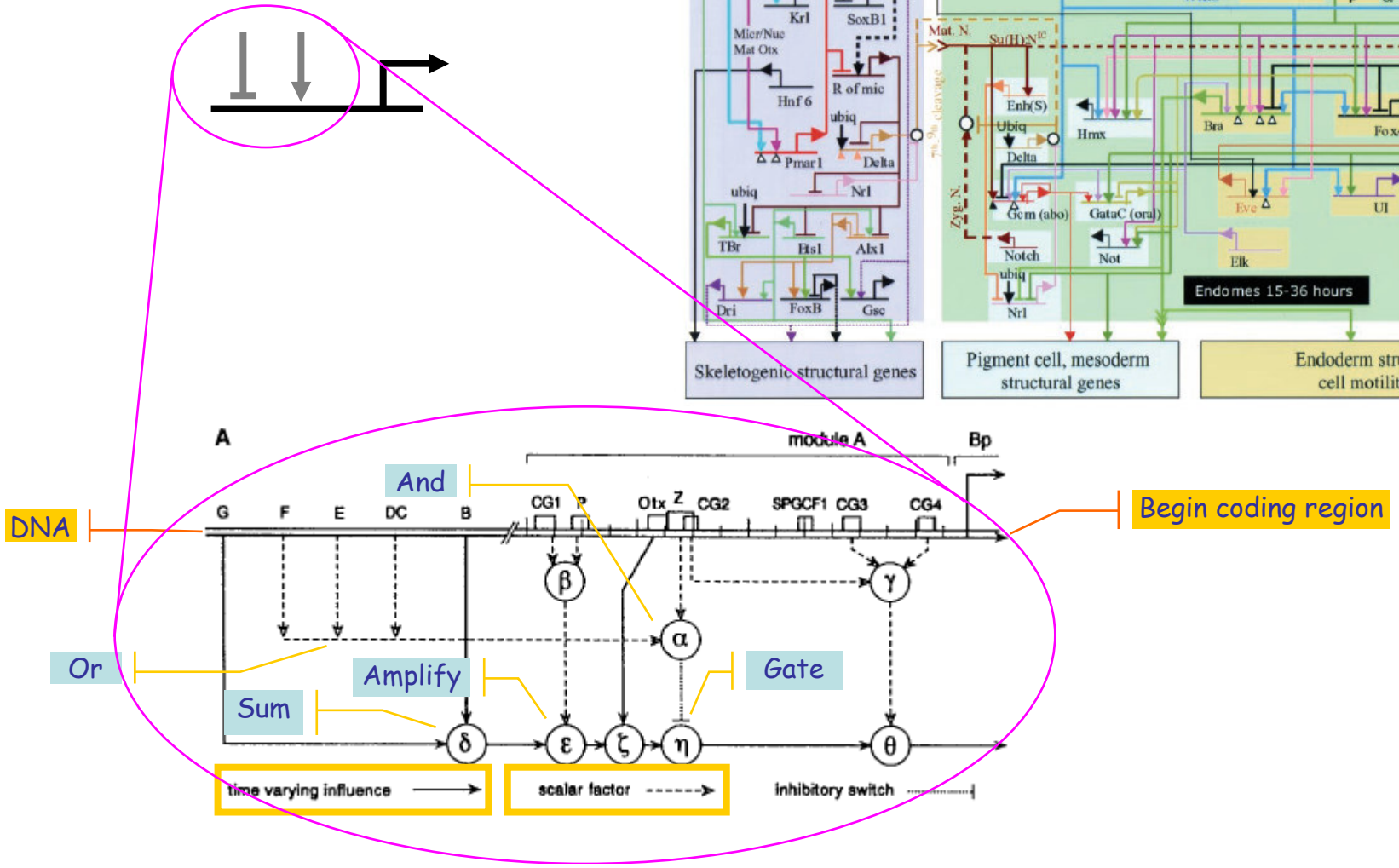
Gene Regulatory Networks

http://strc.herts.ac.uk/bio/maria/NetBuilder/

NetBuilder

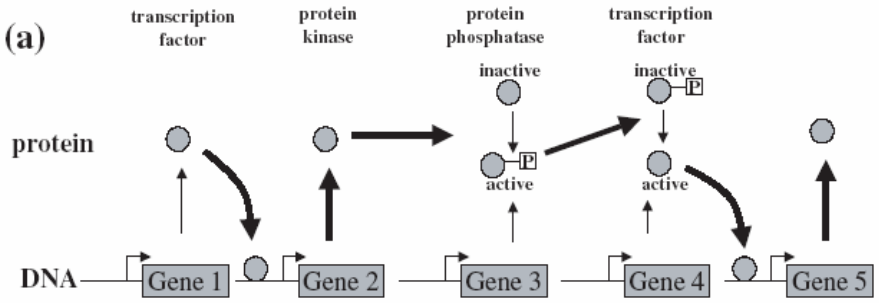


Taken from Eric H Davidson



Indirect Gene Effects

No combination of standard high-throughput experiments can reconstruct an a-priori known gene/protein network [Wagner].



(b)
Aspect of gene activity: mRNA expression
Genetic perturbation: gene deletion

G1:	G2, G5
G2:	G5
G3:	G5
G4:	G5
G5:	

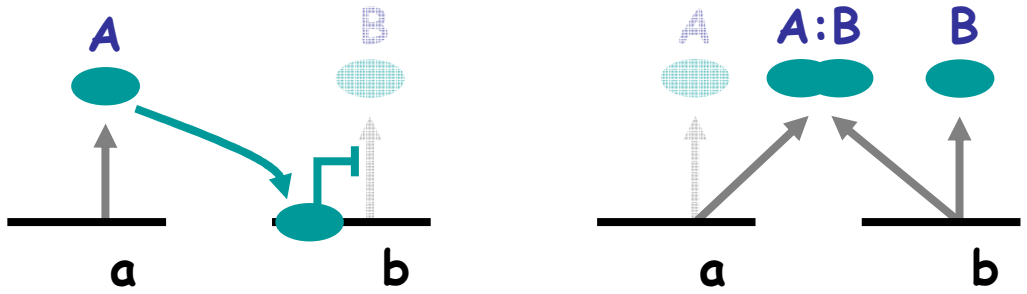
(c)
Aspect of gene activity: phosphorylation state
Genetic perturbation: gene deletion

G1:	G3, G4
G2:	G3, G4
G3:	G4
G4:	
G5:	

Taken from Andreas Wagner

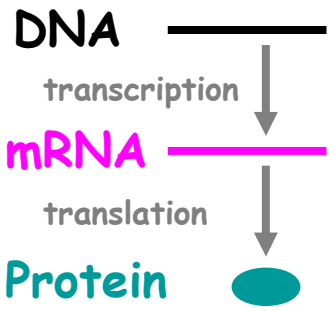
Fig. 1. The importance of specifiying gene activity when reconstructing genetic networks. (a) A hypothetical biochemical pathway involving two transcription factors, a protein kinase, and a protein phosphatase, as well as the genes encoding them. See text for details. (b) Shown is a list of perturbation effects for each of the five genes in (a), when perturbing individual genes by deleting them, and when using mRNA expression level as an indicator of gene activity. The left-most symbol in each line stands for the perturbed gene. To the right of each colon is a list of genes whose activity is affected by the perturbation. (c) Analogous to (b) but for a different notion of gene activity (phosphorylation state).

One of many bistable switches that cannot be described by pure gene regulatory networks [Francois & Hakim].



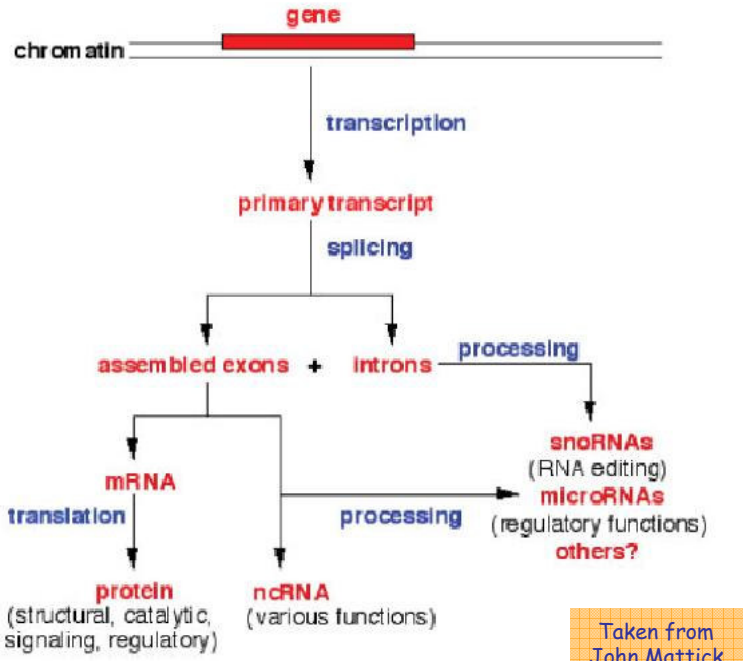
Structure of the Coding Region

The Central Dogma



RNA is not just an intermediary; it can:
- **Fold-up like a protein**
- **Act like an enzyme**
- **Regulate other transcribed RNA**
- **Direct protein editing**
- **…**

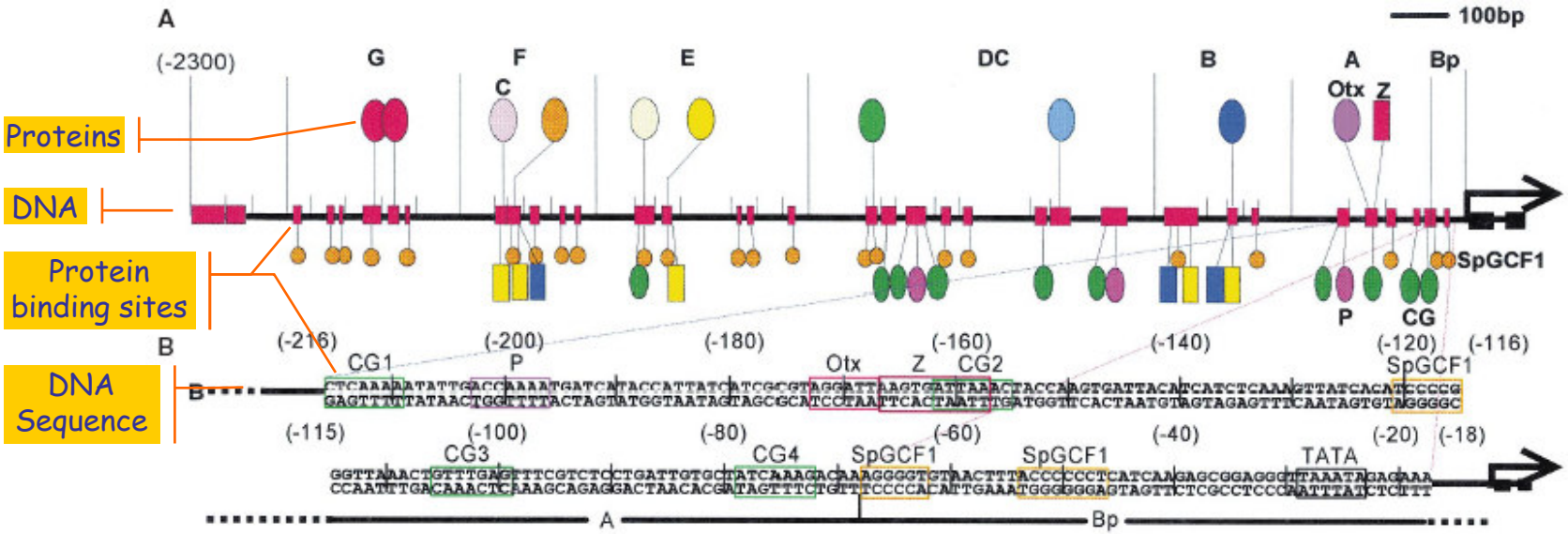
Challenging the Dogma (in higher organisms)



