Bitonal Membrane Systems
Interactions of Biological Membranes

Luca Cardelli

Microsoft Research

Abstract

Inspired by the alternating orientations of cellular membranes, we describe a structure of nested membranes that are colored in two alternating tones. We investigate a class of reactions that maintain the colored regions largely invariant at each step (*bitonal reactions*). These coloring constraints guide us towards a small and non-obvious set of basic reactions that are both realistic and complete. They are realistic because bitonality is related to an independent notion of locality, and because similar reactions are implemented by molecular machinery. They are complete because any bitonal reaction can be obtained from them. Such a set of reactions can then be used as the basis for descriptions of biological processes, and in particular for the description of transport networks in cellular biology.

1 Introduction

In molecular cell biology ([1][2]), interactions between membranes are by nature local *patch interactions*: that is, they result from the interactions of embedded membrane proteins that can inspect only local conditions of relatively small membrane patches. For modeling purposes, though, it is preferable to base discussions on *whole-membrane interactions* that transform membranes in certain global ways, such as merging and splitting. Such interactions are part of the standard terminology of cellular biology, e.g. *endocytosis* (Figure 1).

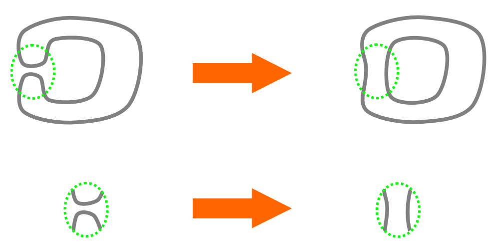

Figure 1 Endocytosis: whole-membrane view (top), and patch view (bottom)

When modeling systems at a global level, two basic questions arise: (1) Are the chosen whole-membrane interactions justifiable by patch interactions? (2) Are all the possible patch interactions modeled by the chosen collection of whole-membrane interactions?

A positive answer to the first question is a matter of choosing our whole-membrane interactions sensibly and realistically: they should be based on observed interactions. The second question is also important, and it is not just as a matter of expressiveness: it too is a matter of realism. If (2) has a negative answer, then it means that there are interactions that are effectively forbidden, but such that the local patch interaction mechanisms cannot “know” that they are forbidden. An example of this situation is given in Figure 2, where if we allow the first interaction, then we should also allow the second one, because they have the same patch view.

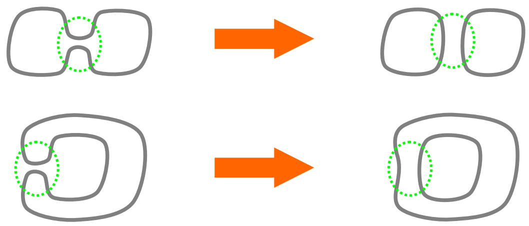

Figure 2 Two membrane interactions with the same patch view

In this paper we aim to justify certain collections of membrane interaction that are standard in biological descriptions, showing that they are both sound and complete with respect to realistic patch interaction. Collections of membrane interaction form the basis for further work [4], where the level of abstraction is raised, and the patch reactions are forgotten.

We base our discussions on a simple geometric model built around curves and transformations on the Cartesian plane, $\mathbb{R}^2$.

2 Membranes

2.1 Membrane Systems

Biological membranes are by nature smooth surfaces. We work in two dimensions, for simplicity (although this is a very significant simplification, as we partially discuss later). We define a *membrane* as a curve in $\mathbb{R}^2$ that is closed, non-self-intersecting, and smooth. A *membrane system* is a collection of membranes such that no two membranes intersect (Figure 3).

Any membrane divides the plane into a bounded *inside* connected region and an unbounded *outside* connected region (Jordan's Curve Theorem). Since membranes do not intersect, each membrane is either inside or outside any other membrane.

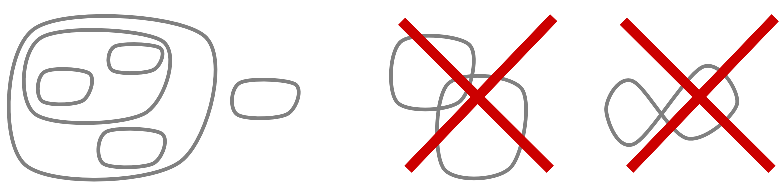

Figure 3 Legal membrane systems (left)

2.1–1 Definition (Membrane Systems)

A *curve*, c, is a continuous map in $[0,1]\to\mathbb{R}^2$, from the closed interval $[0,1] \subseteq \mathbb{R}$. We often identify a curve c with its range rng(c).

A *membrane*, m, is a curve that is simple (that is, injective in the open interval (0,1), hence non-self-intersecting and with a non-empty interior), closed (having m(0)=m(1)), and smooth (infinitely differentiable, and with all derivatives coinciding at m(0),m(1)).[1]

[1] This strong smoothness condition is used to rule out nowhere differentiable curves and related complications. It

A *membrane system* M is a finite set of membranes $\{m_1, \ldots, m_n\}$ whose ranges nowhere intersect in $\mathbb{R}^2$.

□

If we imagine a membrane system as painted on a rubber sheet, then a *deformation* is some stretching of the rubber. Such deformations of the plane are rather subtle mathematical constructions but, since we care only about preserving the containment relations of membranes, we define deformations simply as transformations of the plane that preserve membrane containment relationships.

Deformations are a class of *reactions*, where a reaction is any change in a membrane system. Certain reactions discussed later are not deformations: they, at least conceptually, include intermediate stages where curves become open, intersecting, or not smooth. But any reaction for us is as instantaneous operations between legal membrane systems.

Any membrane system can be colored in two alternating tones, white and blue, starting with white in the outermost region. We effectively consider all our membrane systems to be colored this way (Figure 4).

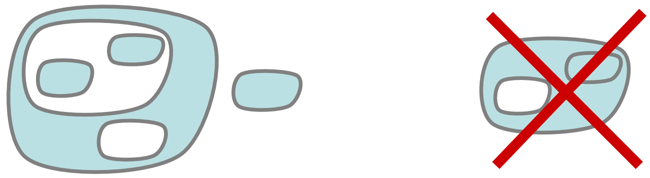

Figure 4 Bitonally colored systems (left)

This bitonal coloring is based on some biological facts. The coloring is meant to indicate that (1) membranes are oriented (each membrane has chemically distinct cytosolic and exoplasmic faces, with the cytosolic face either to the inside or to the outside of the membrane [1][2]), and (2) the orientation of adjacent membranes alternates ([2], p. 556). The bitonal coloring is a convenient pictorial representation of such a structure. Therefore, bitonal systems (1) model membrane orientations, which are fundamental in all membrane functions, and (2) they further model the basic alternating-orientation structure of cells and their organelles. Figure 5 illustrates the connection between tones and orientations: membranes are oriented so that the heads of the orientation arrows fall into (e.g.) the blue regions.

