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

Bitonal
Membrane Systems

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www.luca.demon.co.uk/ArtificialBiochemistry.htm
Membranes are Oriented 2D Surfaces

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

Lipid
Hydrophilic head
Hydrophobic tail

Diffusion (fast)

Extracellular Space (H₂O)
Cytosol (H₂O)

5nm
~60 atoms

Flip (rare)

Embedded membrane proteins
Channels, Pumps (selective, directional)

(Not spontaneous)
Systems of Oriented Membranes

Membranes are closed non-intersecting curves, with an orientation\(^{(1)}\).

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

This alternation is illustrated by using two tones: blue (\textit{cytosol}\(^{(2)}\)) and white (\textit{exosol}\(^{(3)}\)). Bitonal diagrams.

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

\(\text{(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.}
\(\text{(2) Short for Cytoplasmic Solution. (3) Short for Exoplasmic Region (I am making this one up).} \)
**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.

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**Evolutionary explanations of bitonal structure**

- Mitochondria acquisition
- Mitochondria to Chloroplasts
- Pre-Eukarya to Eukarya
Gradual Transformations of Membrane Systems
Locally Realizable Reactions

Membrane System

What transformations “make sense”?

Local (Patch) Reactions

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

Switch

(Symmetric by 90° rotation.)

Froth Fizz

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

A *global reaction* is a pair of membrane systems (before and after), but we are only interested in *gradual changes*, e.g.:

There are three ways to characterize gradual changes:

- Local interactions of membrane patches.  
  (What really happens at the biochemical level.)

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

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

These turn out to be equivalent!
Those Global Reactions are Local Reactions

Reactions that “make sense” from a descriptive, global viewpoint

Switch

Same Local View!
Bitonal Transformations: Operational View
We look for reactions that “preserve” the bitonal coloring of a membrane system. (And hence preserve proper membrane orientation and “well-being”.)
Froth/Fizz Reaction

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

N.B. non-empty membranes should not “spontaneously” be created or deleted: usually only very deliberate processes cause that. However, spontaneous froth/fizz seems be harmless; it means that empty membranes are not observable.

* Phospholipid molecules automatically assemble into closed membranes.
**Mito/Mate Reaction**

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Dual:
✓ Endo/Exo Reaction

Dual:
✓ Peel/Pad Reaction

Dual:
Bud Reaction

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

Can also be seen as Pad + Exo:
Bad Bubbles

Wrong bubbles:

Bubble catastrophe:

Violates bitonality.

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

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

Flooding in context violates bitonality:
Violate bitonality

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

$x$ Ambients
Summary: At Least Four Good Reactions

- Froth/Fizz
- Endo/Exo
- Mito/Mate
- Peel/Pad

Actually, Peel/Pad is NOT a bitonal reaction by my definition, but is the composition of two such. Good enough.
Mito/Mate by 3 Endo/Exo

Diagram showing the interaction between P and Q in an Endo/Exo process.

(dual)
Endo/Exo from Mito/Mate only?
No: depth of nesting is constant in Mito/Mate.
Peel/Pad by Froth/Fizz and Endo/Exo
An (Turing) Complete Set of Reactions

Others bitonal reactions are Derivable, e.g.:

Are all other derivable? YES!
Ex: Eukaryotic Mitosis
Bitonal Transformations: Topological View
The depth of a point is the number of membranes that contain it. The tonality of a point is white/blue iff its depth is even/odd.
A *bitonal* (resp. *layered*) reaction is a pair of membrane systems \(<M,M'>\) such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes). (Layered $\Rightarrow$ Bitonal)

**Def: Bitonal Reactions**

- **Deform**
  - Simple Deformation (Layered & Bitonal)
- **Froth**
  - Layered Bitonal Reaction
- **Mito**
  - Layered Bitonal Reaction
- **Exo**
  - Non-Layered Bitonal Reaction
Non-Bitonal Reactions

A \textit{bitonal} (resp. \textit{layered}) \textit{reaction} is a pair of membrane systems \( \langle M, M' \rangle \) such that the points that change tone (resp. depth) form a simply-connected region (a region not separated by membranes).