Taken from John Mattick

97-98% of the transciptional output of the human genome is non-protein-coding RNA.
30-40,000 "protein genes" (1.5% of genome)
60-100,000 "transcription units" (>30% of genome is transcribed)

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:

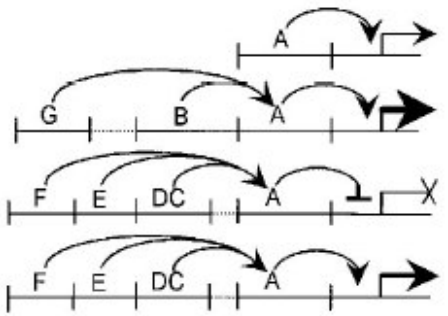
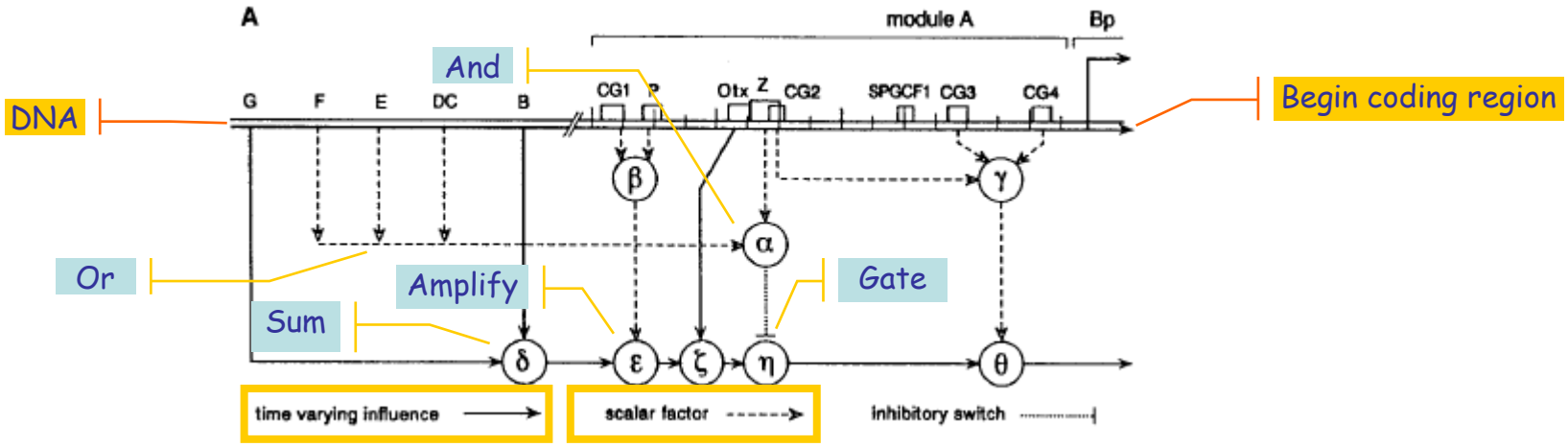


Fig. 1. *Endo16* cis-regulatory system and interactive roles of module A. (**A**) Diversity of protein binding sites and organization into modular subregions [modified from (*7*)]. Specific DNA binding sites are indicated as red blocks; modular subregions are denoted by letters G to A (Bp, basal promoter). 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

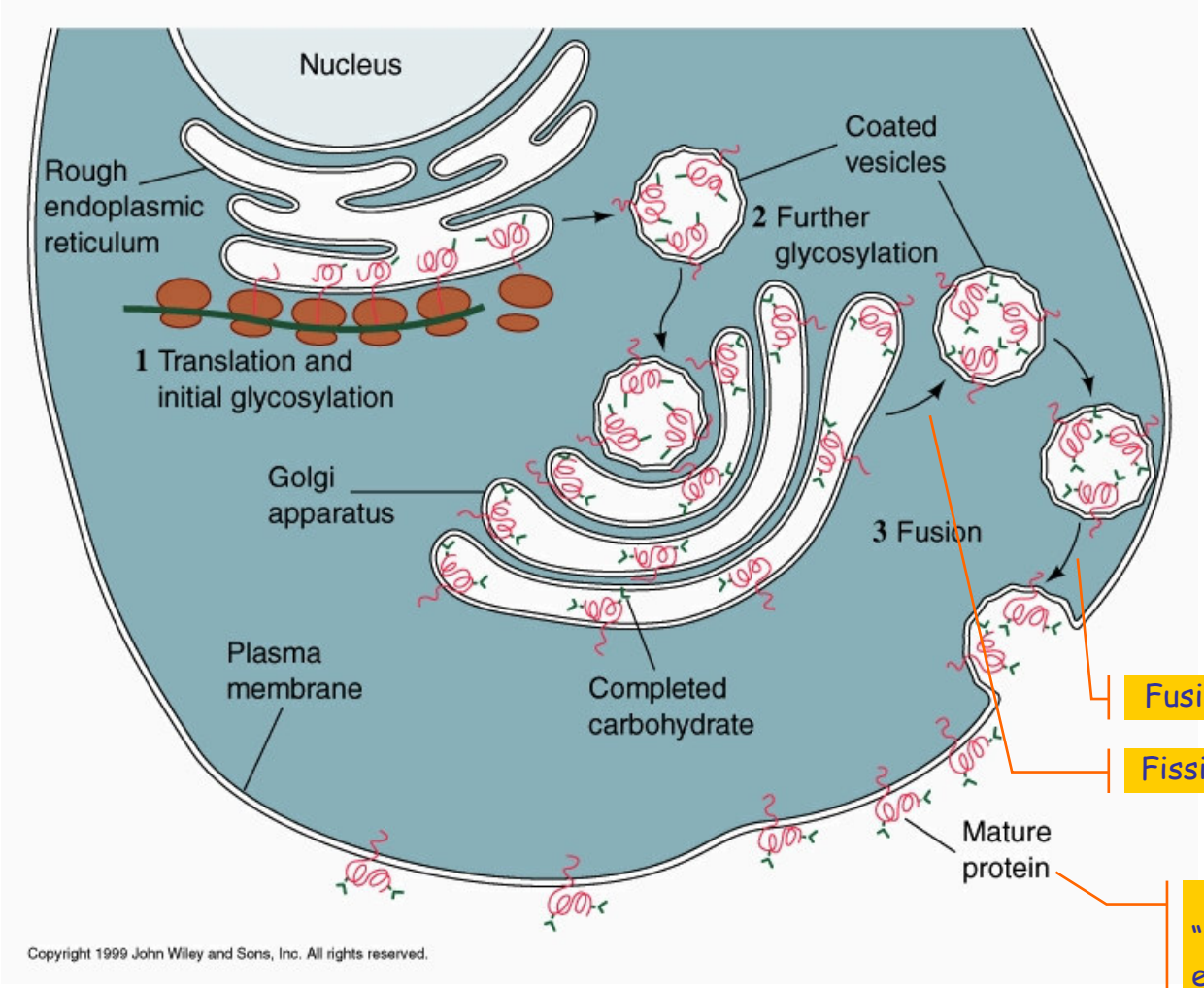
Taken from
Eric H Davidson

Notations for the Gene Machine

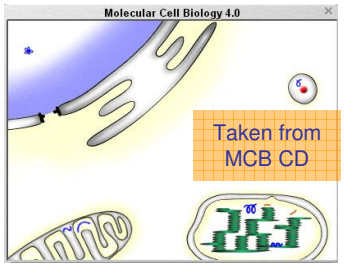
- Many of the same techniques as for the Protein Machine apply.
  - Process Calculi, Petri Nets, Term-Rewriting Systems…
- But the "programming model" is different.
  - Asynchronous control.
  - Biologically poorly understood.
  - Network "motifs" are being analyzed.
- Specific techniques:
  - Hybrid Petri Nets
    - [Matsuno, Doi, Nagasaki, Miyano] Gene Regulation
    - Genomic Object Net www.genomicobject.net
- Gene Regulation Diagrams
- Mixed Gene-Protein Diagrams

3. The Membrane Machine

Very far from the atoms.



Molecular transport and transformation through dynamic compartment fusion and fission.

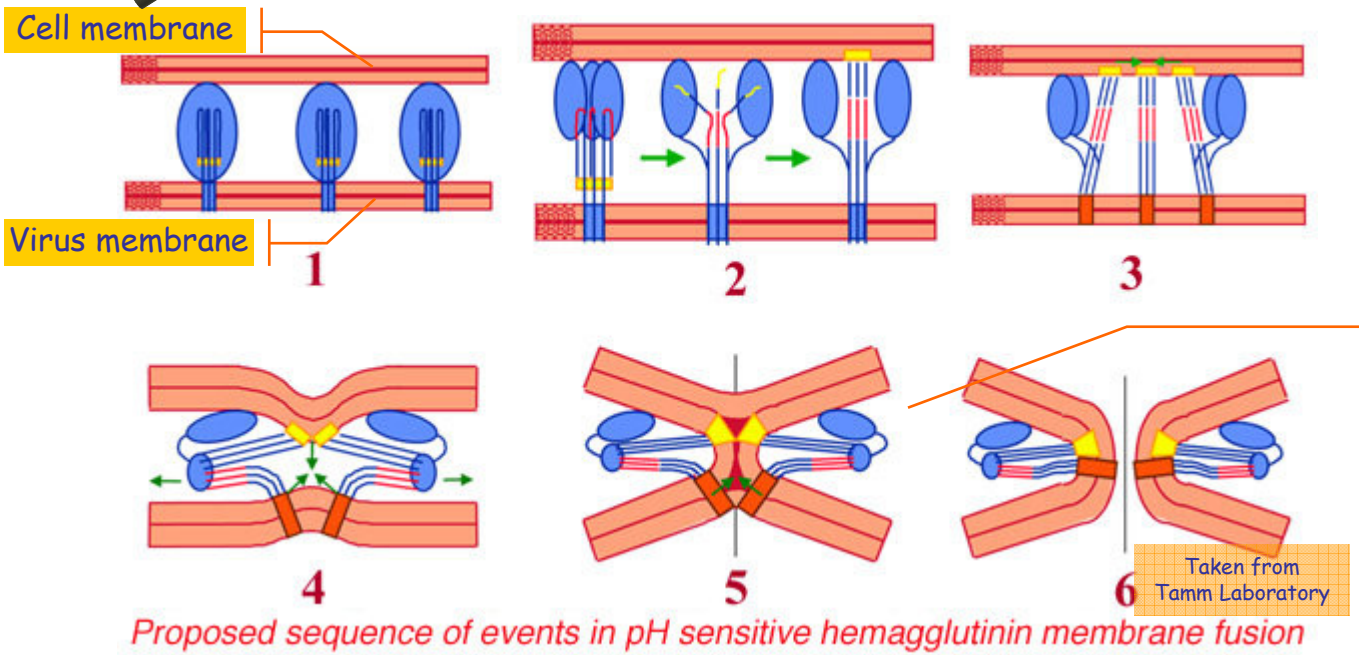


Well, what is all that for?

