Bigraphical molecular systems
Adding dynamics

Troels Damgaard\(^1\) and Jean Krivine\(^2\)

\(^1\)IT University of Copenhagen
Denmark

\(^2\)École Polytechnique
France

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Outline

1 Introduction
   - Design goals and programming paradigms

2 BMS - the dynamics
   - Membrane reconfiguration
   - Domain level interaction
   - Diffusion
   - Membranes and transfer

3 Concluding remarks
   - Wellformedness properties
   - Future work
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Local interactions

- No **distant** communication without a medium in nature.
- Interaction among components and preconditions for reaction should be geometrically **local** in scope.
- In particular, should enforce **projective** or **patch** view for membranes (as studied by Pradalier, Danos and Cardelli).

**Figure:** Preconditions with purely local scope
Rule-based programming

The $\kappa$-calculus has been one of several advocates for rule-based programming. Rules

- can be understood and manipulated separately,
- easily visualized, and,
- easily (inherently) express possible overlapping behaviors of certain configuration.

**Figure**: A local rule on core ingredients
Design goals and programming paradigms (cont.)

Rule-based — but upholding certain invariants

On the other hand, we need to uphold a number of model invariants to ensure that we can interpret model configurations as biological states.

Hence, we advocate a middle-ground for BMS: Programming by rule refinement.

Figure: A non-local rule that would break the local nature of complex formation
Rule generators

We give a set of rule generators that each express a core biological action for membranes and proteins.

Key idea:
- A domain expert may refine core BMS-rules to give a domain-specific sub-calculus for the study of a particular biological application.
- He does this by either
  - giving application conditions that express when an action in a generator may be applied; or,
  - making kinetic refinements, by modifying the stochastic rate of rules. (More on stochastics tomorrow).
- For membranes — generated rules are forced to treat membrane borders projectively.

(For this presentation — disregard creation, deletion and testing on metainformation.)
Application conditions

- Easy to define for bigraphs, due to clear notion of composition of contexts.
- Essentially; for a generator rule $R \rightarrow R'$, $C.R.D \rightarrow C.R'.D$ is a (narrowing) refinement, and we say that the contexts $C$ and $D$ constitute application conditions.

Maintenance rules

- Finally, apart from generated rules, we take a few maintenance rules.
- They serve to add the little bits of implementation needed to preserve the invariants that allow us to interpret the model biologically.
- **Intuition**: Invisible and non-manipulatable by a user of the calculus.
- **Property**: Maintenance rules are normalizing.
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Membrane reconfiguration

Generators for membrane reconfiguration

**Heterogenous** generators — focuses on two regions of different tonality, separated by a single membrane-border.

**Homogenous** generators — focuses on two colocated regions of equal tonality, separated (possibly) by two membrane borders.
Membrane reconfiguration (cont.)

Heterogenous generators — pinch

Figure: Specification for (pinch) rule.

□ || 0 → /x (Gx.0 || M.Gx.□)

Figure: Generator — the (parametric) (pinch).
Membrane reconfiguration (cont.)

Heterogenous generators — merge

Figure: Specification for the (merge) rule.

Figure: Generator — the bigraphical (merge).
Membrane reconfiguration (cont.)

Homogenous rules — touch

Figure: Specification for the (touch) rule.

\[ \begin{array}{c}
\text{P} \\
\text{Q} \\
\end{array} \rightarrow \begin{array}{c}
\text{P} \\
\text{Q} \\
\end{array} \]

\[ 0 \parallel 0 \rightarrow /x (G_x \parallel G_x) \]

Figure: Generator — the bigraphical (touch).
Membrane reconfiguration (cont.)

Homogenous rules — part

Figure: Specification for the (part) rule.

Figure: Generator — the bigraphical (part).
Due to our generic model of protein-domains — need only a single reversible rule for modelling core $\kappa$-semantics:

\[
\vdash x_D^x \mid y_D^y \leftrightarrow z (z/x_D^x \mid y_D^y)
\]

**Figure:** Generator — the bigraphical (complex).
Diffusion

The specification

\[ P 
\]
\[ \text{(diffuse)} \]
\[ Q \]

\[ \rightarrow \]

\[ P \]

\[ T^* \]

\[ Q \]

**Figure:** Specification for the (combined) diffusion rules.

- Implemented using three small-step rules \( \rightarrow \)
Diffusion (cont.)

Initiating diffusion

\[
/ \mathcal{X} ( ((D_b^I \mid G_x \cdot \Box_0) \parallel \Box_1) \rightarrow / \mathcal{X} (G_x \cdot \Box_0 \parallel G_x \cdot (D_b^I \mid \Box_1))
\]

Figure: Generator — initiate diffusion
Diffusion (cont.)