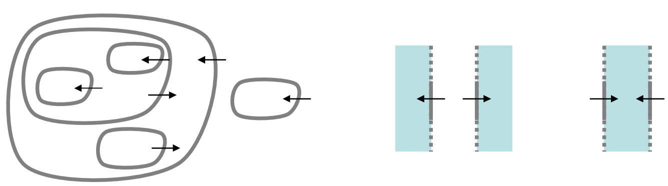

Figure 5 Bitonal systems as alternating orientations

This alternating structure arises naturally from realistic and common membrane interactions, some of which became fixed during evolution, and some of which happen routinely in cellular transport. Certain processes, such as digestion, must at some point violate the bitonal structure. However, these are rather destructive processes, usually localized in

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could be weakened, but this is sufficient for the intended application.

special organs, and we choose not to model them (at least, not until Section 6). On the other hand, many unrealistic membrane interactions violate the bitonal structure, and can thus be ruled out.

Deformations of a membrane system preserve membrane orientations and alternations, and hence preserve the bitonal coloring of corresponding regions. Further, other well-behaved membrane reactions preserve membrane orientations and alternations, and hence (largely) preserve the bitonal coloring of (most) corresponding areas. The exact meaning of "most" is the focus of the following section, after a few definitions.

2.1–2 Definition (Depth and Tonality)

A *connected region* of a membrane system $M=\{m_1, \ldots, m_n\}$ is a region of $\mathbb{R}^2$ not separated by membranes, that is, a connected region of $\mathbb{R}^2 - (\mathrm{rng}(m_1) \cup \ldots \cup \mathrm{rng}(m_n))$.

The *depth of a point* in a membrane system is the number of membranes that have it in their interior. The depth of a connected region is the depth of any point in it. The depth of a membrane, $\mathrm{depth}_M(m)$, is the least depth of its interior points.
The *depth map* $\delta_M \in \mathbb{R}^2 \to \mathbb{N} \cup \{\text{undefined}\}$ of a membrane system M, maps a point in $\mathbb{R}^2$ to undefined if the point is on a membrane in M, otherwise to its depth in M.

A *tone* or *tonality* is a member of the set {white,blue}, with *co-tonality* defined as $\text{white}^{\perp} \triangleq$ blue, and $\text{blue}^{\perp} \triangleq$ white.

The *tone of a point, connected region, or membrane* is white iff its depth is even. The tone of a membrane is indicated by $\mathrm{tone}_M(m)$.
The *tone map* $\tau_M \in \mathbb{R}^2 \to \{\text{white,blue,undefined}\}$ maps a point in $\mathbb{R}^2$ to undefined if the point is on a membrane in M, otherwise to its tonality in M.

□

2.1–3 Definition (Reactions, Deformations, and Transformations)

A *reaction* is a pair of membrane systems <M,M'>: the one before the reaction, M, and the one after the reaction, M'.

A *deformation* is a reaction <M,M'> with a one-to-one correspondence d between the membranes of M and of M' that preserves the inside/outside relationship of any two membranes.

The *composition* of two reactions <M,M'> and <M',M"> is the reaction <M,M">. A *transformation* is a finite composition of reactions.

□

Any given membrane system can be produced by composing the following operators, plus one deformation:

2.1–4 Definition (Operations on Membrane Systems)

{} is the empty membrane system.

If M is a membrane system, then $\llparenthesis M \rrparenthesis$ is the system $\mathrm{unit}(M) \cup \{\text{unitcircle}\}$, where unit(M) is a canonical deformation of the plane to the interior of the unit circle.

If M and M' are membrane systems, then $M \circ M'$ is the system $\mathrm{lft}(M) \cup \mathrm{rht}(M')$, where lft is a canonical deformation into one half of the Cartesian plane, and rht(M') is a deformation into the other half.

□

2.2 Bitonal Reactions

Much of our discussion will be about *bitonal reactions*. A bitonal reaction is one that modifies the tones of a system “only slightly”, for an appropriate definition. Membrane systems on which we perform bitonal reactions are called *bitonal systems* (which is really a short for bitonally transformed membrane systems).

We define a bitonal reaction as a reaction that changes the tonality of at most a simply-connected region of the plane: that is, of a connected region with no holes, and hence of a region not separated by membranes. The intuition is that a realistic reaction cannot change the tonality of a large number of subsystems. Remember that changing tonality means changing orientation, and we would not want a simple reaction to turn a large number of membranes inside-out.

For example, creating an empty membrane is a bitonal reaction, and so is deleting an empty membrane. In those cases, only one simply-connected region changes tone; namely, the interior of those empty membranes. Instead, creating two nested membranes at once is not a bitonal reaction, because it changes the tone of a region that contains a hole. Two nested membranes can be created by two bitonal reactions in sequence, hence bitonal reactions do not compose. But we shall define *bitonal transformations* as sequences of bitonal reactions, and those do compose. *Layered reactions*, similarly preserve depth rather than tonality.

2.2–1 Definition (Layered and Bitonal Reactions)

A *layered reaction* is any reaction <M,M’> such that the set of points that are not on any membrane of M or M’ and that change depth are simply-connected. More precisely, the set of points r for which both depth maps δ_M and $\delta_{M'}$ are defined, and for which $\delta_M(r) \neq \delta_{M'}(r)$, form a simply-connected region of $\mathbb{R}^2$.

A *bitonal reaction* is any reaction <M,M’> such that the set of points that are not on any membrane of M or M’ and that change tone are simply-connected. More precisely, the set of points r for which both tone maps τ_M and $\tau_{M'}$ are defined, and for which $\tau_M(r) \neq \tau_{M'}(r)$, form a simply-connected region of $\mathbb{R}^2$.

□

Each membrane system has a single unbounded region, which by definition has always depth 0 and tone white; hence the simply-connected regions in Definition 2.2–1 are bounded.

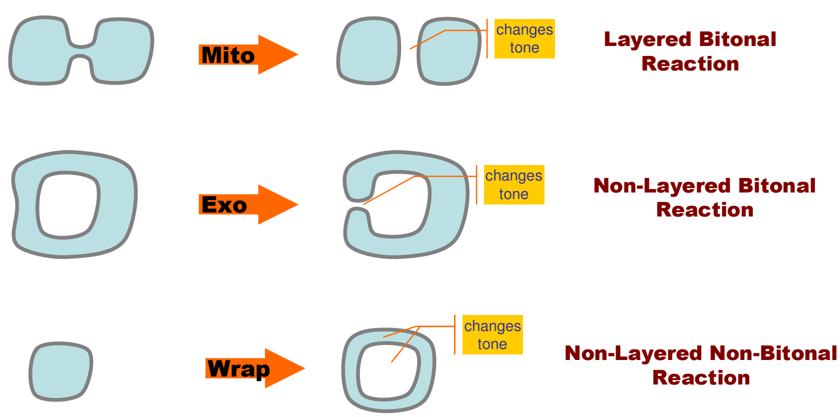

Figure 6 Layered and bitonal reactions

Obviously, a layered reaction is a bitonal reaction, but not vice versa. In Figure 6 we show some example reactions that we revisit later. For the bitonal reactions Mito and Exo, the tone-changing region is simply-connected. For Wrap, which wraps a membrane around an existing one, we have instead (at least) two disconnected tone-changing regions, separated by a membrane. Note that Wrap, in general, inverts all the tones of an arbitrary subsystem.