"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

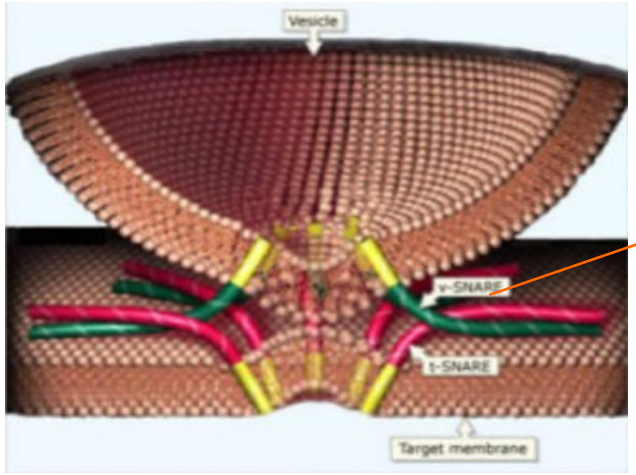
Positive curvature to Negative curvature transition in 3D



Proposed sequence of events in pH sensitive hemagglutinin membrane fusion

Aggressive fusion (virus)

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

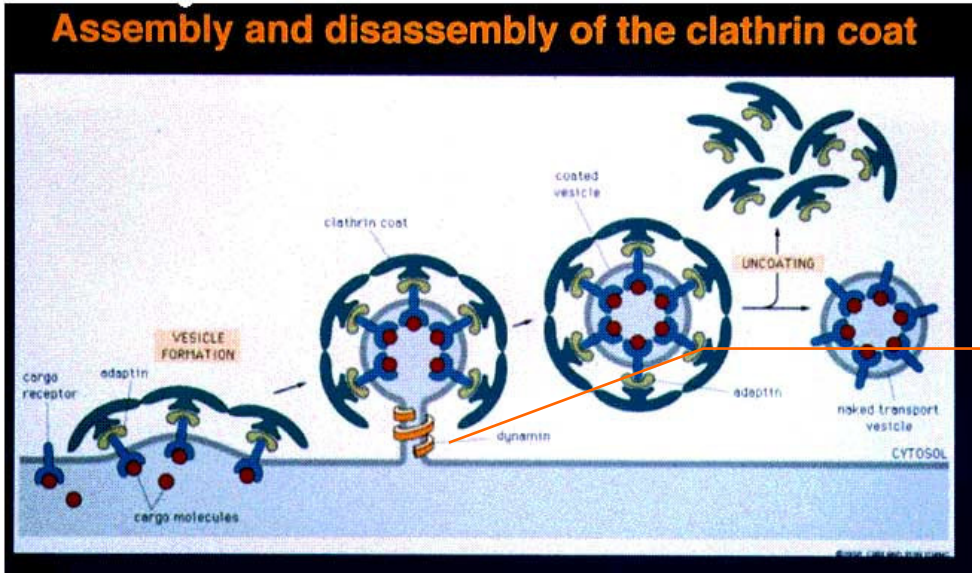


Cooperative fusion (vesicle)

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

Membrane Fission

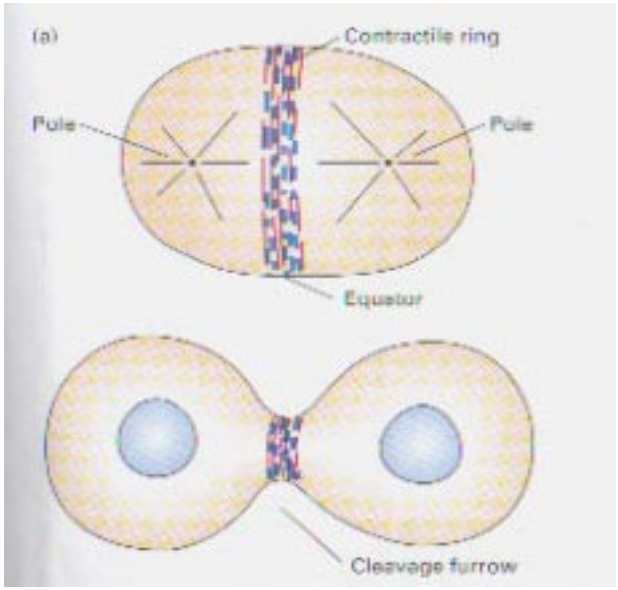
Negative curvature to Positive curvature transition in 3D



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]

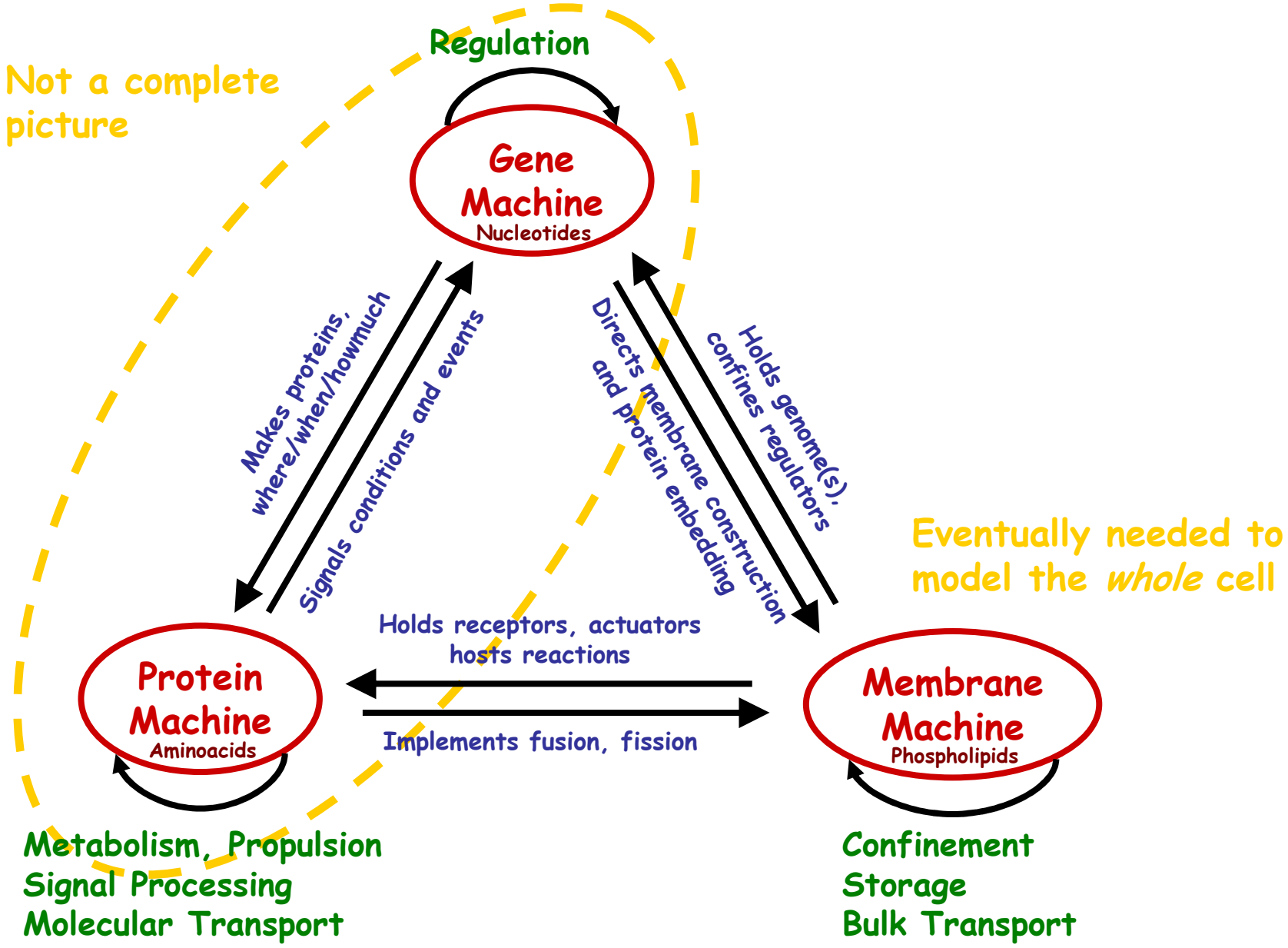


Cytokinesis (Mitosis)

Notations for the Membrane Machine

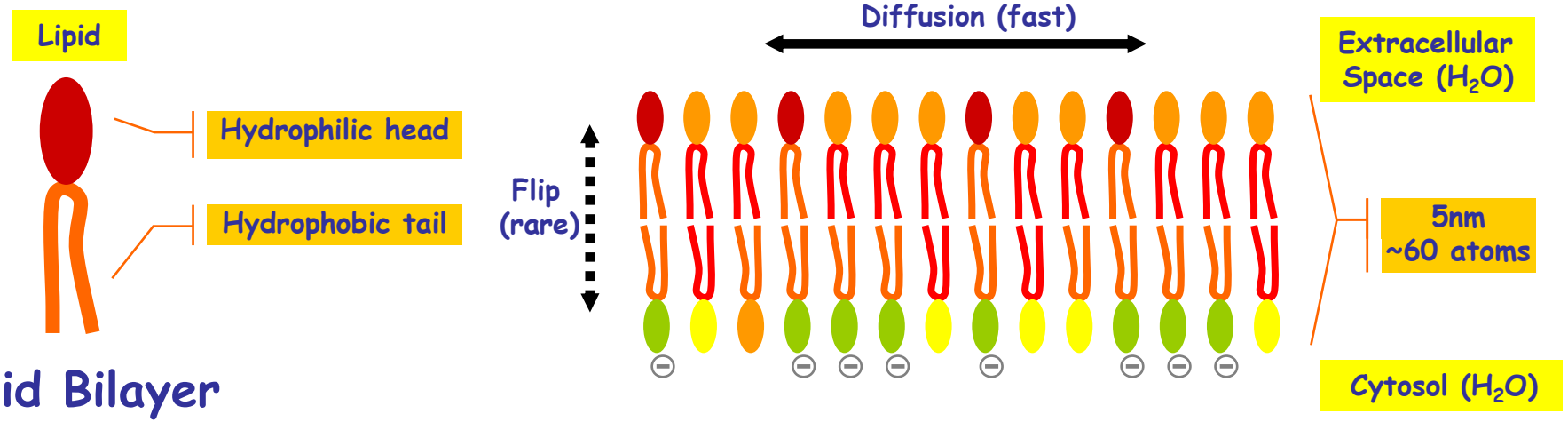
- "Snapshot" diagrams
  - In biology literature.
- P-Systems
  - G.Paun uses ideas from the theory of grammars and formal languages to model "Membrane Computing" (book 2002). http://psystems.disco.unimib.it/.
- BioAmbients
  - An extension of BioSPI along Ambient Calculus lines (with more bio-relevant mobility primitives) to model dynamic compartments.
- Brane Calculi
  - Computation *on* the membrane…

