Une sémantique pour la biologie moléculaire ?

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JFLA 2014

Scientific inputs to systems biology

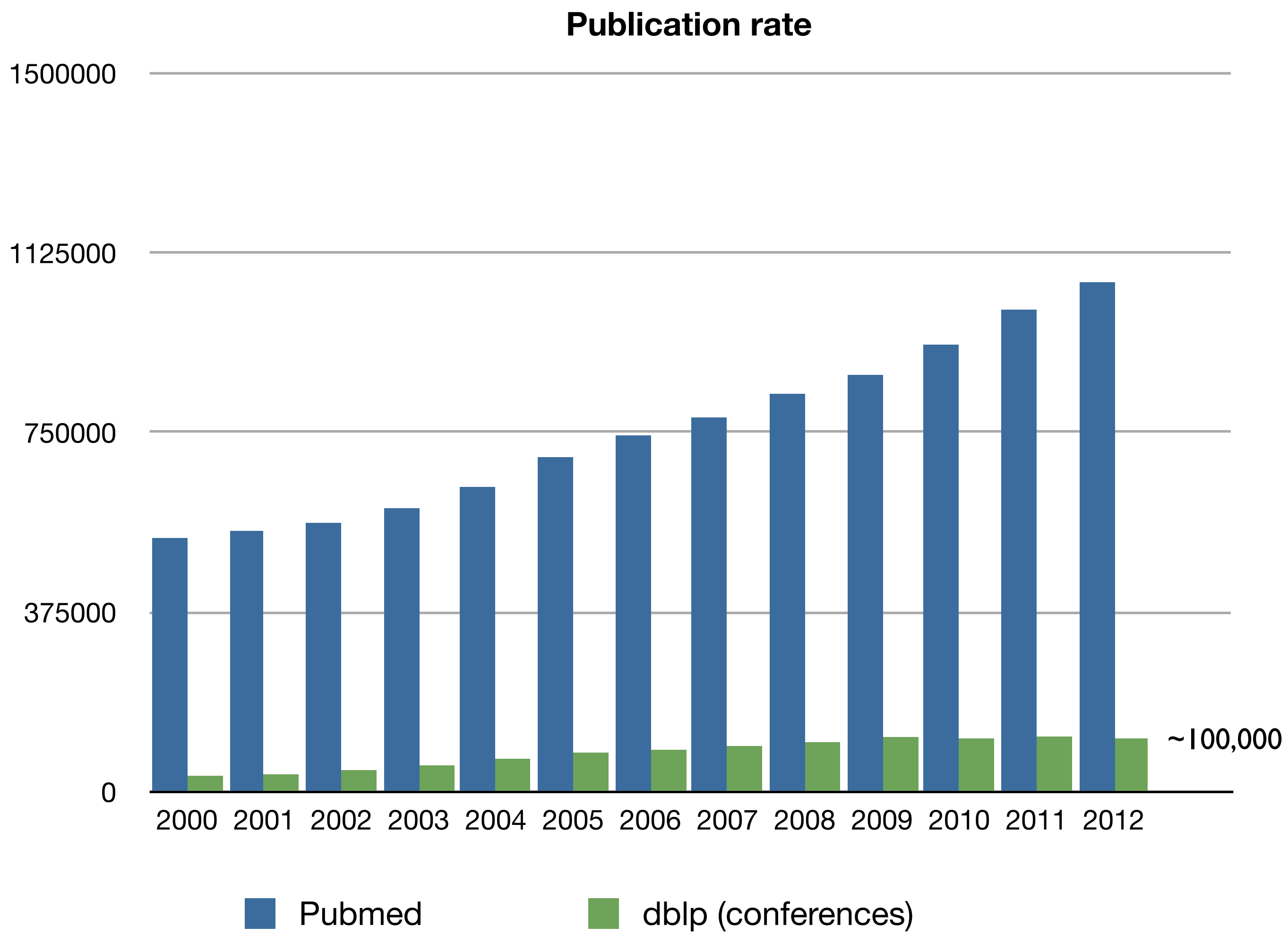
- Physics: population dynamics (Monte carlo), free energy (protein folding)...
- Chemistry (obviously)
- Computer Science (essentially algorithmics)
- Can «semantics» (us) bring anything to them?