Dragging of local connected component

\[
\begin{align*}
/\mathcal{X} \left( \left( \mathcal{D}_{b}^{l_{0}} \parallel \mathcal{G}_{x} \cdot \Box_{0} \right) \parallel \mathcal{G}_{x} \cdot \left( \mathcal{D}_{b}^{l_{1}} \parallel \Box_{1} \right) \right) & \rightarrow /\mathcal{X} \left( \mathcal{G}_{x} \cdot \Box_{0} \parallel \mathcal{G}_{x} \cdot \left( \mathcal{D}_{b}^{l_{1}} \parallel \mathcal{D}_{b}^{l_{1}} \parallel \Box_{1} \right) \right)
\end{align*}
\]

Figure: Domain dragging — on backbones \((\infty\text{-rate})\)

- An \(\infty\text{-rate}\) maintenance rule — ensures that an entire complex is dragged.
- We take a similar rule for complex formation links and domain backbones linked across a membrane border.
- Also handles dragging initiated by (pinch).
Diffusion (cont.)

Terminating diffusion

\[ /x (G_x \cdot \square_0 \parallel G_x \cdot \square_1) \rightarrow /x (G_x \cdot \square_0 \parallel (G_x \mid \square_1)) \]

**Figure:** Flush a gate.

- A maintenance rule, but the only non-\(\infty\)-rate one.
Membranes and transfer

Background

- **Channels** are not intended for supporting diffusion of membranes.
- Thus, we may need to resolve two particular situations, where membranes may get “stuck” in a transfer.
- In general; the right solution may be application-dependent — depending on the intention in the model. Thus, this choice might probably best be left as an option for the domain specialist.
- In each case, there are a few possible solutions →
Membranes and transfer (cont.)

Case 1/2: Stretched membrane channels

- May only happen due to (pinch).
- May take rule that either **severs** channel (by removing two gates), or (with less biological intuition) **drags** a membrane across outer diffusion-channel (at $\infty$-rate).

Figure: A stretched membrane-channel.
Membranes and transfer (cont.)

Case 2/2: Stretched receptors

Figure: A stretched receptor.

- May take a rule that (i) aborts the entire transfer; or, (with less biological intuition) (ii) severs the receptor backbone, or (iii) drags the membrane across the diffusion-channel (at $\infty$-rate).
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Wellformedness properties

Maintenance is a normalizing process

**Definition (Stable configuration)**
A stable BMS configuration is one, where no \( \infty \)-rate rule applies.

**Proposition (\( \infty \)-rate maintenance rules are normalizing)**
On any configuration, the \( \infty \)-rate maintenance rules are *locally confluent* and *terminating*.

**Definition (Stable normalform)**
Means that for any BMS configuration \( g \), there exists a *unique* stable \( \text{nf}(g) \), s.t.,

\[
g \xrightarrow{\infty} \text{nf}(g)
\]
Wellformedness properties (cont.)

Biological consistency

**Definition (Consistent configurations)**
- **(local complex)** complex formation links are mono-located.
- **(fixed backbone)** depth of backbone is preserved across reactions (if backbone crosses $n$ membranes it still does after any reaction).
- **(bitonality)** all gates connect membranes of distance 2 (or 0) in the place-graph.

**Theorem (BMS preserves consistency up to maintenance)**

*If $g$ is consistent and $g \rightarrow *g'$, then $nf(g')$ is consistent.*
Some notes on future work

- **Causality analysis** for subset of bigraphs including BMS.
- **Volume** of membranes and (sizes of complexes).
- **Implementation**.
- A **case-study** of a larger biological example (building on κ experience).
The generator toolbox

**Membrane reconfiguration**

\[ \square \parallel 0 \to /x \ (G_x.0 \parallel M.G_x.\square) \]  
(pinch)

\[ /x \ (G_x.\square_0 \parallel M.(G_x.\square_1 \parallel \square_2)) \to (\square_0 \parallel \square_1 \parallel \square_2) \parallel 0 \]  
(merge)

\[ 0 \parallel 0 \to /x \ (G_x \parallel G_x) \]  
(touch)

\[ G_x.\square_0 \parallel G_x.\square_1 \to \square_0 \parallel \square_1 \]  
(part)

**Diffusion**

\[ /x \ ((D^l_b \parallel G_x.\square_0) \parallel G_x.\square_1) \to /x \ (G_x.\square_0 \parallel G_x.(D^l_b \parallel \square_1)) \]  
(in)

**Complex formation**

\[ /x \ D^x_b \parallel /y \ D^y_b, \leftrightarrow /z \ (z/x \ D^x_b \parallel z/y \ D^y_b,) \]  
(complex)
Thank you for listening!
Appendices

Membranes and transfer — BMS rules
Membranes and transfer — BMS rules

Receptor pullback

\[
/\lambda \left( ( M. (D_{b}^{l_0} \mid □_2) \mid G_{x}.□_0) \parallel G_{x}.(D_{b}^{l_1} \mid □_1) \right) \rightarrow \\
/\lambda \left( (((D_{b}^{l_1} \mid □_2) \mid □_1 \mid M.D_{b}^{l_0} \mid G_{x}.□_0) \parallel G_{x}.0) \right)
\]

Figure: Receptor pullback — aborting transfer (\(\infty\)-rate)
Membranes and transfer — BMS rules (cont.)

Membrane channel snapping

Figure: Membrane snap – (∞-rate)

Need to take also a rule, that handles the special case, where an inward bud is being dragged into an inward bud. (Case not captured by the rule above.)