Biological Systems

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

- Nuclear membrane
- Mitochondria
- Golgi
- Vesicles (storage transport degradation)
- E.R. membranes
- Plasma membrane (<10% of all membranes)

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!

- Hydrophilic head
- Hydrophobic tail
- Flip (rare)
- Diffusion (fast)
- 5nm ~60 atoms
- Extracellular Space (H₂O)
- Cytosol (H₂O)
- Embedded membrane proteins
- Channels, Pumps (selective, directional)

Embedded membrane proteins
Channels, Pumps (selective, directional)
(Not spontaneous)
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
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

On/Off switches

Protein

Binding Sites

Inaccessible

Inaccessible

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.

*cf.* BioCalculus [Kitano Nagasaki], \(\kappa\)-calculus [Danos Laneve]
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 9, 1999)

Taken from Kurt W. Kohler
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 $\pi$-restriction.

- **Stochastic $\pi$-Calculus**
  - Priami formalizes a stochastic version of $\pi$-calculus where channels have communication *rates*.

- **$\kappa$-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

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 “veg1” 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 Sox1 factor interferes with nuclearization of β-catenin (26). For further details see refs. 9 and 10 and www.its.caltech.edu/~mirsky/endomes.htm.
Structure of the Coding Region

• Central Dogma of Molecular Biology:
Structure of a Regulatory Region

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, and CG 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.
Function of a Regulatory Region

\[ \begin{align*}
\text{Begin coding region} \\
\text{DNA} & \quad \text{And} \\
\text{Or} & \quad \text{Sum} \\
\text{Amplify} & \quad \text{Gate} \\
\text{time varying influence} & \quad \text{scalar factor} \\
\text{inhibitory switch} & \quad \\
\end{align*} \]

\[ \begin{align*}
B \\
\text{If } (F = 1 \text{ or } E = 1 \text{ or } CD = 1) \text{ and } (Z = 1) & \quad \text{Represents functions of modules } F, E, \text{ and } \\
& \quad \text{DC mediated by } Z \text{ site} \\
\alpha & = 1 \\
\text{else } & \quad \alpha = 0 \\
\text{if } (P = 1 \text{ and } CG_1 = 1) & \quad \text{Both } P \text{ and } CG_1 \text{ are needed for synergistic link} \\
& \quad \beta = 2 \\
\text{else } & \quad \beta = 0 \\
\text{if } (CG_1 = 1 \text{ and } CG_2 = 1 \text{ and } CG_3 = 1) & \quad \text{Final step up of system output} \\
& \quad \gamma = 2 \\
\text{else } & \quad \gamma = 1 \\
\zeta(t) = B(t) + G(t) & \quad \text{Positive input from modules } B \text{ and } G \\
\xi(t) = \beta \cdot \xi(t) & \quad \text{Synergistic amplification of module } B \\
\text{if } (c(t) = 0) & \quad \text{Switch determining whether } Otx \text{ site in} \\
\zeta(t) & \quad \text{module } A, \text{ or upstream modules (i.e.,} \\
& \quad \text{mainly module } B), \text{ will control level of} \\
\text{else } & \quad \text{activity} \\
\xi(t) & \quad \zeta(t) = \eta(t) \\
\text{if } (\gamma = 1) & \quad \text{Repression function inoperative in} \\
\eta(t) & \quad \text{endoderm but blocks activity elsewhere} \\
\text{else } & \quad \eta(t) = 0 \\
\xi(t) & \quad \gamma \cdot \eta(t) \\
\zeta(t) & \quad \text{Final output communicated to } BTA
\end{align*} \]
Where/When/HowMuch

3 genes encoding transcription factors

6 genes encoding proteins

Taken from Eric H. Davidson
Formalization of the Gene Machine

- Hybrid Petri Nets
  - [Matsuno, Doi, Nagasaki, Miyano]
- Stochastic $\pi$-calculus
  - [?] seems natural
These “Life of a Saint” diagrams (all temporal stages shown at once) are popular because this is what people actually see in microscopes.

Molecular transport and transformation through dynamic compartment fusion and fission.

“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

Proposed sequence of events in pH sensitive hemagglutinin membrane fusion

1. Cell membrane
2. Virus membrane
3. Aggressive fusion (virus)
4. Taken from Tamm Laboratory
5. Cooperative fusion (vesicle)
6. By unknown mechanisms, the exoplasmic leaflets of the two membranes fuse” [MCB p745]
7. “Fusion of the two membranes immediately follows prefusion, but precisely how this occurs is not known” [MCB p742]
Membrane Fission

Vesicle Formation

“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

Gene Machine

Protein Machine

Membrane Machine

Regulation

Not a complete picture

Metabolism, Propulsion
Signal Processing
Molecular Transport

Confinement
Storage
Bulk Transport

Holds receptors, actuators hosts reactions
Implements fusion, fission

Holds genome(s), confines regulators
Directs membrane construction and protein embedding
Signals conditions and events
Makes proteins, where/when/howmuch

2004-03-24
Bitonal Membrane Systems

A high-level descriptive view of basic membrane properties but with very little “mechanism”
Membranes are closed non-intersecting curves, with an orientation\(^{(1)}\).  

