SMT Solving for Vesicle Traffic Systems in Cells

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Biological interest: What is the form of an eukaryotic membrane traffic?

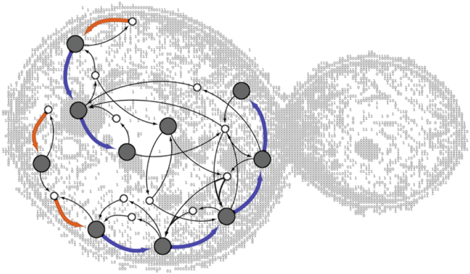
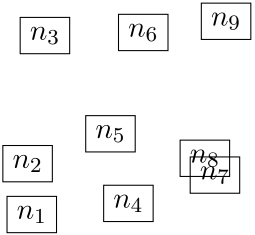
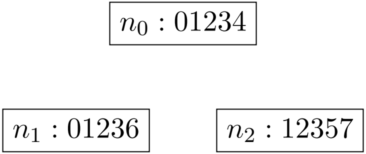


Figure from mukund's recent paper [mani16a].

Vesicular Transport in eukaryotic



- Cells consist of compartments (nodes) 10.



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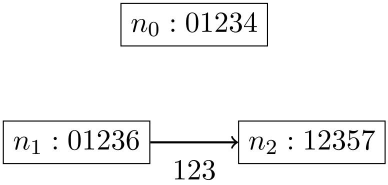
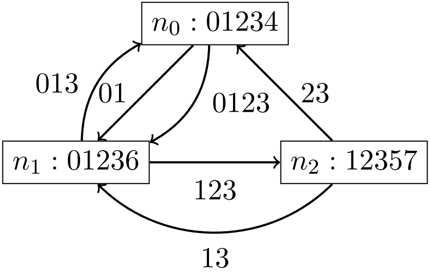


- Cells consist of compartments (nodes) 10.
- Compartments contain molecules (labels).
- Molecules moves around via "transfer **vesicles**" among compartments. (edges label: transferred molecules).

VTS ≡ labeled directed graph...



that follows certain biological rules.

Problem?

- Find a VTS that satisfies some **biological rules**.

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- However, encoding is treacherous!! [1]

Contribution: an effective encoding.

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Find VTS that satisfied these constraints

1. Activity constraint.
2. Fusion constraint.
3. Pairing function.
4. Stability constraint.
5. Connectivity constraint.

1. "Activity constraint": a molecule may or may not be active on the edge/nodes.

[2] A VTS is k-connected if every pair of compartments remain reachable after dropping k 1 vesicles.

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5. “Connectivity constraint”: resulting graph is not k-connected [2].

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Formal VTS

A *Formal VTS* is a tuple

Definition

G = (N, M, E, L, P, f).

where

- N set of *nodes* representing compartments.
- M is a different type of *molecules* in the system.
- E is the set of edges with molecule sets as *labels*.
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- P is the *pairing relation*.
- $f : M \to \wp(M) \to \mathbb{B}$ are the *activity maps*.

The search problem

Fix **k, M, N**; find a G such that following constraints are satisfied:

1. Activity constraint.
2. Fusion constraint.
3. Pairing function.
4. Stability constraint.
5. Connectivity constraint.

Results

Variant	Constraints		Graph connectivity
	Rest	Activity	
A.	F + P + S + C	N + N	No graph
B.		$\mathbb{B}$ + N	No graph
C.		N + $\mathbb{B}$	3-connected
D.		$\mathbb{B}$ + $\mathbb{B}$	2-connected
E.		N + P	No graph
F.		$\mathbb{B}$ + P	4-connected

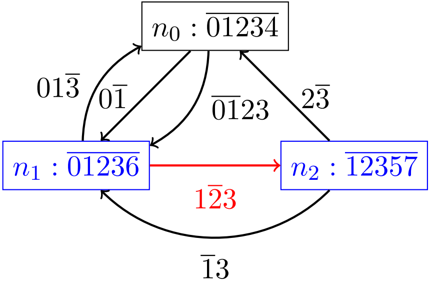
N: No regulation. Every present molecule is active.

$\mathbb{B}$: Use boolean function for regulation.

P: Use pairing matrix for regulation.

