Bitonal Membrane Systems

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Introduction
Related Work

- **Membrane Computing**
  - From computability theory (now being applied to biological modeling)

- **BioAmbients**
  - From distributed systems theory (then applied to biological modeling)

- **Brane Calculi**
  - Bio-inspired membrane operations

- **Beta-Binders**
  - Bio-inspired process interfaces

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**BioAmbients**: An abstraction for biological compartments

Aviv Regev a, Ekaterina M. Panina b, William Silverman c, Luca Cardelli d, Ehud Shapiro e

**Brane Calculi**

Interactions of Biological Membranes

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**Beta Binders for Biological Interactions**

 AUTHORS: Corrado Priami, Paola Quaglia

 SOURCE: In Proceedings of "Computational methods in system biology (CMSB04)", Parigi 2004 308221-34
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)**
- **5nm ~60 atoms**
- **Cytosol (H₂O)**
- **Embedded membrane proteins**
- **Channels, Pumps (selective, directional)**
- **Flip (rare)**

(Not spontaneous)
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, by definition, or by fusion/fission dynamics)

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

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

(1) A membrane is built from a phospholipid bilayer that is asymmetrical. Moreover, all real membranes are heavily sprinkled with proteins: “each type of integral membrane protein has a single specific orientation with respect to the cytosolic and exoplasmic faces of a cellular membrane, and all molecules of any particular integral membrane protein share this orientation. This absolute asymmetry in protein orientation confers different properties on the two membrane faces.” MCB p162.
(2) Short for Cytoplasmic Solution. (3) Short for Exoplasmic Region (I am making this one up).
Bitonal Structure

**Bitonality**
Blue and white areas alternate.

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

**Bitonal Duality**
Reactions come in complementary-tone versions.

The cell maintains a strong compartment-based separation between inside fluids and outside fluids even when incorporating foreign material.

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**Evolutionary explanations of bitonal structure**

- Mitochondria acquisition
- Mitochondria to Chloroplasts
- Pre-Eukarya to Eukarya
Before We Formalize Anything...

- What are the fundamental operations?
- What are the fundamental invariants?

A complete set of bitonal reactions.
Gradual Transformations of Membrane Systems
Membrane Systems

Good Systems
(Closed non-intersecting curves)

Bad Systems
Bitonal Membrane Systems

Good Bitonal Systems
(Alternating oriented curves)

Bad Bitonal Systems
Locally Realizable Reactions

Membrane System

Q: What transformations "make sense"?

Local (Patch) Reactions

A: Transformations that obviously "make sense" from a local, molecular viewpoint

Switch

(Froth Fizz)

(Symmetric by 90° rotation.)

(Phospholipids thrown in water self-assemble into empty vesicles)
A *global reaction* is a pair of snapshots (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!
These Global Reactions are Local Reactions

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

Mito (Fission)

Mate (dual) (Fusion)

Endo (dual) (Fission)

Exo (Fusion)

Same Local View!
Bitonal Transformations: Operational View
Bitonal Reactions

We look for reactions that “preserve” the bitonal coloring of a membrane system. (And hence preserve proper membrane orientation.)
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

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:

Violates bitonality.

Bubble catastrophe:

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

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

Ex: flooding in context violates bitonality:
Ambients

Violate bitonality

Preserve bitonality, but violate stability for subsystem \( P \) (i.e. all membranes of \( P \) must be “flipped” inside-out).
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
Endo/Exo from Mito/Mate only? No: depth of nesting is constant in Mito/Mate.
Peel/Pad by Froth/Fizz and Endo/Exo
"A (Turing) Complete Set of Reactions"

Other bitonal reactions are Derivable, e.g.:

Are all other derivable? YES!
Some Examples
Ex: Eukaryotic Mitosis
Ex: Molting

- Pad
- or
- Froth
- Endo

Aged

Exo
**Ex: Autophagic Process**

Lysosome and target don’t just merge.

1. Lysosome
2. E.R.
3. Enzymes
4. Target

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:

Or:
Membrane Algorithms

Protein Production and Secretion

Viral Replication

LDL-Cholesterol Degradation


A Note on Locality
Locality Postulate

Interactions should be local to small membrane patches (to be biologically implementable). E.g., they should be independent of global membrane properties such as overall curvature that cannot be observed locally.
Local-view Mito/Mate Reaction

Dual: might curve together or apart

Both: curve apart

and: curve together

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

Locally, we cannot distinguish between a mito-mate and a co-endo-exo reaction.
Hence, a calculus that includes mito-mate reactions but does not include endo-exo reactions “violates locality”, because a local reaction could not distinguish between the two.
Local-view Endo/Exo Reaction

Dual:

Both:

and:

Ah!
Local Endo/Exo = co-Mito/Mate
Locally, we cannot distinguish between an endo-exo and a co-mito-mate reaction.

But fortunately, (co-)endo-exo can encode (co-)mito-mate. So a calculus with only endo-exo does not prevent mito-mate from happening. (As long as the dual reactions are included!)
Locality needs “enough” Global Operations

- 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 better justified after which we may forget about local-view reactions.
- But we cannot go around inventing calculi without considering whether their operations are “locally implementable” even in the sense of making sure we do not have too few global operations!

- Problem: how to formally represent the local-view reactions, so that they can be formally related to the global-view reactions, e.g. to prove completeness?
Bitonal Transformations: Relating Local and Global Reactions Through Topology
Membrane Systems

- **Def:** a curve $c$ (on the plane) is a continuous map in $[0,1] \rightarrow \mathbb{R}^2$.