Each membrane has two faces. A cytosolic (\textit{\~inner}) face and an exoplasmic (\textit{\~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.
Membrane Reactions

Membrane System

Local (Patch) Reactions

Reactions that “make sense” from a local, molecular viewpoint

Switch

(Symmetric by 90° rotation.)

Froth Fizz

(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!

Switch
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:

- **In** → **Out**
- **Wrap** → **Open**

**Violate bitonality.**

**Non implementable by “local” membrane operations.**

**Not observed (except gradual Open during “digestion”).**

**Happen to be the Ambient Calculus operations!!**
Lysosome and target don’t just merge.

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

Virus → Nucleocapsid (Capsid, Membrane, Envelope protein) → Cytosol → Cytoplasmic translation → RNA replication → Assembly → Budding → Progeny

Infection → Replication → Progeny

[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** (\(\sigma\)) inside a **2D fluid** (\(P\))

Two commutative monoids instead of one of normal process calculi

\[
\sigma(P) \quad \sigma|\tau(P)
\]

\[a.\sigma|\tau = (a.\sigma)|\tau\]

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

\begin{align*}
P \circ Q & \equiv Q \circ P \\
P \circ (Q \circ R) & \equiv (P \circ Q) \circ R \\
P \circ \circ & \equiv P \\
!P & \equiv P \circ !P \quad \text{etc.}
\end{align*}

\begin{align*}
0 \diamond \circ & \equiv \circ \quad \text{Froth/Fizz} \\
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)
\end{align*}

\begin{align*}
\sigma | \tau & \equiv \tau | \sigma \\
\sigma | (\tau | \rho) & \equiv (\sigma | \tau) | \rho \\
\sigma | 0 & \equiv \sigma \\
!\sigma & \equiv \sigma | !\sigma \quad \text{etc.}
\end{align*}

\begin{align*}
1. \sigma & \equiv \sigma \quad \text{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
\end{align*}

\begin{align*}
P \equiv P' & \wedge P' \rightarrow Q' \wedge Q' \equiv Q \Rightarrow P \rightarrow Q
\end{align*}
actions
\[ a ::= \ldots \mid \gamma_n \mid \gamma_n^- (\rho) \mid \gamma_n \mid \gamma_n^- \mid \odot (\rho) \]

phago \(\varphi\), exo \(\psi\), pino \(\odot\)

Old “spontaneous” endo splits into phagocytosis (phago, often still pronounced endo) and pinocytosis (pino).
N.B.: in Phago (and Pino), one could perhaps require $\rho$ to be, conservatively, a piece of $\tau$, by a non-linear rewrite:

\[
\text{Phago} \; \psi_n.\sigma|\sigma'(P) \circ \psi_n(\rho).\tau|\tau'(Q) \rightarrow \tau|\tau'(\rho(\sigma|\sigma'(P)) \circ Q)
\]

\[
\text{Exo} \; \psi_n.\tau|\tau'(\psi_n.\sigma|\sigma'(P) \circ Q) \rightarrow P \circ \sigma|\sigma'|\tau|\tau'(Q)
\]

\[
\text{Pino} \; \otimes(\rho).\sigma|\sigma'(P) \rightarrow \sigma|\sigma'(\rho(\circ) \circ P)
\]

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 $\rho$ to be, conservatively, a piece of $\tau$, by a non-linear rewrite:

\[
\text{CPhago} \; \psi_n.\sigma|\sigma'(P) \circ \psi_n(\rho).\tau|\tau'(\rho(Q) \rightarrow \tau|\tau'(\rho(\sigma|\sigma'(P)) \circ Q)
\]
Abbreviations: Mate

\[
\text{Mate } \quad \text{mate}_n^\sigma \ = \ \mathcal{V}_{n'} \mathcal{V}_n^\sigma \\
\text{mate}^\perp_n^\tau \ = \ \mathcal{V}_n^{\perp n'} \mathcal{V}_n^{\perp n''} \mathcal{V}_n^{\perp n''} \tau
\]
A budding version of old "spontaneous" mito, to avoid arbitrary splits. Follows the pattern of inverse-mate.
Abbreviations: Drip

\[ \text{Drip} \quad \text{drip}_n(\rho).\sigma = \otimes(\otimes(\rho).\otimes_n).\otimes_n^\perp.\sigma \]