Summary


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

Membrane Systems

Membranes are Oriented 2D Surfaces



Lipid Bilayer

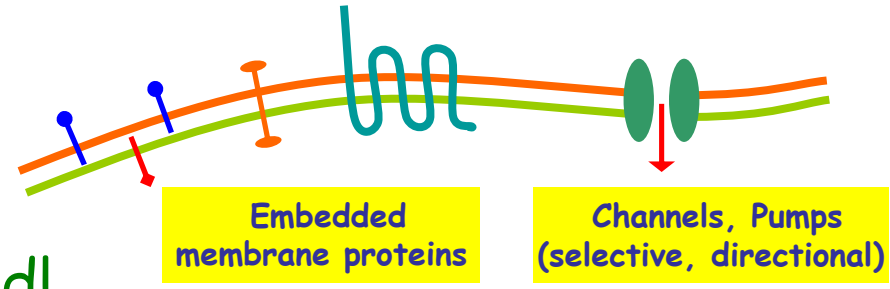
Self-assembling

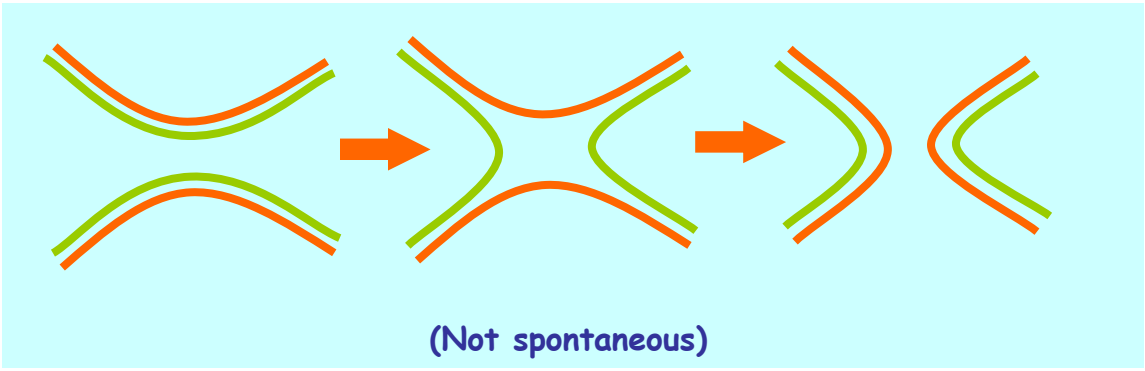
Largely impermeable

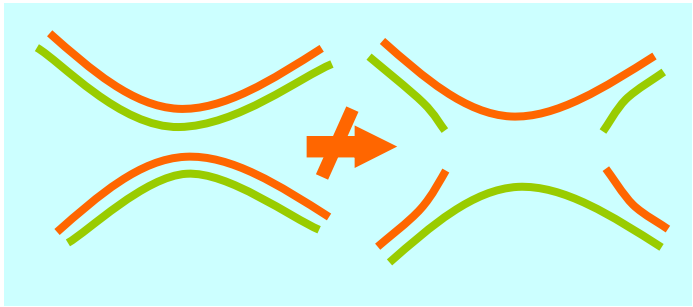
Asymmetrical (in real cells)

With embedded proteins

A 2D fluid inside a 3D fluid!

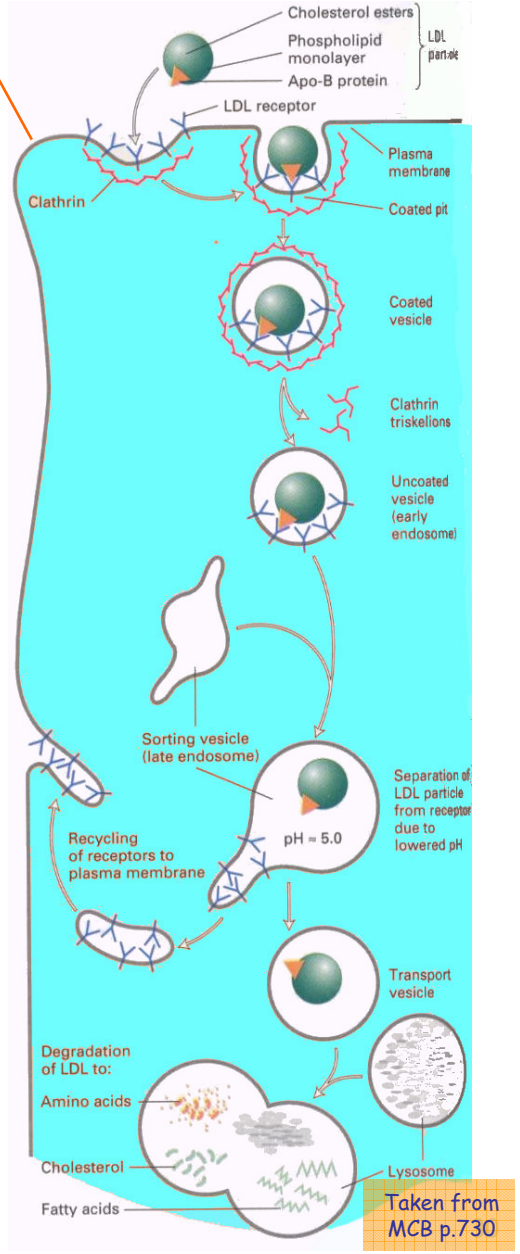






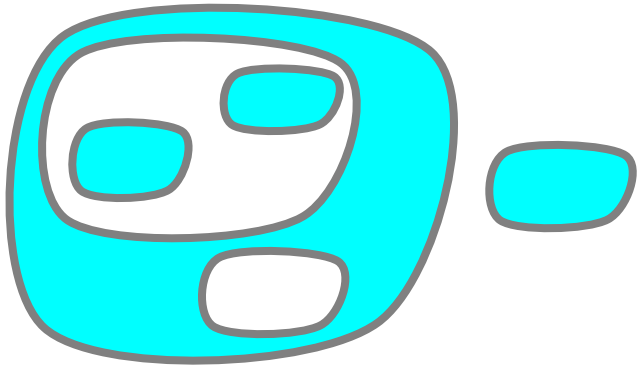
A Membrane Algorithm

- 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 millions of molecules.
- Some very fancy chemistry
  - But its "purpose" is to reliably implement a specific sequence of discrete steps.



Local Membrane Reactions

Membrane System



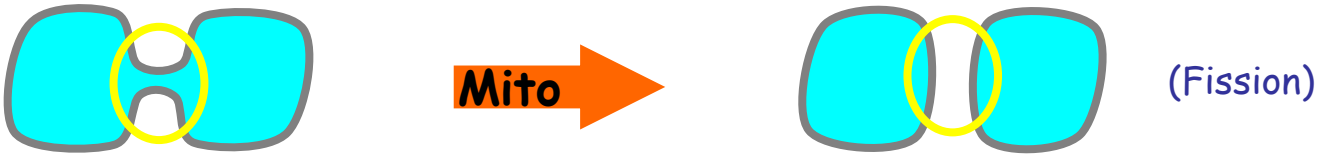
What reactions "make sense"?

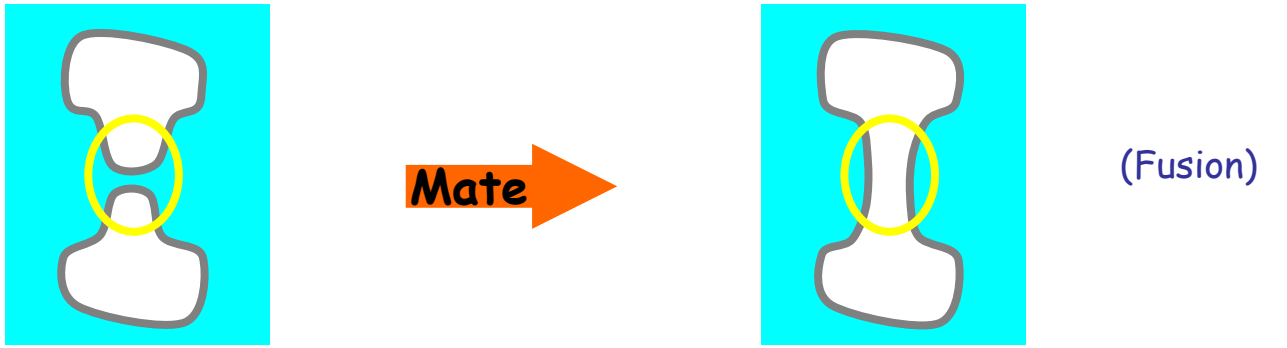
Reactions that "make sense" from a local, molecular viewpoint

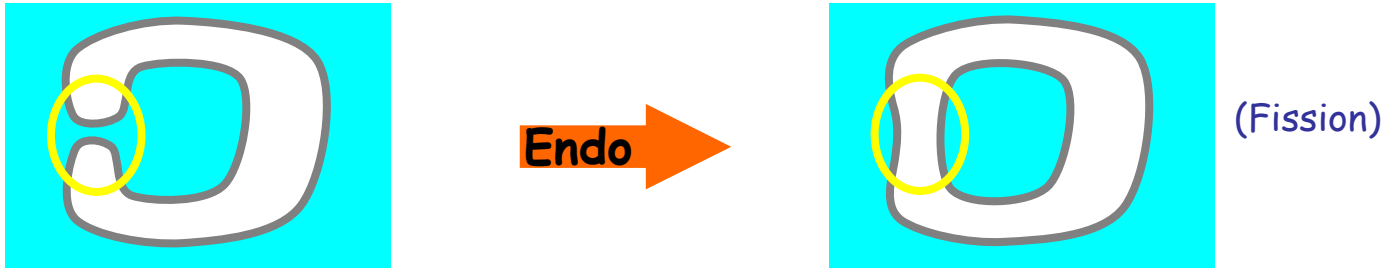
(Symmetric by 90° rotation.)