A *layered deformation* is a deformation that is also a layered reaction; similarly for a *bitonal deformation*, but note that a deformation is layered iff it is bitonal.

The requirement that tone-changing regions are connected makes them intuitively local. But the no-holes assumption is also important; note that if we change the "simply-connected" requirement in the definition of bitonality to "connected" then a bitonal reaction could for example create a double layer around and between two whole subsystems: this would not have a local flavor.

2.2–2 Definition (Layered and Bitonal Transformations)

A *layered transformation* is the composition of a finite sequence of layered reactions.

A *bitonal transformation* is the composition of a finite sequence of bitonal reactions.

□

2.2–3 Proposition

Any deformation of a membrane system can be obtained as a finite sequence of layered deformations.

Proof

A single empty circular membrane can be translated by two layered deformations (stretching and shrinking) to a "far" unoccupied region of the plane. This can be extended to translating a set of empty circles without any complex interference between them, and then to translating any hierarchy of circles proceeding outside-in. Assume <M,M'> is a deformation. Starting at the innermost levels of M, deform each membrane into a circle, after turning into circles and possibly regrouping by translation its contained membranes. Then translate the whole structure to a "far" location disjoint from M'. By a reverse process, that structure can then be deformed into M', all the while preserving the depth-preserving bijection between M and M'.

□

2.2–4 Corollary

A transformation is a layered (resp. bitonal) transformation iff its pre- and post-composition with deformations is a layered (resp. bitonal) transformation.

□

2.3 Three Patch Reactions

We now consider three membrane reactions that are obviously local, since their activity is limited to a connected region containing up to two patches and no extra curves. These are depicted in Figure 7, where *Froth/Fizz* are inverse operations that create and delete empty membranes, and *Switch* is a self-inverse operation (up to deformation) that switches patches on two membranes. The dotted circles are the *interaction discs*: regions assumed to be free of any other curves. Note that Froth and Fizz can be obtained from Switch if there is any other membrane in the system both before and after. This is one reason we consider Froth/Fizz as patch reactions, even though they create/delete ("small") whole membranes.

Let us define Switch more precisely by geometric constructions. A *membrane patch* is a segment of a membrane delimited by two points. We say that two membrane patches within a system are *contiguous* if by deformation of their system they can be placed in the *switch configuration* (Figure 7, top left). The configuration is defined as follows, modulo scale. The tangents at points A,B,C,D are at 45 degrees, and divide the interaction disc ABCD into four quarters. The point E is in the center, with the segment AC entirely in the left quarter, and the segment BD entirely in the right quarter. There must be no other curves inside the disc ABCD, either before or after the reaction.

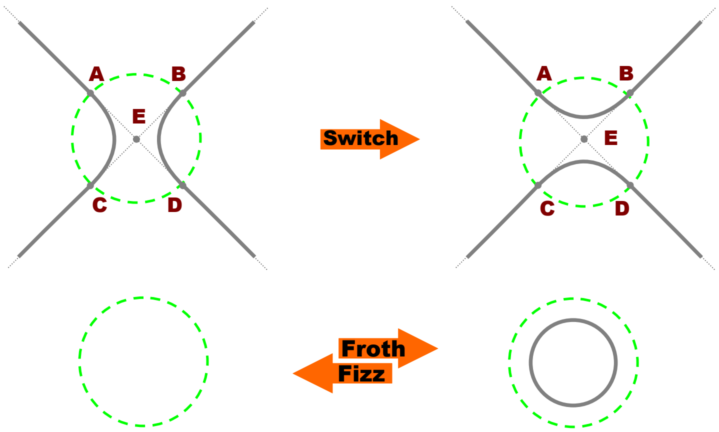

Figure 7 Patch reactions

2.3–1 Definition (Patch Reactions and Transformations)

A Switch is any reaction <M,M'> that replaces two patches AC and BD of a *switch configuration*, as in Figure 7, by two patches AB and CD; it otherwise does not change M. (That is, the range of all the curves of M in $\mathbb{R}^2$ differs from the range of all the curves of M' only as indicated.)
Froth is a reaction that adds a circular membrane containing no membranes.
Fizz is a reaction that removes a circular membrane containing no membranes.

A transformation of membrane systems is a *patch transformation* iff it can be realized by a finite sequence of patch reactions (one of Switch/Froth/Fizz) and deformations.

□

A sequence consisting of a deformation, a Switch, and another deformation, is also often informally called a Switch; but in formal arguments we stick to the more restrictive definition; similarly for the other reactions.

2.3–2 Proposition (Patch Reactions)

A Switch reaction on a membrane system produces a membrane system; similarly for Froth and Fizz.

Proof

In Switch, all curves remain closed (no loose ends are introduced), smooth (by construction), and simple (assuming there are no intersections to start with, Switch does not introduce new intersections). Fizz obviously produces a membrane system. Froth also produces a membrane system because the new curve is by definition a membrane, and it does not intersect any existing membranes.

□

It is obvious that Froth and Fizz are bitonal (and layered) reactions. More interestingly:

2.3–3 Proposition (Any Switch is a Bitonal Reaction)

Suppose we apply a Switch reaction to a membrane system. Then, the only points that change tonality, and that do not belong to curves, are found in a simply-connected region inside the interaction disc.

Proof

Consider the switch configuration of Figure 7, where the disc ABCD is free of any other curves. We analyze the possible connectivity outside the interaction disc.

Suppose c(AC) (the curve containing the points A and C) and c(BD) are separate curves and are not inside each other; then, since they are contiguous, they are sibling curves of the same depth. A Switch then preserves the (depth and) tonality of all points outside of the interaction disc. (Outside the disc, each point inside c(AC) and c(BD) remains inside the same number d of membranes; each point immediately outside them preserves its depth d-1; and so on.) Inside the interaction disc, the only points not on membranes that change (depth and) tonality are within the 4-pointed star ABCD, which is a simply-connected region since by assumption no membranes cross it.

Suppose c(AC) and c(BD) are separate curves and c(AB) is inside c(BD). In this situation Switch decreases the depth of the points inside c(AB) by 2, and hence maintains their tonality. All the other points maintain their depth except in the interacting region, as above; similarly, if c(BD) is inside c(AC).

Suppose that c(ABCD) is a single curve. If E is inside the curve, then Switch preserves the (depth and) tonality of all the points outside of the interaction disc, and again the only points changing tonality are within the 4-pointed star ABCD. If E is outside the curve, then there are two symmetric cases in which, after Switch, the curve c(AB) is found inside c(CD) or vice versa; with the depth of the points inside the inner curve increasing by 2, and hence preserving tonality, and only the points in the 4-pointed star ABCD changing tonality.

□

Note that Switch is not always a layered reaction (see Exo in Figure 6).

2.3–4 Proposition (All Bitonal Reactions from Switch, Froth and Fizz)

Any bitonal reaction can be implemented by a finite sequence of Switch, Froth, and Fizz reactions, plus deformations.