- **Wrap**: change tone & depth not connected
- **In**: change tone & depth not connected
- **Pad**: change tone & depth not connected

but obtainable as the composition of two bitonal reactions (Froth+Endo)
A transformation is a finite sequence of reactions. A bitonal transformation is a finite sequence of bitonal reactions.

We want all “legal” transformations to be bitonal transformations (and hence “gradual” transformations). E.g.: padding:

Some transformations are inherently non-bitonal.
Characterization

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

- **Proof Sketch**
  1. All local reactions are bitonal reaction. E.g., Switch:
     - By cases on the external connectivity of A,B,C,D.
2. All bitonal reactions can be obtained by sequences of local reactions (switch/froth/fizz) and deformations.
   - By analysis of the simply connected regions that change tonality, and induction on the number of membranes that cross such a region.

3. Endo/Exo and Mito/Mate are bitonal reactions.
   - They can all be locally implemented by Switch, which is bitonal.

4. Any instance of Switch is an instance of either Endo, Exo, Mito, or Mate, plus deformations.
   - By cases on A,B,C,D connectivity around Switch.

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

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

Systems
\[ X ::= \Diamond | \Diamond X | DX \]

membrane

Axioms
\[ \Diamond \Diamond \] is a comm. monoid

F/F:
\[ \Diamond \leftrightarrow (\Diamond \Diamond) \]

E/E:
\[ \Diamond \Diamond Y \leftrightarrow (\Diamond \Diamond \Diamond) Y \]

Facts

M/M:
\[ (\Diamond \Diamond \Diamond \Diamond) X \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) X \]
\[ (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) X \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) X \]

(without using commutativity)

P/P:
\[ X \leftrightarrow X \Diamond \Diamond \leftrightarrow X \Diamond \Diamond \Diamond \Diamond \]
\[ \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) \]

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

Subject reduction theorem.
Bitonal coloring is preserved by reductions.

Alternative axiomatization: take M/M and P/P as axioms and derive F/F and E/E as theorems:

F/F:
\[ (\Diamond \Diamond) \leftrightarrow (\Diamond \Diamond \Diamond) \leftrightarrow (\Diamond \Diamond \Diamond \Diamond) \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond) \leftrightarrow (\Diamond \Diamond \Diamond \Diamond \Diamond \Diamond) \]

E/E:
\[ \Diamond \Diamond Y \leftrightarrow (\Diamond \Diamond \Diamond) \Diamond Y \leftrightarrow (\Diamond \Diamond \Diamond \Diamond) \Diamond Y \]
Atonal Calculus

**Systems**

\[ X ::= \diamond | X \odot X | \op \]  

**Axioms**

- \( \diamond \diamond \) is a comm. monoid

- **F/F:**  
  \( \diamond \Leftrightarrow \op \)  

- **I/O:**  
  \( X \odot (Y) \Leftrightarrow (X \odot Y) \)  

**Facts**

Atonal emulates bitonal (obviously):

\[ X \odot (Y) \Leftrightarrow X \odot (Y) \Leftrightarrow X \odot (X \odot (Y)) \Leftrightarrow (X \odot (X \odot (Y))) \Leftrightarrow (X \odot (X \odot (Y))) \Leftrightarrow (X \odot (X \odot (Y))) \]

Bitonal emulates atonal, based on this translation:

- \( \diamond^* = \diamond \)
- \( (X \odot Y)^* = X^* \odot Y^* \)
- \( \op \odot \odot (X)^* = \op \odot \odot (X)^* \)  
  “double walling”
Summary

• **Bitonal Membrane Systems**
  - Algebraically capturing the notion that cytosol/exosol do not “usually” mix during membrane transformations.
  - Characterization theorem: membrane reactions are locally implementable (switch) iff globally implementable (endo/exo) iff topologically gradual (bitonal).