A zero-expelled-membranes version of old “spontaneous” mito, to avoid arbitrary splits. Follows the pattern of inverse-mate.
Ex: Viral Reproduction

Virus

Endosome

Phago

Mate

Exo

Cytosol

Nucleocapsid

RNA

Capsid

Membrane

Envelope protein

Disassembly

Translation

RNA Replication

Assembly

Budding

Endoplasmic Reticulum

Nucleus

Exo

Drip

Vesicle

Infection

Replication

Progeny

[MBC p.279]
Ex: Viral Infection

virus

\(\overset{\text{nucap}}{\phi}\) \(\overset{\text{mate}}{\phi}\) \(\overset{\text{cytosol}}{\phi}\)

membrane

endosome

\(\overset{\text{Phago}}{\text{mate}}\)

membrane

vesicle

endosome

\(\overset{\text{Mate}}{\text{mate}}\)

membrane

endosome

\(\overset{\text{Exo}}{\text{mate}}\)

membrane

endosome

\(\overset{\text{nucap}}{\phi}\) \(\overset{\text{cytosol}}{\phi}\)
Ex: Viral Progeny

Assume:
\[ \text{nucap} \circ \text{cytosol} \Rightarrow \text{nucap}^n \circ \text{envelope-vesicle}^m \circ \text{cytosol}' \]
by available cellular machinery

Then:
\[ \text{cell} \]

\[ \text{envelope-vesicle} \leftarrow \text{nucap} \]

\[ \text{bud}^\perp (\cdot \cdot \cdot) \leftarrow \text{bud} \circ \sigma (\text{vRNA}) \circ \text{cytosol}'' \]

Exo

\[ \text{envelope} \leftarrow \text{nucap} \]

\[ \text{bud}^\perp (\cdot \cdot \cdot) \leftarrow \text{bud} \circ \sigma (\text{vRNA}) \circ \text{cytosol}'' \]

Bud

\[ \text{cell} \]

\[ \text{virus} \]

\[ \text{cytosol}'' \circ \cdot \cdot \cdot (\text{nucap}) \]
Molecular Actions

 systems

\[ P, Q ::= \ldots | \ m \quad m \in M \quad \text{molecules} \]
\[ p, q ::= m_1 \circ \ldots \circ m_k \quad \text{molecule multisets} \]

 actions

\[ a ::= \ldots | \ p_1(p_2) \Rightarrow q_1(q_2) \quad \text{bind\&release} \]

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 \( \kappa \)-calculus by adding complex molecules.
B&R \quad p_1 \circ p_1(p_2) \Rightarrow q_1(q_2).\alpha|\sigma(p_2 \circ P) \Rightarrow q_1 \circ \alpha|\sigma(q_2 \circ P)

(multiset rewriting, inside and outside membranes)

Simple bindings and releases - “◊(◊)” is omitted:

\begin{align*}
m(◊) &\Rightarrow \text{bind out} & \Rightarrow m(◊) &\Rightarrow \text{release out} \\
◊(m) &\Rightarrow \text{bind in} & \Rightarrow ◊(m) &\Rightarrow \text{release in}
\end{align*}
Chemical reaction catalysis (inside a compartment):

\[ p \rightarrow q \triangleq ! p(\vartriangle) \Rightarrow q(\vartriangle) \Downarrow \uparrow \]
\[ p \leftrightarrow q \triangleq p \rightarrow q \circ q \rightarrow p \]

E.g. peptide bond between two aminoacids \( R^1 \) \( R^2 \):
\[ R^1\text{-COOH} \circ H_2\text{N-R}^2 \rightarrow R^1\text{-CO-HN-R}^2 \circ H_2\text{O} \]

Compartment conditions (on the brane of a compartment):

\[ p \rightarrow q \triangleq ! \vartriangle (p) \Rightarrow \vartriangle (q) \]
\[ p \rightarrow q|\sigma (P) \]

Condition affecting \( P \)

E.g. a condition-driven reaction:
\[ p \rightarrow q|\sigma (p) \rightarrow p \rightarrow q|\sigma (q) \]
Ex: Virus Replication

\[ \text{nucap} \odot \text{cytosol} \rightarrow \rightarrow \text{nucap}^n \odot \text{envelope-vesicle}^m \odot \text{cytosol}' \]

\[ \text{ER} \triangleq \text{vRNA}(\diamond) \Rightarrow \text{vRNA}(\diamond). \text{drip}(\odot.\text{bud}^{\uparrow}(\odot.\odot)) \downarrow \text{Nucleus} \]

(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


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