Proof

Suppose <M,M’> is a bitonal reaction. Then, tonality changes only in a bounded simply-connected *tone-changing* region, whose boundary is determined by a finite number of membranes in either M or M’. By deformation, the (bounded) tone-changing region can be placed inside a chosen interaction disc. Moreover, any curve that is not on the boundary of the tone-changing region can be pushed out of the interaction disc by deformation.

Consider the membranes of either M or M’ that now still intersect the (interior of the) interaction disc. If there are none, then the tone-changing region is empty, and the reaction is the identity, which is obtainable by an empty sequence of deformations.

If the membranes intersecting the interaction disc are all entirely inside the interaction disc, then, to be simply-connected, we must have a single membrane around the whole tone-changing region. This membrane can come either from M, in which case we have a Fizz reaction, or from M’, in which case we have a Froth reaction. (The membrane cannot be in both M and M’ because it would not cause tone changes.)

Otherwise, some membrane crosses the boundary of the interaction disc. But then, they must all cross the boundary, or the tone-changing region would not be simply-connected. So, we are left to consider a number of membranes, all on the boundary of the tone-changing region, and all crossing the boundary of the interaction disc. The rest of the proof is about such a *bear-skin configuration*, in Figure 8 left.

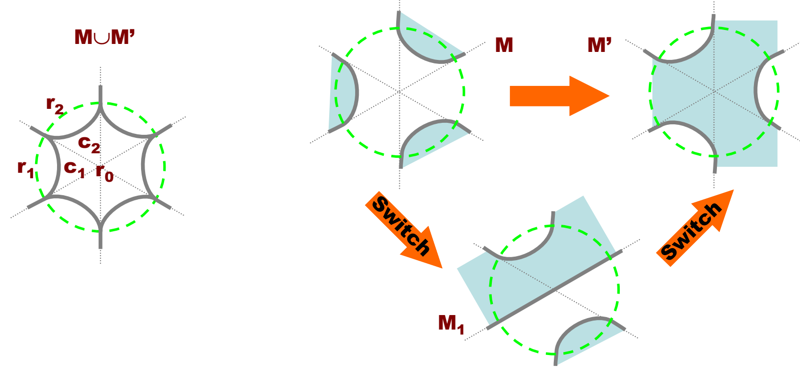

Figure 8 Bear-skin configurations

We know that the central region r_0 changes tone in the reaction, say from white to blue. Then, pick any curve c_1 on the boundary of r_0; the region r_1 on the other side of c_1 does not change tone in the reaction; let us say its color is blue, then c_1 belongs to M (otherwise to M'). Now pick the next curve c_2 along the boundary of r_0; it borders a region r_2. Since c_1 is also on the boundary of r_2, the tone of r_2 must be the opposite of the tone of r_1, that is white, and c_2 must belong to M'. Therefore, going around the border of r_0, because of the alternation of tones of the regions r_i, there must be an even number of such regions. Hence, there must be an even number of curves c_i, alternatively belonging to M and to M'.

If the number of such curves c_i is just 2, then the bitonal reaction is a simple deformation of a curve within the interaction disc. If the number of curves c_i is 4, then the reaction is a Switch (up to deformation). If the number of curves c_i is 6 (Figure 8, right), then there are 3 in M, and (up to deformation) we can perform a Switch between two of them (two adjacent ones, in general) obtaining a membrane system M_1. In M_1 we can push one of the two resulting curves out of the interaction disc, and the remaining transformation from M_1 to M', is in the shape of a bear-skin diagram with 4 curves; hence we are back to the previous case. Note also that the region we pushed out is colored as in M'. This process works by induction for any even number n of curves c_i on the boundary of r_0, and with (n-2)/2 Switch operations we can reproduce the entire bitonal reaction from M to M'.

□

Exercise: Draw the membrane reactions resulting from bear-skins with 6 and 8 curves.

Hence we have:

2.3–5 Theorem (Patch Transformations same as Bitonal Transformations)

A bitonal transformation can be expressed as a finite sequence of Switch, Froth, and Fizz reactions, along with deformations. Conversely, any such finite sequence is a bitonal transformation.

□

N.B., it is possible to give a wider definition of "local transformation" as one that arbitrarily rewires membrane patches within an interaction disc that contains no whole membranes. This too can be reduced to Switch, Froth, and Fizz, as shown in Appendix.

3 Soundness of Membrane Reactions

We have so far constructed a model consisting of membrane systems and bitonal reactions, with Switch as the basic reaction. This model respects the locality of realistic interactions: Switch is inspired by basic membrane fusion activities in cellular membranes, driven by local protein bindings (although carried out by still “unknown mechanisms” [1] p. 745). Froth also has some justification, since lipids thrown in water spontaneously assemble into closed membranes. Froth and Fizz happen continuously at the boundary of a cell membrane (but only towards the inside of the cell, so the membrane is not depleted).

For modeling reasons, however, it is not convenient to say: *a Switch happened between these two patches*. Rather, we usually would like to say: *a reaction happened between these two membranes*. This is consistent with normal descriptions of transport networks in cellular biology, with the related terminology of endocytosis, exocytosis, phagocytosis, pinocytosis, fusion, fission, budding, etc. A question then is: could such global transformations be “cheating” by taking a global view of the system (e.g. global membrane curvature) that they should not be allowed to obtain?

In this section we investigate the soundness of several membrane reactions, showing that they can be implemented by patch reactions. In fact, all these reactions are implementable by Switch. Note, though, that there are simple membrane operations that are not implementable by Switch (and are not bitonal), such as Wrap from Figure 6.

As a matter of presentation, rather than defining membrane reactions and showing how they are implemented, we show how various membrane reactions arise from Switch under different circumstances, when “zooming out” of the patch view.

3.1 Endo, Exo, Mito and Mate.

Switch is a very versatile reaction, when seen from a distance: different membrane reactions arise from it, depending on the global curvature of the membranes involved.

When Switch is applied to two different membranes, it decreases the cardinality of a system. Depending on whether the two membranes are nested or not, it generates two distinct reactions of whole membranes, which we call Mate and Exo (Figure 9, right).[2,3]

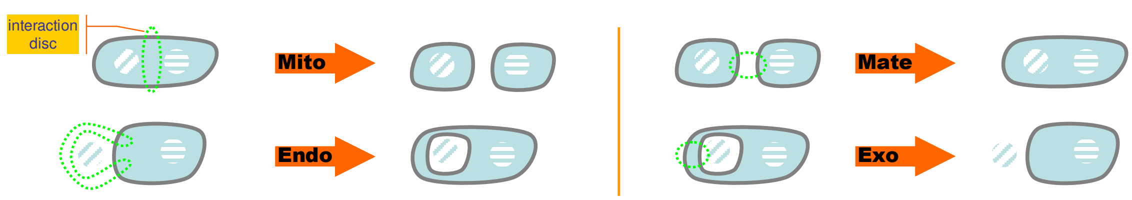

Figure 9 Endo, Exo, Mito, Mate resulting from Switch

When switch is applied to two patches of the same membrane, it increases the cardinality of a system. Depending on whether the patches face inside or outside of the membrane, we obtain two distinct reactions of whole membranes that we call Mito and Endo (Figure 9, left).