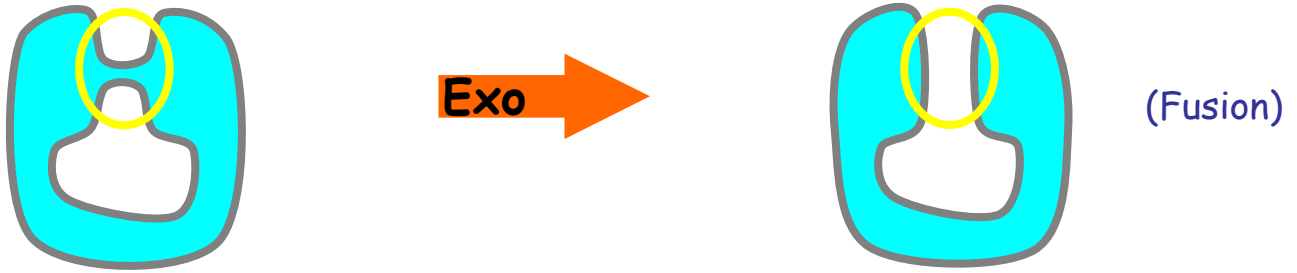
Global Membrane Reactions

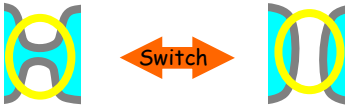
Reactions that "make sense" from a descriptive, global viewpoint





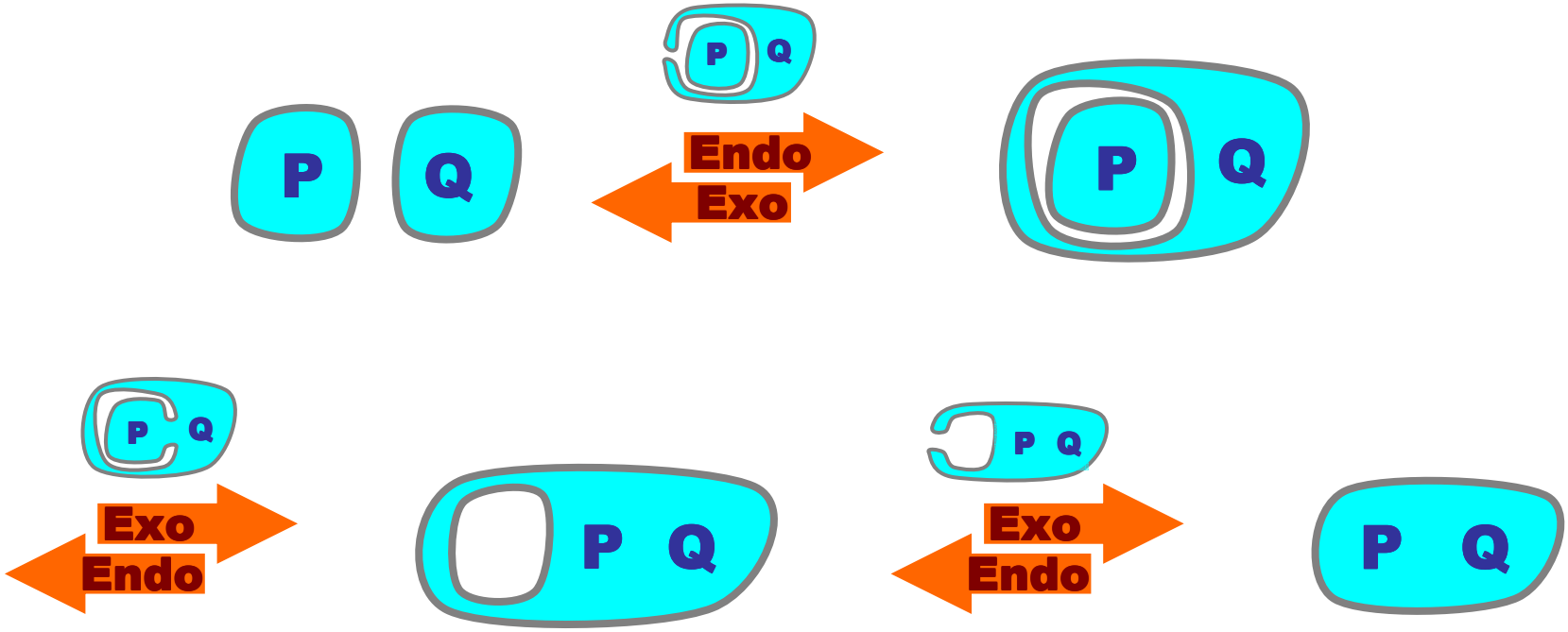






Same Local View!

Mito/Mate by 3 Endo/Exo



What makes Endo happen?

- Membrane transformations are "meant":
  - They do not happen spontaneously. They are regulated by membrane-embedded proteins.
  - We need to explain how/when certain membrane reactions happen.
- Formalization
  - A calculus of membrane interactions (as opposed to an algebra of membrane transformations).
  - 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

"When you want to have a predictive science, you have to be able to calculate." - Sydney Brenner

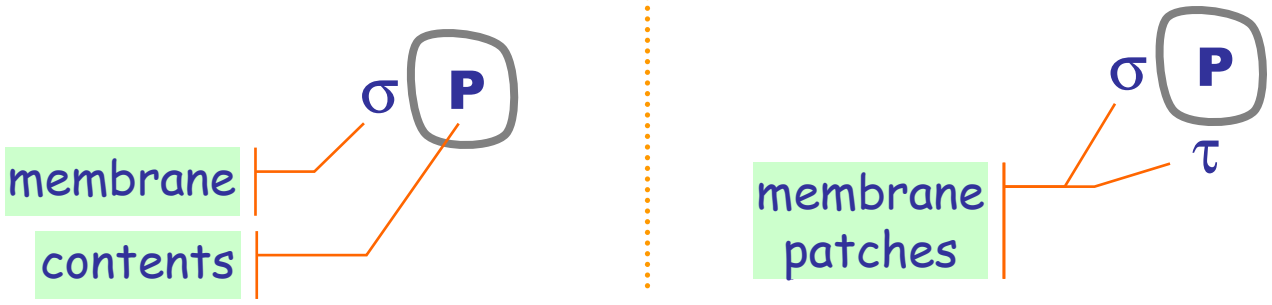
Brane Calculi

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

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



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

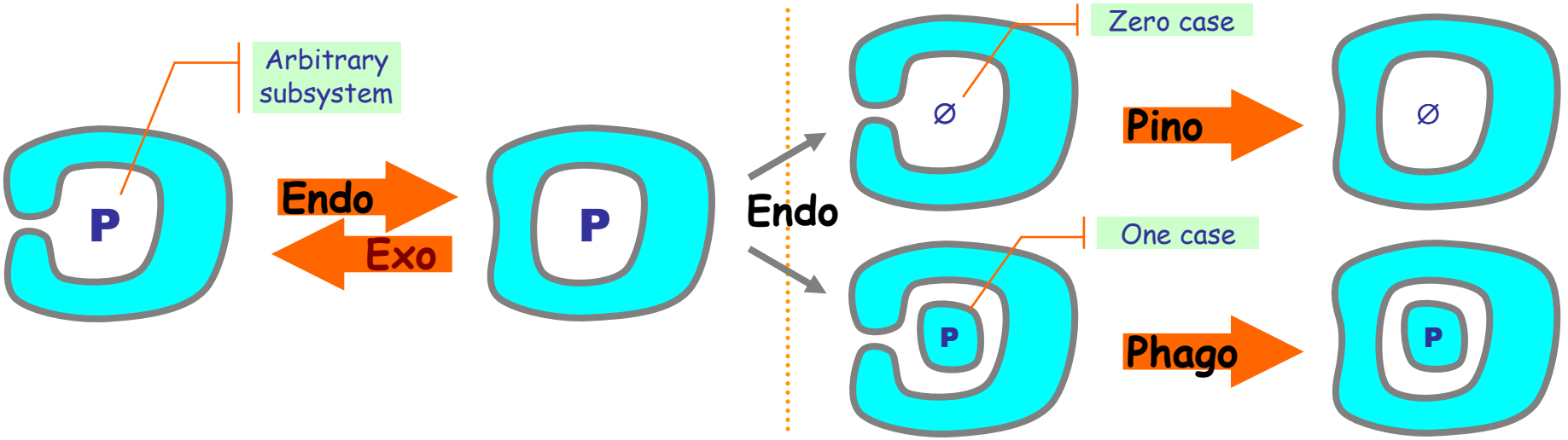
Congruence ≡ and Reaction ➡

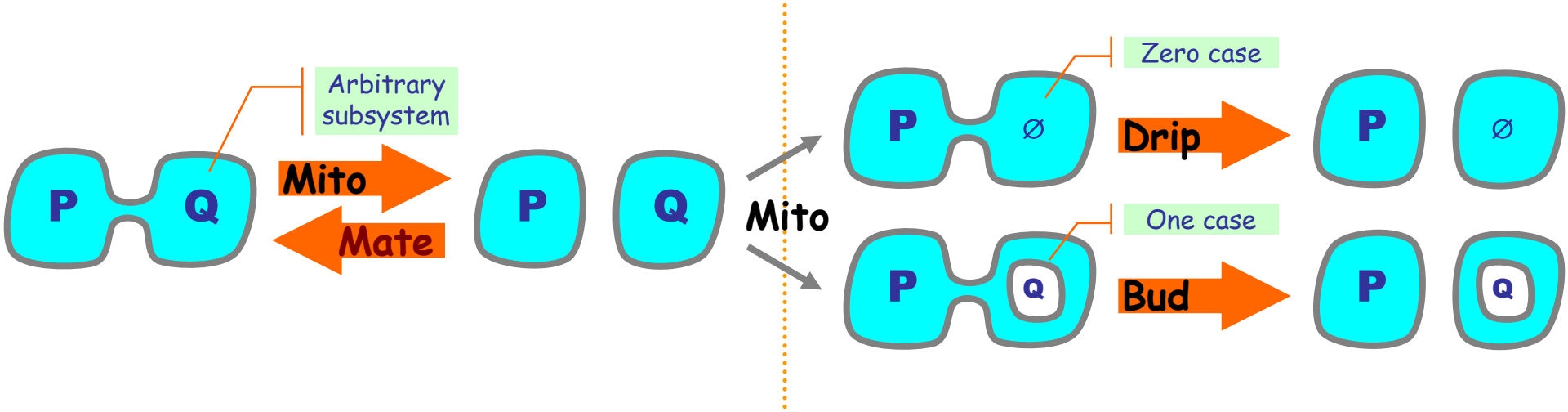
	System	Brane
Fluidity	$P \circ Q \equiv Q \circ P$ $P \circ (Q \circ R) \equiv (P \circ Q) \circ R$ $P \circ \diamond \equiv P$	$\sigma \mid \tau \equiv \tau \mid \sigma$ $\sigma \mid (\tau \mid \rho) \equiv (\sigma \mid \tau) \mid \rho$ $\sigma \mid 0 \equiv \sigma$
Plentitude	$!P \equiv P \circ !P$ 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 $\mathcal{O}_n.\sigma|\sigma'\langle P\rangle \circ \mathcal{O}^{\perp}_n(\rho).\tau|\tau'\langle Q\rangle \rightarrow \tau|\tau'\langle\rho\langle\sigma|\sigma'\langle P\rangle\rangle\circ Q\rangle$

Exo $\mathcal{O}^{\perp}_n.\tau|\tau'\langle\mathcal{O}_n.\sigma|\sigma'\langle P\rangle\circ Q\rangle \rightarrow P \circ \sigma|\sigma'|\tau|\tau'\langle Q\rangle$