- **Def:** a membrane $m$ is a curve that is
  - *simple* (i.e., injective in the open interval $(0,1)$, hence non-self intersecting and with a non-empty interior).
  - *closed* (having $m(0) = m(1)$).
  - *smooth* (infinitely differentiable and with all derivatives coinciding at $m(0), m(1)$). (So that we can tell when a point is inside a membrane.)

- **Def:** a membrane system $M$ is a finite set of membranes $\{m_1, \ldots, m_n\}$ whose ranges nowhere intersect in $\mathbb{R}$. 

![Diagram of membranes intersecting]
Def: the depth of a point (in a membrane system, and not on a membrane) is the number of membranes that contain it.

Def: the tonality of a point is white/blue iff its depth is even/odd.
Reactions and Transformations

- **Def**: a reaction is a pair of membrane systems \( <M,M'> \): the one before \( M \) and the one after \( M' \) the reaction.

- **Def**: a deformation is a reaction \( <M,M'> \) with a 1-1 mapping between membranes in \( M,M' \) that preserves containment.

- **Def**: a transformation is a finite sequence of zero or more reactions.
Def: 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 of the plane (a region not separated by membranes).

(N.B.: Layered $\Rightarrow$ Bitonal)
Non-Bitonal Reactions

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

- **Wrap**: change tone & depth not connected
- **In**: 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.
Local Reactions (on the plane)

- Def: A switch is (up to deformations) a reaction that changes a membrane system $M$ only as indicated (say, in the unit circle):

- Def: A froth (fizz) is (up to deformations) a reaction that changes a membrane system $M$ only as indicated:
**Prop:** In any membrane system, a switch is a bitonal reaction. (So is froth and fizz.)
- That is, switch changes tonality of only a simply connected region of the plane.
  Proof by cases on the external connectivity of switch end-points.

**Prop:** All bitonal reactions can be obtained as a finite sequence of switch, froth, fizz, and deformations.
- By analysis of the simply connected region that changes tonality, and by induction on the number of membranes that cross such a region (using switch for the induction step, and froth, fizz for the base case).

**Th 1:** Local Transformations = Bitonal Transformations.
Def: “global” Endo, Exo, Mito, Mate, Froth, Fizz are the following normalized starting configurations and related reactions (up to deformations):

- **Soundness:** Any Endo, Exo, Mito, Mate reaction can be implemented by switch.
  - Proof obvious: a single switch will do it in each case (plus deformations).

- **Completeness:** any switch in a membrane system can be represented as either an Endo, Exo, Mito, or Mate global reaction.
  - Proof by cases on the external connectivity of switch end-points.
  - Further, a sequence of Endo/Exo will suffice, since they can code Mito/Mate.
Global = Bitonal

- **Th 2: Global Transformations = Bitonal Transformations.**
  - Any bitonal transformation can be expressed as a finite sequence of Endo, Exo, Froth, Fizz, and deformations (because every bitonal reaction can be expressed as local transformations, and those as global ones).
  - Any sequence is of global transformations is bitonal (because each step can be implemented by either switch, froth, fizz, or deformations, which are all bitonal).
Bitonal Calculus
The Most Trivial Prototype for Membrane Calculi
Bitonal Calculus

Systems

\[ X ::= \circ \mid X \cdot X \mid (X) \]

membrane

Axioms

\( \circ \circ \) is a comm. monoid

\[
\begin{align*}
F/F: & \quad \circ \iff (\circ) \\
E/E: & \quad X \cdot (Y) \iff (X) \cdot (Y)
\end{align*}
\]

Facts

\[
\begin{align*}
M/M: & \quad (X \cdot (X')) \iff ((X) \cdot (X')) \iff ((X) \cdot (X')) \\
& \quad \iff ((X) \cdot (X')) \iff ((X) \cdot (X')) \iff (X \cdot (X'))
\end{align*}
\]

(Without using commutativity)

\[
\begin{align*}
P/P: & \quad X \iff X \cdot (X) \iff X \cdot (X)
\end{align*}
\]

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

\[ \circ \iff (\circ) \]

\[ X \cdot (Y) \iff (X) \cdot (Y) \]

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:

\[
\begin{align*}
F/F: & \quad (\circ) \iff (\circ) \iff (\circ) \iff (\circ) \iff (\circ) \\
E/E: & \quad X \cdot (Y) \iff (X) \cdot (X) \cdot (Y) \iff (X) \cdot (Y)
\end{align*}
\]

This algebra is a minimal “subset” of more sophisticated process calculi for membranes that one may devise.
Atonal Calculus

Systems

\[ X ::= \Diamond | X \circ X | \langle X \rangle \]

membrane

Axioms

\[ \Diamond \circ \Diamond \text{ is a comm. monoid} \]

\[ F/F: \quad \Diamond \leftrightarrow \langle \Diamond \rangle \]

\[ I/O: \quad X \circ Y \leftrightarrow \langle X \circ Y \rangle \]

violates bitonality

Facts

Atonal emulates bitonal (obviously):

\[ X \circ (Y) \equiv X^{\circ \circ} \circ (Y) \equiv X \circ \langle X \circ \circ \circ \circ Y \rangle \equiv \langle X \circ \circ \circ \circ Y \rangle \equiv \langle X \circ \circ \circ \circ \circ \circ Y \rangle \equiv \langle \langle X \circ \circ \circ \circ \circ \circ \circ Y \rangle \rangle \]

Bitonal emulates atonal, based on this translation:

\[ \Diamond^* = \Diamond \]

\[ (X \circ Y)^* = X^* \circ Y^* \]

\[ \langle X \rangle^* = \langle \langle X \rangle^* \rangle \] “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.