We could define these membrane reactions in terms of inside/outside relationships in membrane systems; but this is a bit tedious. Instead we define them on the basis of the

[2] The reactions in Figure 9 are colored for emphasis. With reversed tonality they are sometimes called co-Mate co-Exo, etc., even though they are really the same reactions on membranes.
[3] The differently striped areas in figures indicate different subsystems, i.e., they are used as metavariables.

geometric configurations of Figure 10, from which we can also leverage more information about the Switch reaction.

3.1–1 Definition (Endo, Exo, Mito, and Mate Reactions)

Four configurations of membrane systems are defined as shown in Figure 10, where the ABCD discs are Switch configurations (free of any other curves).

An Endo reaction consists of a Switch reaction on an Endo configuration. (Any other curves in the system are preserved.) Similarly for Exo, Mito, and Mate (Figure 11, which is just a more geometric version of Figure 9).

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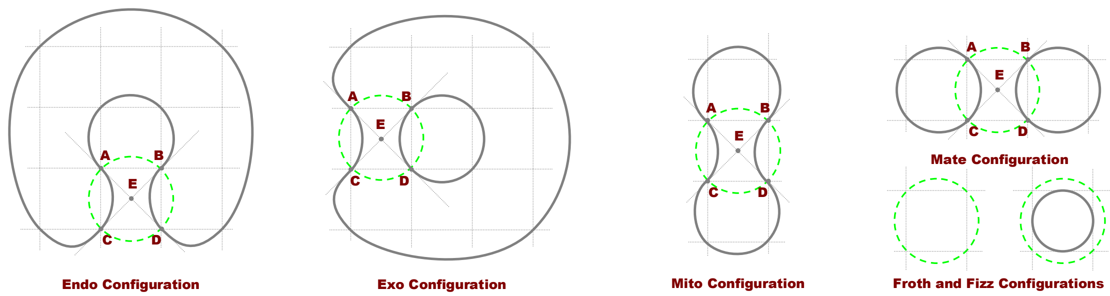


Figure 10 Configurations

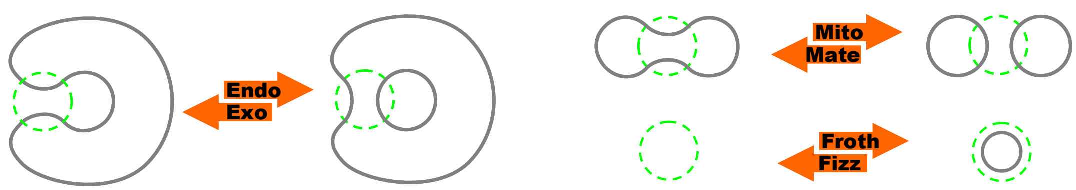


Figure 11 Membrane reactions

A sequence of a deformation, an Endo, and another deformation, is also often informally called an Endo; but in formal arguments we stick to the more restrictive definition; similarly for the other reactions.

3.1–2 Proposition (Soundness)

The reactions Endo, Exo, Mito, and Mate, are bitonal reactions.

Proof

The reactions are bitonal because, by Definitions 3.1–1, and by Proposition 2.3–3, in each case only a single connected patch changes tonality inside the Switch interaction region.

□

Remark: Bitonal Reactions in 3D. We deal only with membranes in two dimensions; extensions to 3D require more sophistication. In 3D, we can say that a positive-curvature Switch happens when two 2D membrane patches with positive curvature meet at a point, the point widens to a circle, and the membranes become connected through a negative-curvature patch (a hole or a channel, depending on interpretation). In the reverse process, a negative-curvature Switch happens when a negative-curvature patch shrinks to a point and results in two disconnected patches with positive curvature. For example, note that there are two different 3D-Switch reactions on a sphere: a positive-curvature one that punches a toroidal hole through it (keeping it connected), and a negative-curvature one that splits it into two spheres (making it disconnected). In cross section, both situations look like Mito, but are distinct in 3D. Similarly, a cross section like Endo may correspond to creating a torus or creating nested spheres; the first one by a positive-curvature Switch, and the second one by a negative-curvature Switch. Standard biological terminology maps to 3D as follows: Endo and Mito are the negative-curvature Switches (they split membranes), Exo and Mate are the positive-curvature Switches (they merge membranes). Although the set of patch reactions may need refinements in 3D, the notion of bitonal reaction remains essentially unchanged.

3.2 Pinch and Coat

We now discuss, as an aside, some derivable bitonal reactions that are common in descriptions of cellular dynamics. We consider first two *patch-membrane* reactions, that is, reactions between a whole membrane and a membrane patch. We see how they derive from Switch.

The first patch-membrane reaction is Pinch: a reaction that creates an empty bubble next to a membrane patch:

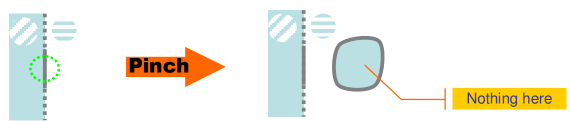


Figure 12 Pinch

When zooming out to membrane operations, Pinch induces two reactions that we call Drip and Pino (Figure 13).

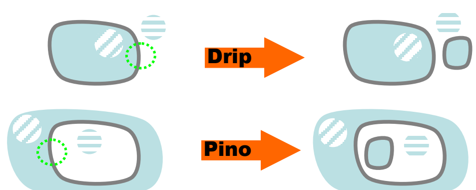


Figure 13 Drip and Pino resulting from Pinch

Pinch is of course derivable from Switch, hence it is bitonal, and so are Drip and Pino:

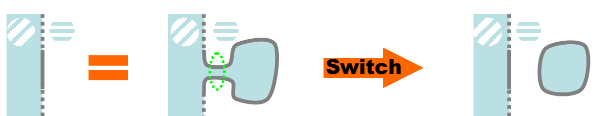


Figure 14 Pinch resulting from Switch

We next consider another patch-membrane reaction, and how it derives from Switch. Here, a whole membrane crosses a patch, and is tightly coated with another membrane:

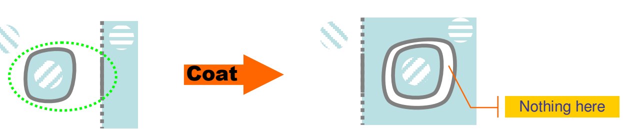


Figure 15 Coat

The following are two global views of Coat, called Phago and Bud; these are really special cases of Endo and Mito, respectively:

 2008-04-30 22:30:28

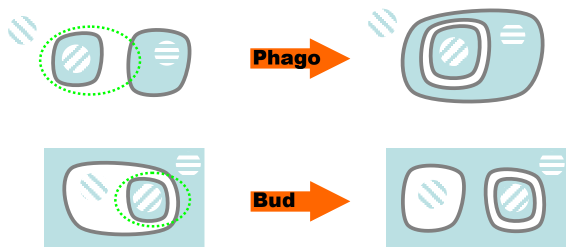


Figure 16 Phago and Bud resulting from Coat

Coat can be derived from Switch as follows. Hence, it is a bitonal reaction, along with Phago and Bud:

Figure 17 Coat resulting from Switch

4 Completeness of Membrane Reactions

A collection of membrane reactions can be incomplete, obviously, by some measure of expressiveness. But more is at risk than just expressiveness. A given membrane reaction, such as Exo, is usually described in terms of global structure (for Exo: a membrane inside another membrane). Any local mechanism that implements such a reaction, however, could not know about global containment relations. As a result, not only that reaction could be an incomplete description of the dynamics, but there might be no possible local implementation of that reaction *alone*.