Example: Variation C

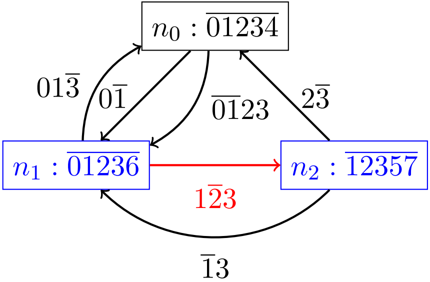
Regulation on node: **None**
Regulation on edge: **Boolean function**



- $\mathrm{N} = \{n_0, n_1, n_2\}$
- $\mathrm{M} = \{\mathrm{M0}, ..., \mathrm{M7}\}$

M1 $\rightarrow$ M6
M2 $\rightarrow$ M5
M3 $\rightarrow$ M4

Our favorite VTS: Our favorite edge



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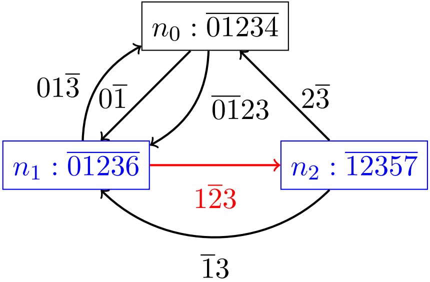

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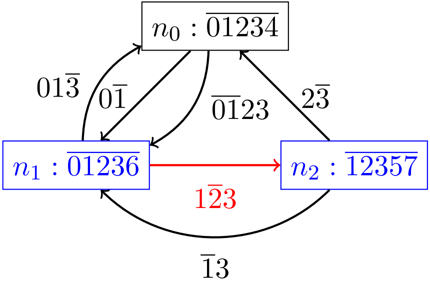

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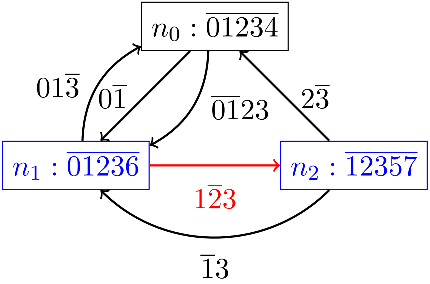

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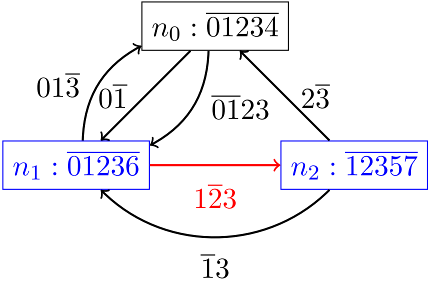

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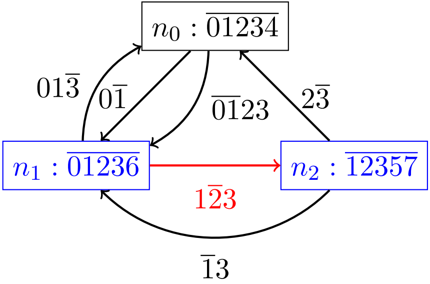

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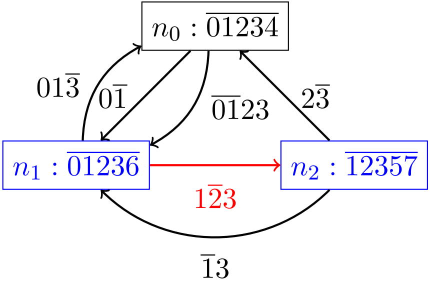

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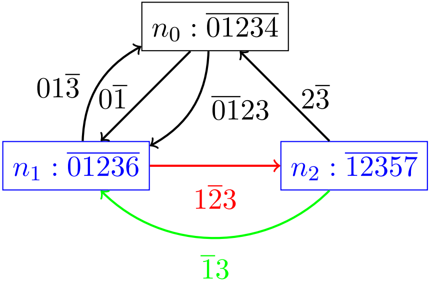
- Stability constraint.

Example: Our favorite edge, Stability condition



- Stability constraint. **M1**, **M3** come back direct edge.