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

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

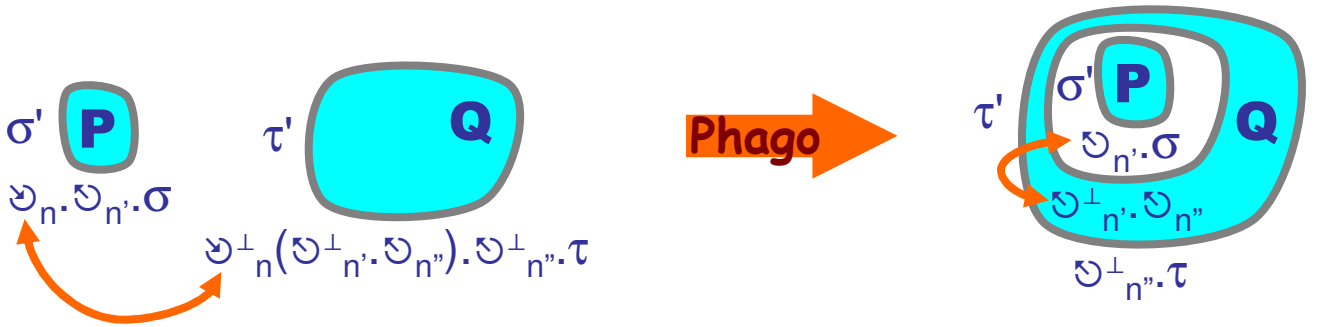
N.B.: in Phago (and Pino), one could perhaps require r to be,
conservatively, a piece of t, by a non-linear rewrite:

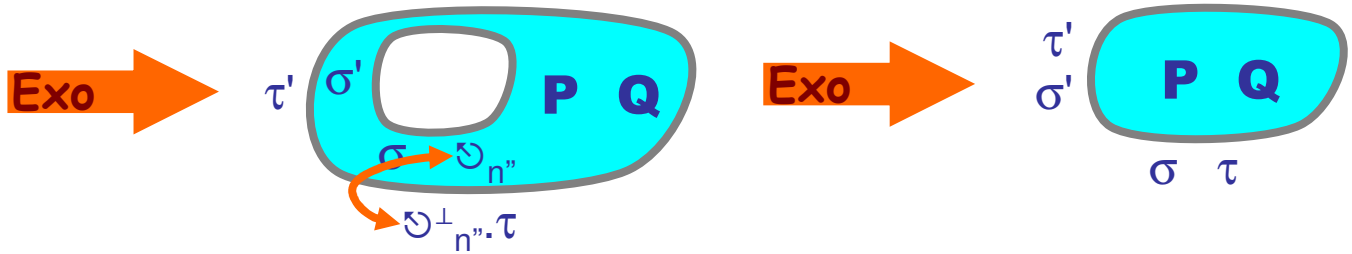
CPhago $\mathcal{O}_n.\sigma|\sigma'\langle P\rangle \circ \mathcal{O}^{\perp}_n(\rho).\tau|\tau'|\rho\langle Q\rangle \rightarrow \tau|\tau'\langle\rho\langle\sigma|\sigma'\langle P\rangle\rangle\circ Q\rangle$

Abbreviations: Mate

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

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



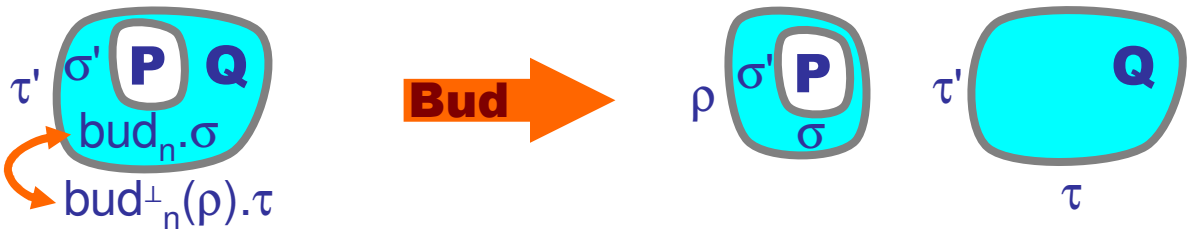


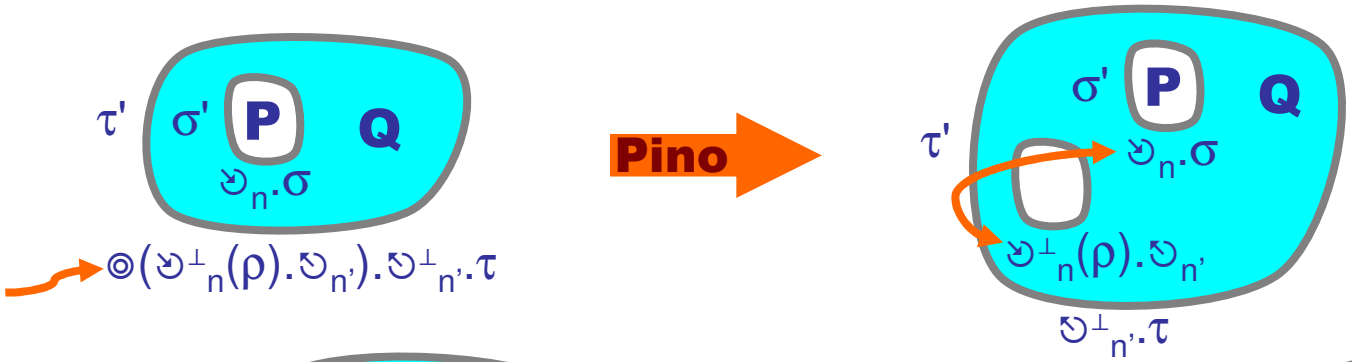
Abbreviations: Bud

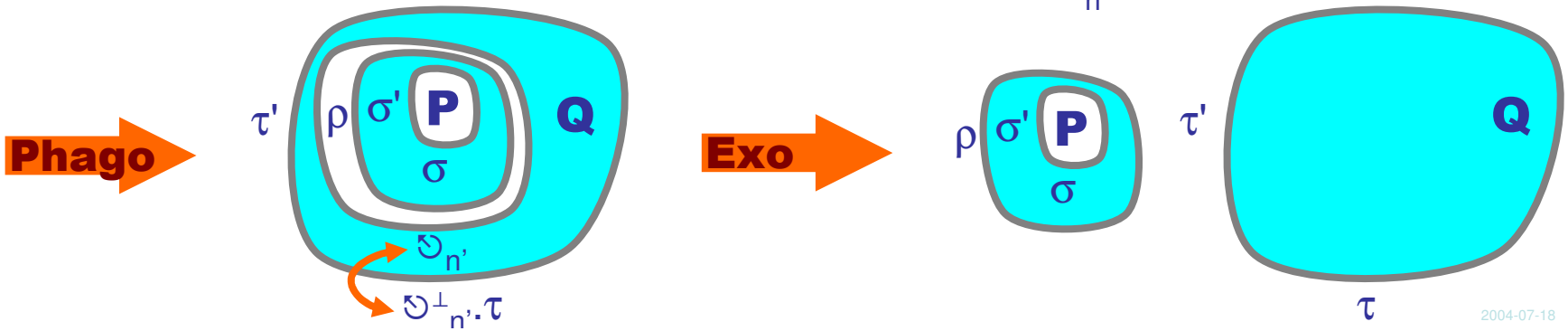
Bud $\mathrm{bud}_n.\sigma = \circlearrowright_n.\sigma$