For example, suppose we allow only Mito and co-Mito as reactions of a membrane system. In Figure 18, the first reaction is a Mito situation. The "patch view" of the reaction is shown in the circle; this is in fact the patch view of a Switch reaction. Note that the second reaction has the same patch view within the circle: Switch could not distinguish between the two cases because the two reactions differ only in the global curvature of the membranes. The second reaction, however, is not a Mito: it is a co-Mate. Therefore, if we allow Mito reactions we must also allow Mate reactions, and vice versa. But this is not enough.

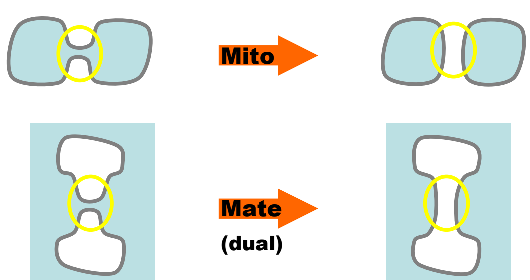


Figure 18 Same patch view

Suppose now we allow only Mito/Mate and co-Mito/Mate as reactions of membrane systems. In Figure 19 the first reaction is a Mito/Mate situation. The “patch view” is again shown in the circle, and the second reaction has the same patch view within the circle. The second reaction, however, is not a Mito/Mate: it is a co-Endo/Exo. Moreover, Endo/Exo reactions are not representable from Mito/Mate because they change the nesting depth of a system. Therefore, a membrane system that allows only Mito/Mate reactions is not locally implementable (by Switch).

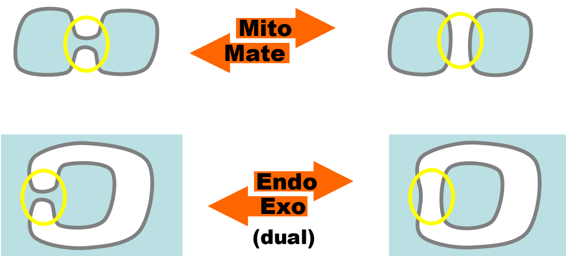


Figure 19 Same patch view

4.1 Endo/Exo/Froth/Fizz as a Complete Set of Reactions

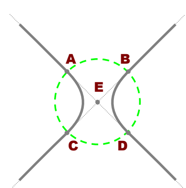
We show that Endo/Exo and Froth/Fizz form a complete set of reactions for bitonal systems, in the sense that all bitonal transformations can be performed by those reactions together with deformations. Due to Propositions 2.3–4 and 2.2–3, we only need to show that every instance of Switch is an instance of Endo/Exo, modulo deformations; this is done in two steps.

4.1–1 Prop (Completeness)

Every instance of a Switch reaction can be represented by an Endo, Exo, Mito, or Mate reaction, together with deformations.

Proof

We assume that the point E is on a white region, for simplicity; the other case is symmetric. The deformations that we mention below are intended to keep the ABCD circular region fixed on the plane.



Suppose that c(AC) and c(BD) are sibling curves. Then they can be brought into the Mate configuration by an appropriate deformation; in this case Switch performs a Mate.

Suppose that c(AC) is inside c(BD). Then the curves can be brought into the Exo configuration by an appropriate deformation; in this case Switch performs a (co-)Exo. Similarly, if c(BD) is inside c(AC).

Suppose c(ABCD) is a single curve. If E is inside the curve, then the curve can be brought into a Mito configuration by an appropriate deformation, and then Switch performs a (co-)Mito. If E is outside the curve, then the curve can be brought into one of two rotationally symmetric Endo configurations by appropriate deformations; then Switch performs an Endo resulting in either c(AB) or c(BD) being inside the other.

Hence, Endo, Exo, Mito, and Mate are all the reactions necessary to cover the situations in which a Switch can be performed.
□

Next we show that Endo/Exo are sufficient, by encoding Mito/Mate from them.

4.1–2 Proposition (Mito/Mate from Endo/Exo)
The reactions Mito and Mate can be represented by Endo and Exo.
Proof

□

Hence we have:

4.1–3 Theorem (Membrane Transformations same as Bitonal Transformations)
A bitonal transformation can be expressed as a finite sequence of Endo, Exo, Froth, and Fizz reactions, along with deformations. Conversely, any such finite sequence is a bitonal transformation.
□

In conclusion, membrane transformations (arising from Endo/Exo/Froth/Fizz) are acceptable because they are bitonal transformations, which are patch transformations (arising from Switch/Froth/Fizz). Moreover, membrane transformations can express all bitonal transformations, which can express all patch transformations.

5 A Simple Bitonal Calculus

At this point, having established that certain collections of membrane reactions are acceptable, we may introduce a syntactic notation that takes these reactions as basic. Note that we do not know how to come up with a syntactic notation that takes patch reactions like Switch as basic.

We adopt the following syntax; any membrane system can be easily written in this form by mapping membranes to brackets. By ⦇X⦈ we intend a membrane that surrounds a subsystem X.

Membrane System Syntax

X ::=	membrane system
◇	empty system
X∘X	composition of subsystems
⦇X⦈	subsystem inside membrane

Any expression in this syntax denotes some canonically chosen membrane system (e.g., by Definition 2.1–4). We then define a relation of structural congruence on expressions, so that two canonical systems that are deformable into each other are represented by equivalent expressions. We can then say that each expression, up to structural congruence, represents an equivalence class of membrane systems, up to deformation.

Structural Congruence (Deformability)

$X_1 \circ X_2 \equiv X_2 \circ X_1$
$X_1 \circ (X_2 \circ X_3) \equiv (X_1 \circ X_2) \circ X_3$
$X \circ \diamond \equiv X$

$X \equiv X$
$X \equiv X' \Rightarrow X' \equiv X$
$X \equiv X',\ X' \equiv X'' \Rightarrow X \equiv X''$
$X \equiv X' \Rightarrow X \circ X'' \equiv X' \circ X''$
$X \equiv X' \Rightarrow \llparenthesis X \rrparenthesis \equiv \llparenthesis X' \rrparenthesis$

We next define the core of the reaction relation, $X \rightarrow X'$, which is then extended with different axioms to obtain different membrane calculi. We write $X \leftrightarrows X'$ for two inverse reactions $X \rightarrow X'$ and $X' \rightarrow X$.