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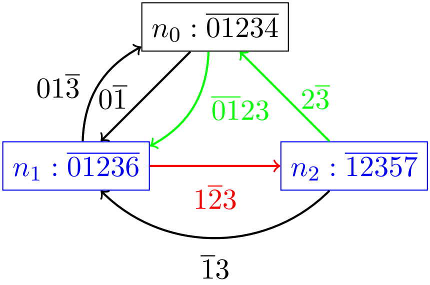
Example: Our favorite edge, SS condition



- Stability constraint. M1, M3 come back direct edge. **M2** comes back using node n_0.

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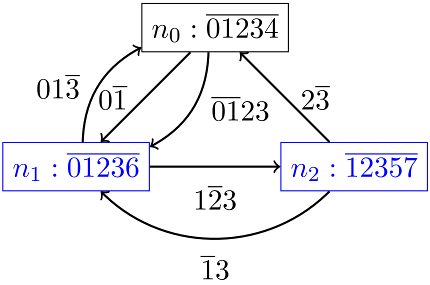

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- Stability constraint.
  M1, M3 come back direct edge.
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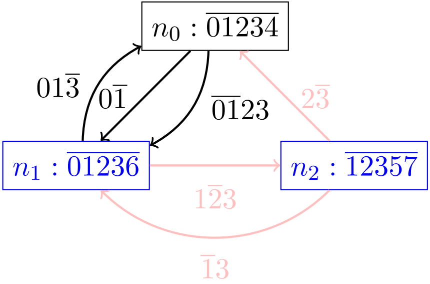
- Connectivity constraint.

Example: Our favorite edge, CC



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- Stability constraint. M1, M3 come back direct edge. M2 comes back using node n_0.
- Connectivity constraint. Drop edge $d_{2,1}, d_{1,2}, d_{2,0}$.

1. Activity constraint.
2. Fusion constraint.
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Constraint for stability condition:

"*Every outgoing molecule come back in a cycle*"

$\forall$ leaving m $\in$ M... $\exists$ cycle [..]

Stability encoding

Encode stability using the reachability variables.

$$\bigwedge_{i,j,m} (e_{i,j,m} \implies$$

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- μ : N − 2.

Steady state encoding

Use reachability to encode the stability condition in VTSs.

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- Recursively define reachability

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- Recursively define reachability

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The following constraints encode that only existing edges can be dropped and exactly $k-1$ edges are dropped.

$$\begin{aligned} \bigwedge_{i,j} d_{i,j} \implies e_{i,j} \\ \sum_{i,j} d_{i,j} = k-1 \end{aligned} \tag{1}$$

but, in my opinion.

$$\bigwedge_{i,j} [(e_{i,j} \wedge \neg d_{i,j}) \vee (\bigvee_{i' \neq i} r'_{i',j} \wedge (e_{i,i'} \wedge \neg d_{i,i'})] \implies r'_{i,j} \tag{2}$$

$$\bigvee_{i,j} \neg(r'_{i,j} \vee r'_{j,i}) \tag{3}$$

Previous work

Old-e

- **CBMC:** C bounded model checker.
- Encode stability condition using *non-determinism* and *enumeration*.
- Not very optimal.

Run-times for searching for models (in secs)

Size	Variant A		Variant C		Variant D		Variant F	
	2-connected		3-connected		2-connected		4-connected	
	MAA	Old-e	MAA	Old-e	MAA	Old-e	MAA	Old-e
2	!0.085	!2.43	0.15	2.12	!0.13	!1.89	0.35	5.12
3	!0.54	!8.04	0.95	7.65	0.62	7.66	1.36	23.94
4	!2.57	!297.93	2.33	22.74	2.85	48.35	4.81	123.34
5	!7.7	!3053.8	7.60	500.03	10.27	890.84	33.36	2482.71
6	!22.98	M/O	19.52	M/O	30.81	M/O	147.52	M/O
7	!57.07	M/O	81.89	M/O	82.94	M/O	522.26	M/O
8	!164.14	M/O	630.85	M/O	303.19	M/O	2142.76	M/O
9	!307.67	M/O	2203.45	M/O	971.01	M/O	4243.34	M/O
10	!558.34	M/O	7681.93	M/O	2274.30	M/O	7786.82	M/O

Conclusion

1. Novel encodings of reachability and 3-4 connectivity.
2. Direct encoding into the SMT solver.
3. A user friendly and scalable tool based on well known SMT solver Z3.

Thank You !