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

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



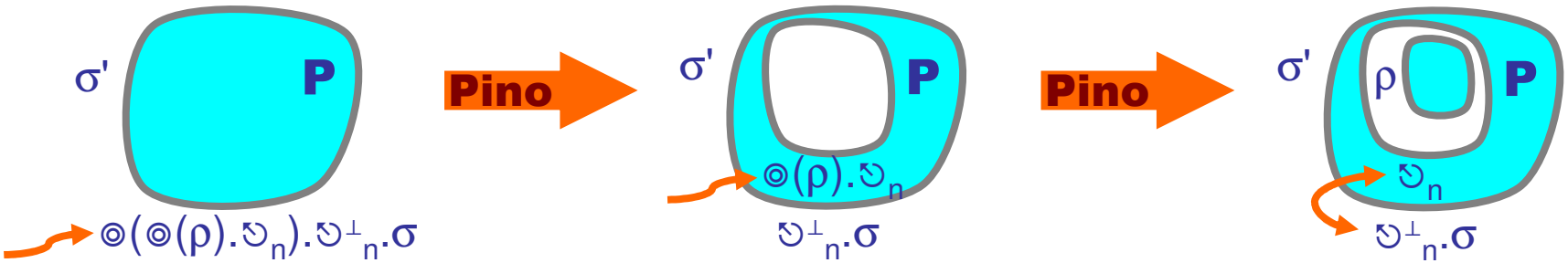


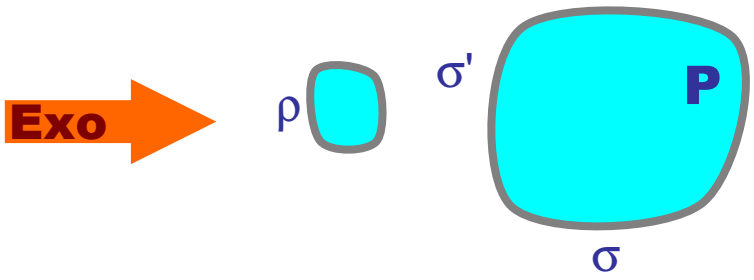


Abbreviations: Drip

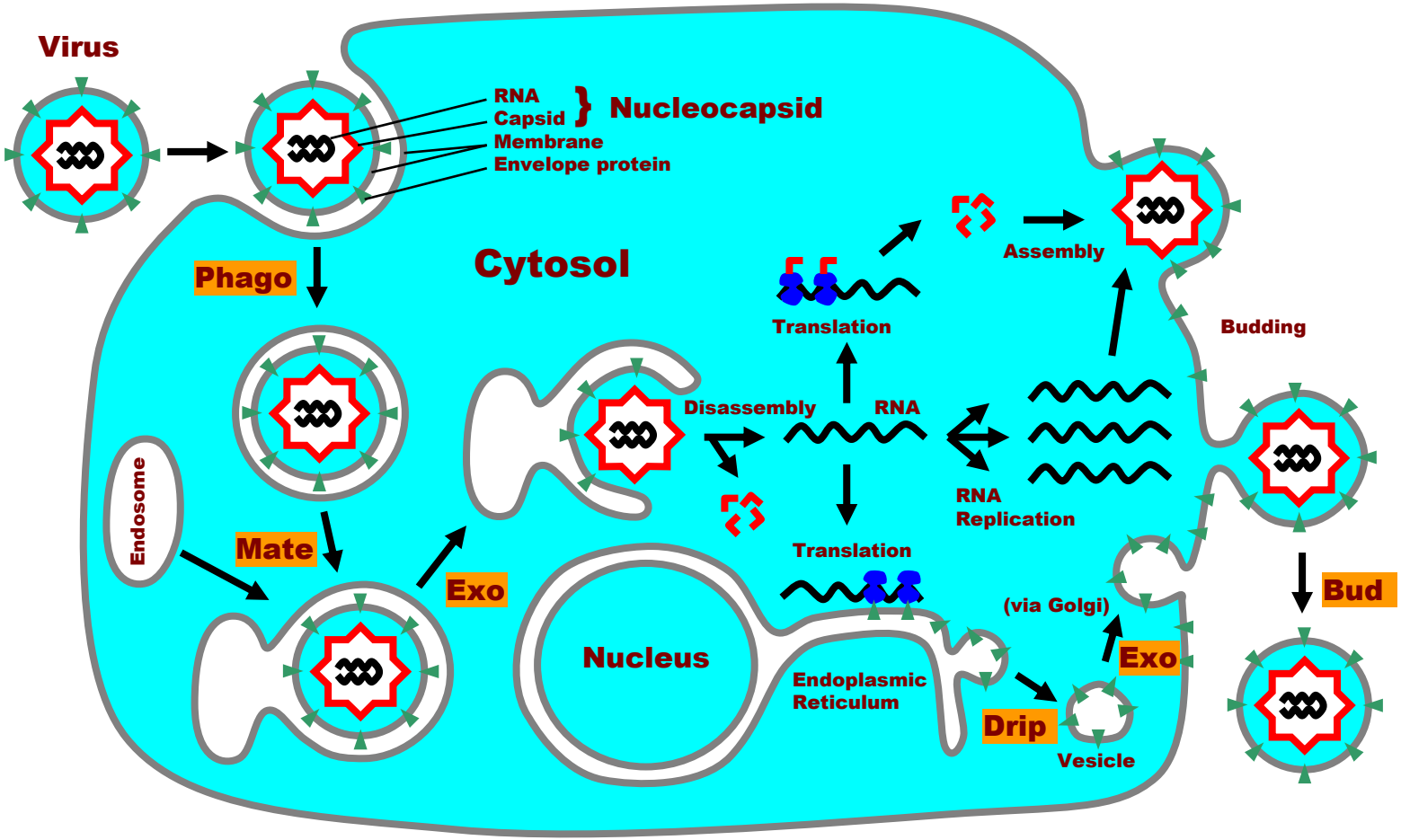
Drip $\mathrm{drip}_n(\rho).\sigma = \circledcirc(\circledcirc(\rho).\circlearrowleft_n).\circlearrowleft^{\perp}_n.\sigma$

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



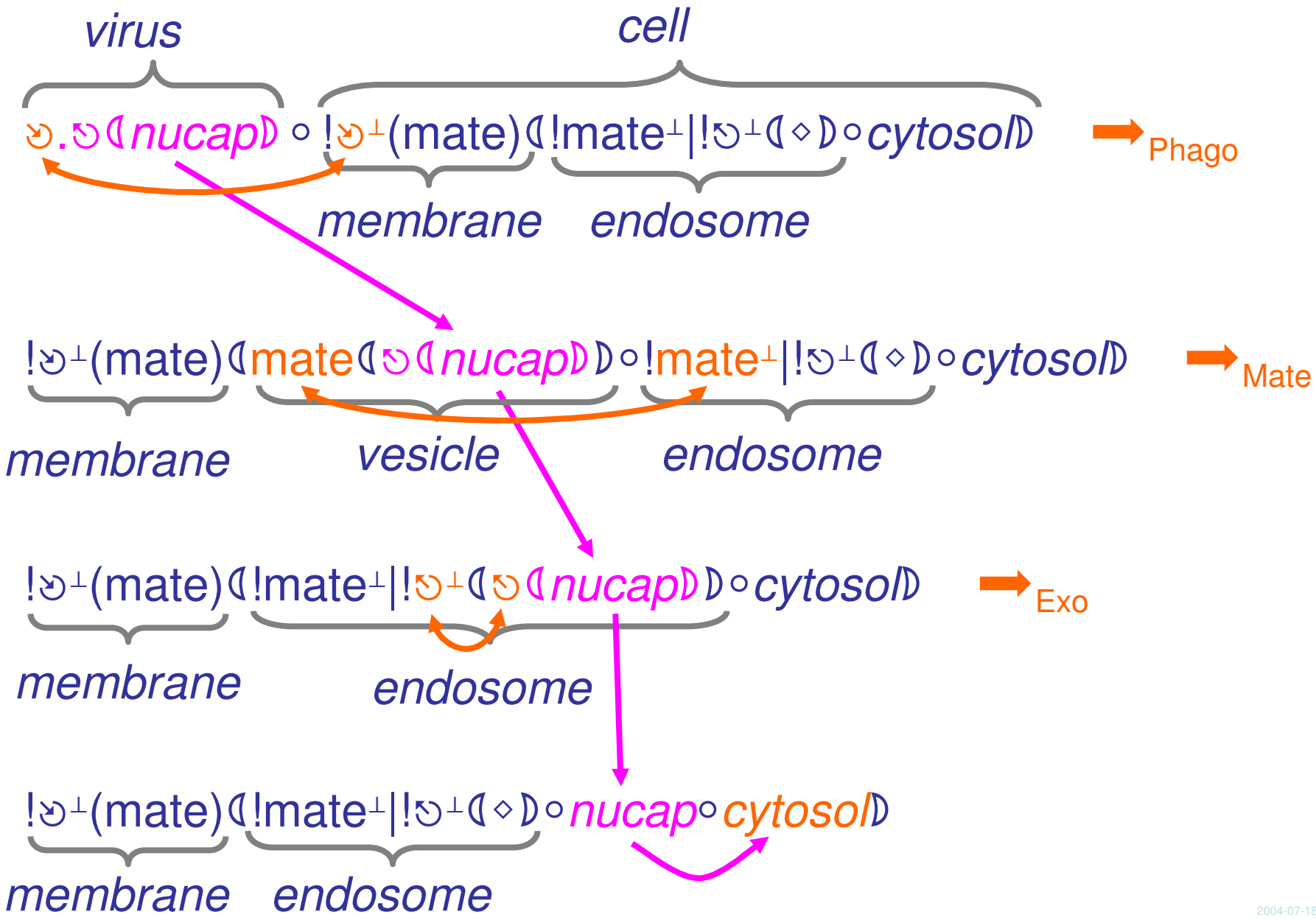


Ex: Viral Reproduction



[MBC p.279]
annotated

Ex: Viral Infection



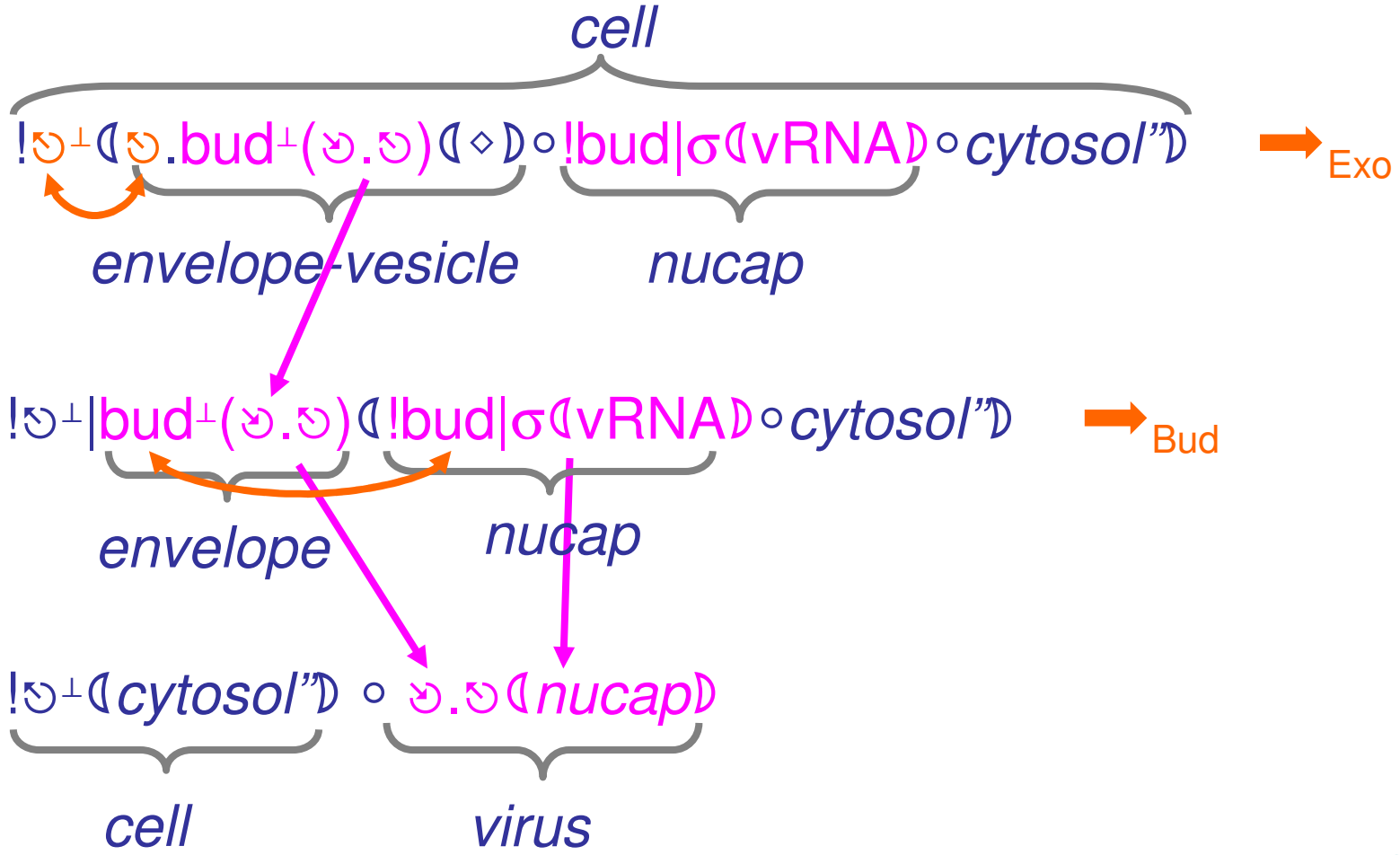
Ex: Viral Progeny

Assume:

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

by available cellular machinery

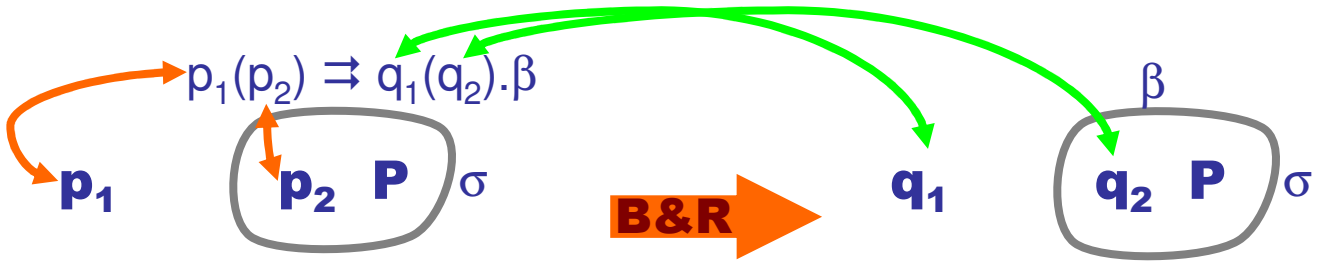
Then:



Molecules

We now add *molecules* to the model:

systems	$P,Q ::= \ldots \mid m$	$m \in M$ 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 $p_1 \circ p_1(p_2) \rightrightarrows q_1(q_2).\alpha|\sigma\langle p_2 \circ P\rangle \rightarrow q_1 \circ \alpha|\sigma\langle q_2 \circ P\rangle$

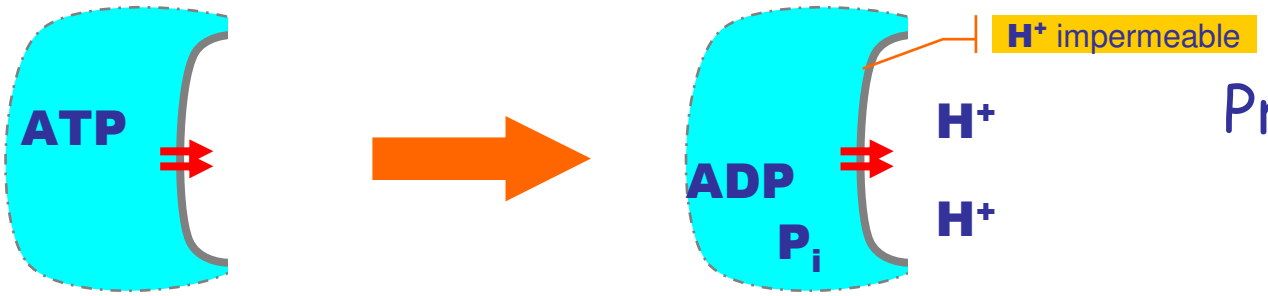
(multiset rewriting, inside and outside membranes)

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

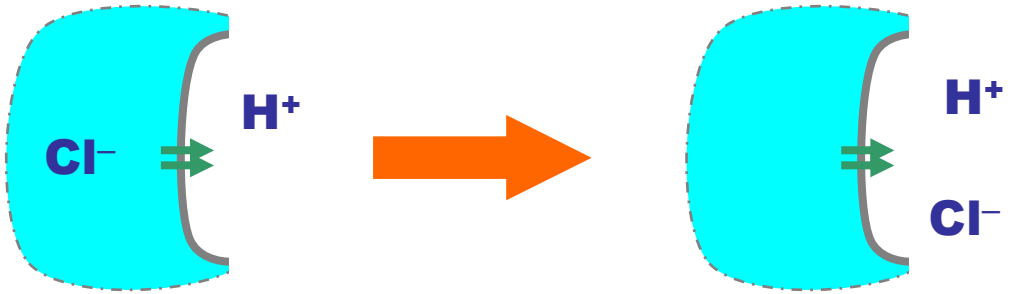
Ex: Molecular Pumps and Channels

E.g. plant vacuole (white).

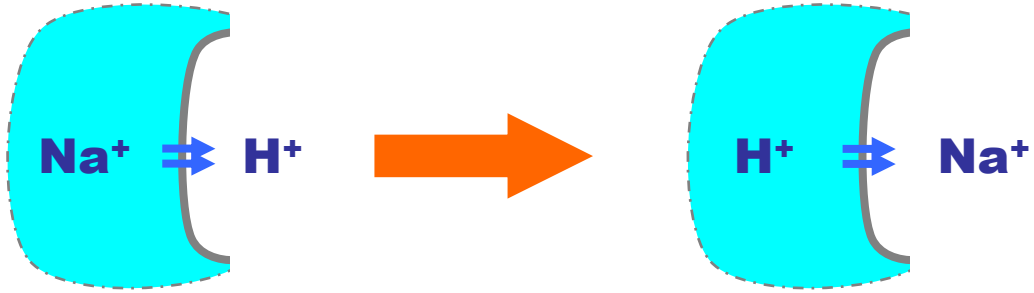


Proton Pump

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 membrane of a compartment)

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

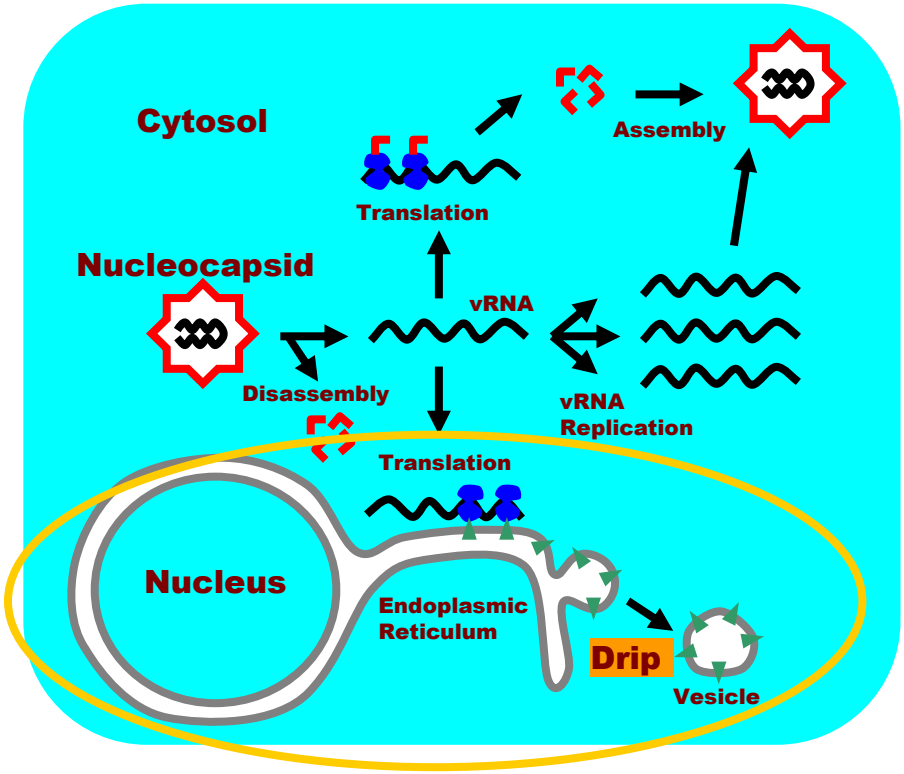
$p \dot{\rightarrow} q|\sigma\text{⦇}P\text{⦈}$ Condition affecting P

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

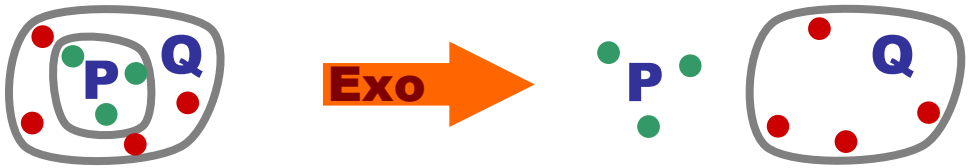
(See paper for the other two vRNA pathways)

Summary of Instruction Set So Far

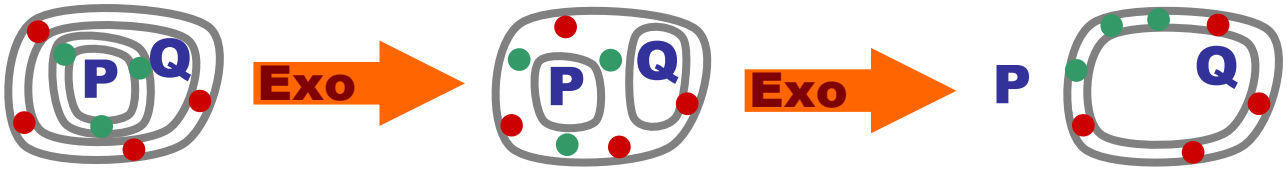
- Phago-exo-pino for the Membrane Machine
  - Plus mate-bud-drip, in principle definable.
- Bind&Release for the Protein Machine
  - Still could add complexation
    - Helps remove another need for π-restriction, which makes almost any analysis easier.
    - Helps avoid unrealistic uses of membranes for complexation.
- What about the Gene Machine?
  - Much can be done already (especially with either restriction or complexation).
  - Need some special etensions?

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"

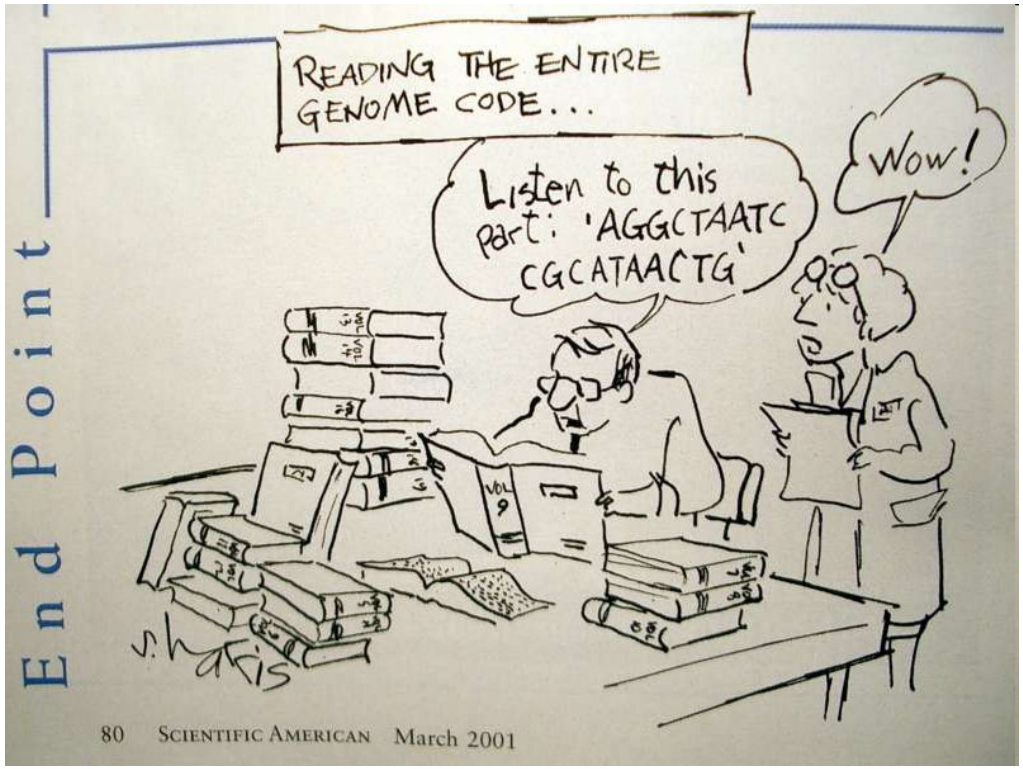
Awkward encoding. And all kinds of things can go wrong in the intermediate state.

- 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: do not try to extend needlessly.
- 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



Q: "The data are accumulating and the computers are humming, what we are lacking are the words, the grammar and the syntax of a new language..."

D. Bray (TIBS 22(9):325-326, 1997)

A: "The most advanced tools for computer process description seem to be also the best tools for the description of biomolecular systems."

E.Shapiro (Lecture Notes)

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 Pi-Calculus.

Papers

BioAmbients

a stochastic calculus with compartments.

Brane Calculi

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

Bitonal Systems

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

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