Structural Membrane Reactions

$X_1 \rightarrow X_2 \Rightarrow X_1 \circ X \rightarrow X_2 \circ X$
$X_1 \rightarrow X_2 \Rightarrow \llparenthesis X_1 \rrparenthesis \rightarrow \llparenthesis X_2 \rrparenthesis$
$X_1 \equiv X'_1 \rightarrow X'_2 \equiv X_2 \Rightarrow X_1 \rightarrow X_2$

The Bitonal Calculus is based on the bitonal reactions Froth, Fizz, Endo, and Exo:

Bitonal Calculus

$\diamond \leftrightarrows \llparenthesis \diamond \rrparenthesis$	Froth/Fizz
$X \circ \llparenthesis Y \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ Y \rrparenthesis$	Endo/Exo

As done before geometrically, we can now show by syntactic manipulation that Mito/Mate reactions are representable from Endo/Exo. And so of course are the other reactions from Section 3.2. Another interesting derivable reaction is Peel/Pad:

5.1–1 Proposition (Mito/Mate and Peel/Pad from Endo/Exo and Froth/Fizz)

$\llparenthesis X \rrparenthesis \circ \llparenthesis X' \rrparenthesis \leftrightarrows \llparenthesis X \circ X' \rrparenthesis$	Mito/Mate
$X \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis$	Peel/Pad

Proof

$$\llparenthesis X \rrparenthesis \circ \llparenthesis X' \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis \circ X' \rrparenthesis \equiv \llparenthesis \llparenthesis \diamond \circ \llparenthesis X \rrparenthesis \rrparenthesis \circ X' \rrparenthesis$$
$$\leftrightarrows \llparenthesis \llparenthesis \diamond \rrparenthesis \circ X \circ X' \rrparenthesis \leftrightarrows \diamond \circ \llparenthesis X \circ X' \rrparenthesis \equiv \llparenthesis X \circ X' \rrparenthesis$$

$$X \equiv X \circ \diamond \leftrightarrows X \circ \llparenthesis \diamond \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X \rrparenthesis \circ \diamond \rrparenthesis \equiv \llparenthesis \llparenthesis X \rrparenthesis \rrparenthesis$$

□

Conversely, one can take Mito/Mate and Peel/Pad as axioms, and derive Endo/Exo and Froth/Fizz. However, Peel/Pad, with its sudden deletion/creation of two nested membranes around an arbitrary system, should seem a bit strange as an axiom or a primitive. In fact, it is not a bitonal reaction, although it is a bitonal transformation.

A simple type system for tonalities can be defined as follows, with types $T \in \{W,B\}$ (White and Blue), where $W^{\perp}=B$ and $B^{\perp}=W$. To make the system non-trivial, we add two constants to the syntax: w and b, which have no congruence or reduction rules. Then, $w^{\perp}=b$ and $b^{\perp}=w$, and $X^{\perp}$ is the system obtained by swapping all w and b in it.

Bitonal Typing

$$\frac{}{w : W} \qquad \frac{}{b : B} \qquad \frac{}{\diamond : T} \qquad \frac{X : T \quad X' : T}{X \circ X' : T} \qquad \frac{X : T}{⦇X⦈ : T^{\perp}}$$

5.1–2 Proposition (Duality and Subject Reduction)

$X \rightarrow X' \Rightarrow X^{\perp} \rightarrow X'^{\perp}$

$X{:}T \Rightarrow X^{\perp}{:}T^{\perp}$

$X{:}T \wedge X \equiv X' \Rightarrow X'{:}T$

$X{:}T \wedge X \rightarrow X' \Rightarrow X'{:}T$

□

6 Atonal Systems

Finally, we consider membrane reactions that violate bitonality. Note that there are no natural patch reactions that violate bitonality: an option is a reaction that punches a hole in a membrane patch in order to begin deleting the membrane, but this turns the membrane into an open curve, and therefore does not produce a legal membrane system (as we have defined them).

Membrane systems equipped with reactions that are not bitonal (*atonal reactions*) are called *atonal system*, for emphasis. In Figure 20, we have a few possible atonal reactions, along with the familiar Froth/Fizz. We take Enter/Exit and Froth/Fizz as basic, although another option is to take In/Out and Wrap/Open as basic. Note that In/Out is a special case of Enter/Exit, and Froth/Fizz is a special case of Wrap/Open.

The collection In/Out/Open comes from Ambient Calculus [5], while BioAmbients [3] take In/Out/Mate; in both cases Wrap corresponds to creating a new ambient with a given content. Enter and Exit are found in process calculi where processes move across locations. Therefore, process calculi with locations have so far been based largely on atonal reactions.

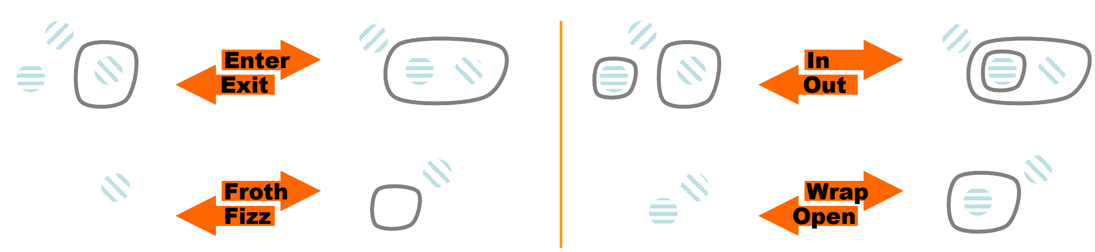


Figure 20 Atonal reactions (except for Froth/Fizz)

These reactions can be defined via precise geometric configurations, as we have done before; we omit the (arbitrary) details, except to say it is convenient to keep the entire membrane system geometrically fixed, except for the rightmost membrane in Enter/Exit and In/Out, and the distinguished membrane in Froth/Fizz and Wrap/Open.

6.1–1 Proposition (Enter/Exit/In/Out/Open/Wrap are not Bitonal Reactions)

Enter, Exit, In, Out, Open, and Wrap are not (always) bitonal reactions.

Proof

By Corollary 2.2–4, we can work up to deformations. For In, we keep the left membrane fixed, so its interior points must change depth by 1, and hence tonality, in the reaction. Moreover, a neighborhood outside the membrane must also change its depth by 1, and hence its tonality. These are then two regions separated by a membrane, and hence are disconnected; similarly for Out.

Enter/Exit have In/Out as special cases, and therefore are not always bitonal. Open is not bitonal, unless it removes an empty membrane. Wrap is not bitonal, unless it creates an empty membrane.

□

6.2 A Simple Atonal Calculus

We can now define a simple calculus corresponding to atonal systems. We take Enter/Exit and the familiar Froth/Fizz as primitives. The Syntax, Structural Congruence, and Structural Membrane Reactions are the same as in Section 5, we only need to specify:

Atonal Calculus

$\diamond \leftrightarrows \llparenthesis \diamond \rrparenthesis$	Froth/Fizz
$X_1 \circ \llparenthesis X_2 \rrparenthesis \leftrightarrows \llparenthesis X_1 \circ X_2 \rrparenthesis$	Enter/Exit

It is easy to compute the following derivable reactions:

Wrap/Open	$X \leftrightarrows \llparenthesis X \rrparenthesis$
In/Out	$\llparenthesis X_1 \rrparenthesis \circ \llparenthesis X_2 \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X_1 \rrparenthesis \circ X_2 \rrparenthesis$
Mito/Mate	$\llparenthesis X_1 \rrparenthesis \circ \llparenthesis X_2 \rrparenthesis \leftrightarrows \llparenthesis X_1 \circ X_2 \rrparenthesis$
Endo/Exo	$X_1 \circ \llparenthesis X_2 \rrparenthesis \leftrightarrows \llparenthesis \llparenthesis X_1 \rrparenthesis \circ X_2 \rrparenthesis$

Note that the equivalent of proposition 5.1–2 fails, e.g., because $w \circ \llparenthesis b \rrparenthesis \rightarrow \llparenthesis w \circ b \rrparenthesis$ by Enter: the atonal calculus does not admit bitonal typing.