• **Bitonal Calculus**
  - A minimalist membrane calculus.
  - Bitonal can emulate atonal.
Q?
Appendix
More Examples
Ex: Molting

Aged

Pad

Exo
Ex: Autophagic Process

Lysosome and target don’t just merge.

Biologically, Mito/Mate clearly happens. However, weird sequences of Endo/Exo are also common.
(fake) Ex: Clean Eating
(why Endo/Exo is “healthier” than Mito/Mate)

Either: Fizz

Or: Pad

Dirty!!

Clean!
Appendix
A Note on Locality
**Locality Postulate**

Interactions should be local to small membrane patches. E.g., independent of global membrane properties such as overall curvature that cannot be observed locally.
Endo/Exo Violates Locality?

Oops…

(not a direct instance of endo/exo)
Local-view Endo/Exo Reaction

Dual:

Both:

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

Dual:

Both:

and:

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

might curve together or apart
Locality is Not Violated

- Hence, even though Endo/Exo and Mito/Mate strictly violate locality, locality is indirectly preserved in a bigger system that includes them both and their duals.
- This needs to be somewhat justified (L.Cardelli: “Bitonal Systems”) after which we can forget about local-view reactions.
- Problem: how to formally represent the local-view reactions?
Appendix
Molecules as Small Membranes
Molecules as Small Membranes

\[ \text{Mol} \]
\[ \text{mol}_n = \text{mate}_n + \otimes_n \]
\[ \text{Mol}_n = \text{mol}_n \otimes \bullet \]

\[ n(\otimes) \Rightarrow = \text{mate}_n \]
\[ \otimes(n) \Rightarrow = \otimes_n \]

\[ n(\otimes) \Rightarrow \otimes(m) = n(\otimes) \Rightarrow \otimes(m) \text{ etc.} \]

\[ \text{Mol}_n \circ n(\otimes) \Rightarrow \otimes(n) \sigma \sigma_0 \downarrow P \rightarrow \sigma \sigma_0 \downarrow \text{Mol}_n \circ P \]
Appendix

Local Membrane Reactions
Membrane Systems

Good Systems
(Closed non-intersecting curves)

Bad Systems
Bitonal Membrane Systems

Good Bitonal Systems
(Alternating oriented curves)

Bad Bitonal Systems
Local Unoriented Interactions

Switch

Klein

Unravel
Switch as a Bitonal Reaction
Global Effects of Switch

Switch

Decrees Cardinality

Mate

Exo

Increases Cardinality

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

Mito

Endo

Preserves Bitonality
Global Effects of Klein

Violates Proper Containment

Produces Unorientable Curves
Global Effects of Unravel

- Pop
- Squish
- Burst
- Open

Decreases Cardinality

Violates Bitonality
Global Effects of Pinch

Preserves Bitonality
Global Effects of Pass

Pass

Preserves Cardinality

In

Out

Violates Bitonality

Luca Cardelli
Global Effects of Coat

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

Coat by Switch

Pass by Switch and Unravel
Unoriented Local Reactions

<table>
<thead>
<tr>
<th>Switch (Irreversible) Fusion</th>
<th>Coat</th>
<th>Pass</th>
<th>Unravel</th>
<th>Undo Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Switch Diagram]</td>
<td>![Coat Diagram]</td>
<td>![Pass Diagram]</td>
<td>![Unravel Diagram]</td>
<td>![Undo Diagram]</td>
</tr>
</tbody>
</table>
## Oriented Local Reactions

<table>
<thead>
<tr>
<th>+duals</th>
<th>Good Initial Bitonality</th>
<th>No Initial Bitonality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Switch</strong></td>
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</tr>
</tbody>
</table>

- **Irreversible Fusion**
- **Violates Membrane Orientation**
- **Violates Bitonality**
- **Coat**
Local Brane Algebra?

- Hence, Switch and Coat are the “good” oriented reactions.

- Moreover, Coat can be obtained by Switch, and Pass can be obtained by Coat and Unravel.

- Can we build a membrane algebra just out of local operations such as Switch and Unravel?