Finally, we show that the bitonal calculus can emulate the atonal calculus, by “double walling” all the membranes:

6.2–1 Definition (Translation of Atonal Calculus to Bitonal Calculus)

$\diamond^{\circledast} \triangleq \diamond$

$(X_1 \circ X_2)^{\circledast} \triangleq X_1^{\circledast} \circ X_2^{\circledast}$

$\llparenthesis X \rrparenthesis^{\circledast} \triangleq \llparenthesis \llparenthesis X^{\circledast} \rrparenthesis \rrparenthesis$

□

6.2–2 Proposition

The Bitonal Calculus can emulate the Atonal Calculus.

Proof

First, if $X \equiv X'$ in the atonal calculus, then $X^{\circledast} \equiv X'^{\circledast}$ in the bitonal calculus, by an easy induction on the derivations. Then we show that if $X \rightarrow X'$ in the atonal calculus, then $X^{\circledast} \rightarrow$

$X'^{✪}$ in the bitonal calculus. This is again by easy induction on the derivations, with the following calculations for the basic axioms:

$$\diamond^{✪} = \diamond \leftrightarrows \llparenthesis \diamond \rrparenthesis \leftrightarrows \llparenthesis\llparenthesis \diamond \rrparenthesis\rrparenthesis \equiv \llparenthesis\llparenthesis \diamond^{✪} \rrparenthesis\rrparenthesis = \llparenthesis \diamond \rrparenthesis^{✪}.$$

$$(X_1 \circ \llparenthesis X_2 \rrparenthesis)^{✪} = X_1{}^{✪} \circ \llparenthesis\llparenthesis X_2{}^{✪} \rrparenthesis\rrparenthesis \leftrightarrows \llparenthesis\llparenthesis X_1{}^{✪} \rrparenthesis \circ \llparenthesis X_2{}^{✪} \rrparenthesis\rrparenthesis \leftrightarrows \llparenthesis\llparenthesis X_2{}^{✪} \circ X_2{}^{✪} \rrparenthesis\rrparenthesis = \llparenthesis X_1 \circ X_2 \rrparenthesis^{✪}$$

□

In particular, Open, is emulated under this double-walled encoding by Exo plus Fizz, and Wrap is emulated by Froth plus Endo.

$$\llparenthesis X \rrparenthesis \equiv \llparenthesis X \circ \diamond \rrparenthesis \leftrightarrows X \circ \llparenthesis \diamond \rrparenthesis \leftrightarrows X \circ \diamond \equiv X \qquad \text{(Open/Wrap)}$$

$$\llparenthesis X \rrparenthesis^{✪} = \llparenthesis\llparenthesis X^{✪} \rrparenthesis\rrparenthesis \equiv \llparenthesis\llparenthesis X^{✪} \rrparenthesis \circ \diamond \rrparenthesis \leftrightarrows X^{✪} \circ \llparenthesis \diamond \rrparenthesis \leftrightarrows X^{✪} \circ \diamond \equiv X^{✪}$$

7 Conclusions

We have seen that bitonal transformations, which incrementally, locally, modify tonality, characterize both low-level "patch" transformations and high-level "whole-membrane" transformations of membrane systems. Thus, a collection of membrane reactions can be related to plausible molecular mechanisms, and can be used as the basis for a language or a calculus of membrane interactions, for describing biological algorithms. One such calculus is investigated in a companion work [4].

It is possible to extend our definitions to deal with *molecules* as well as membranes. (Molecules can cross membranes, and hence do not have a fixed tonality.) It is sufficient to relax the definition of membrane systems to include points as well as non-intersecting curves. Bitonal transformation are then the ones that re-tone a region that is simply-connected up to a set of measure zero (the points/molecules). Then, for example, In/Out becomes a bitonal reaction when applied to points, and we can correctly model the fact that molecules can cross membranes, but membranes cannot cross membranes.

8 Appendix: Local Reactions

In this Appendix we investigate a plausible general definition of "local transformation" (any transformation that happens in a bounded region containing only membrane patches), and we show that it coincides with the notion of bitonal transformation.

8.1–1 Definition (Local Reactions and Transformations)

A *local reaction* is any reaction <M,M'> such that all the membrane points that appear in only one of the two membrane systems, are found inside a circular region that contains no whole membranes except empty ones.

A transformation of membrane systems is a *local transformation* iff it can be realized by a finite sequence of local reactions and deformations

□

8.1–2 Proposition (All Local Reactions from Switch/Froth/Fizz)

Any local reaction can be implemented by a finite sequence of Switch/Froth/Fizz reactions and deformations.

Proof

Any empty membrane that is created or deleted can be treated as a Froth or Fizz and deformed out of the configuration. Therefore, we only need to consider transformations where all the membrane points that differ are found inside a circular region that contains no whole membranes.

By construction, before and after the local reaction there must be the same number of crossing points on the border of the interaction disc (otherwise we would have a difference outside the disc). These crossing points are connected in pairs, and a local reaction can only change the pairings, up to deformation. Moreover, any two such pairs AB and CD of crossing points must be “properly bracketed” (not in the cyclic order ACBD or ADBC) to prevent intersections.

If there is only one pair, the reaction is, up to deformation, the identity (the empty sequence of reactions). If there are two pairs, the reaction is, up to deformation, either the identity or Switch (a third case causes intersection).

If there are more than two pairs, we first “untangle” the initial configuration as follows. We say that a pair is simple if it is contiguous in the cyclic order of crossing points on the disc; there is always at least one simple pair, or we would have an intersection. Suppose there are two pairs that are simply nested, that is such that one pair is simple, and the other pair is nested immediately around it. Then, a Switch (with appropriate deformations) can unnest them into two simple pairs. We continue this process until there is no simple nesting left. Now we can have a pair that immediately wraps around a number of simple pairs; we do a Switch with the leftmost simple pair, say, and we obtain a new simple pair, and a pair that wraps around all the other simple pairs (reduced by one). We continue until we obtain a simple nesting, and then we eliminate that one as above. We continue until only simple pairs are left.

By an inverse process, we can “retangle” the interaction disc into the final configuration.

□

By Definition 2.2–1, Switch is a local reaction, and so of course are Froth and Fizz. Hence we obtain:

8.1–3 Theorem (Patch Transformation same as Local Transformations)

A local transformation can be expressed as a finite sequence of Switch, Froth, and Fizz reactions, along with deformations. Conversely, any such finite sequence is a local transformation.

□

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