Them?

Them?

Total Publication volume?

Them?


Publication rate
1500000
1125000
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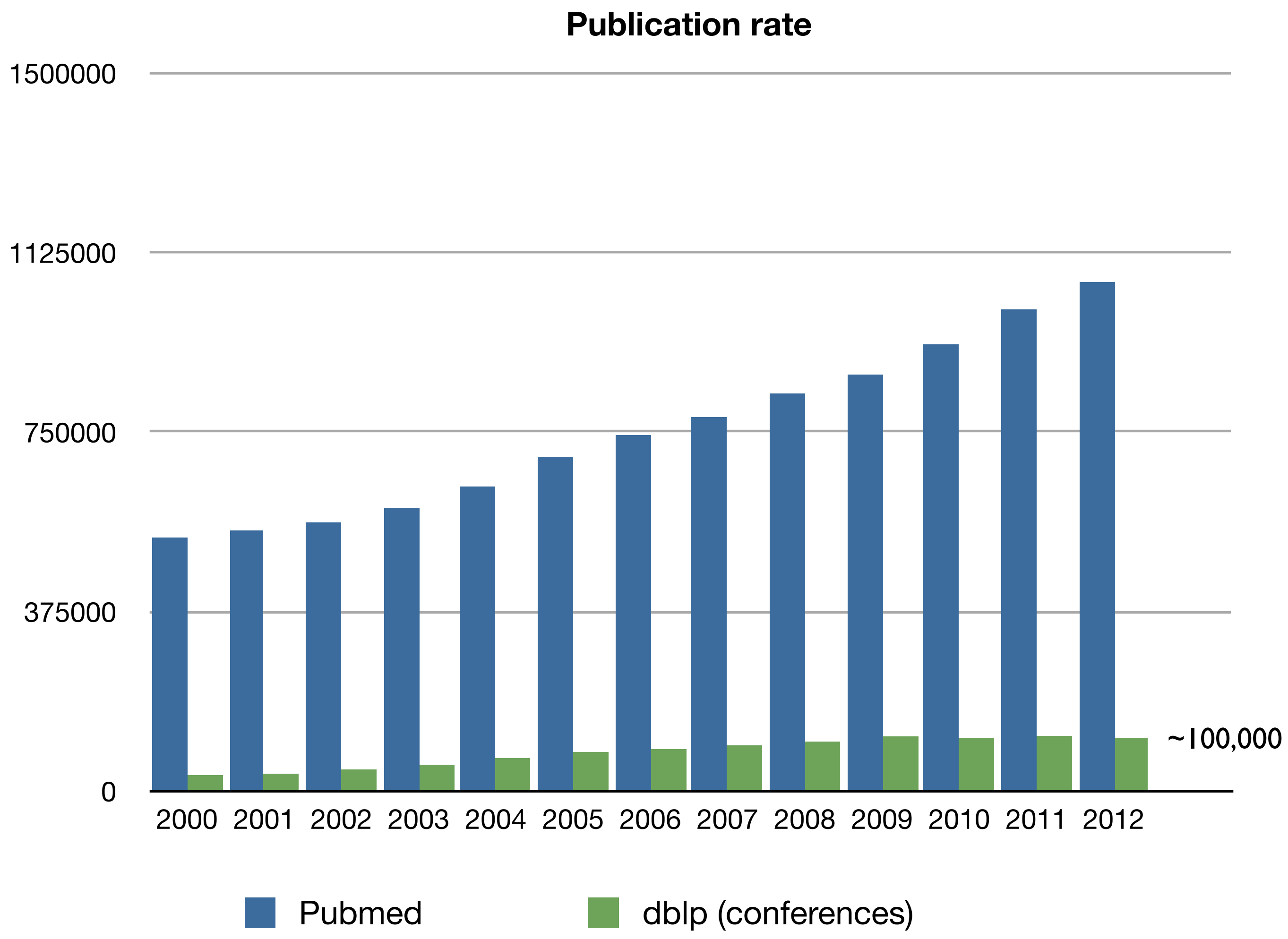
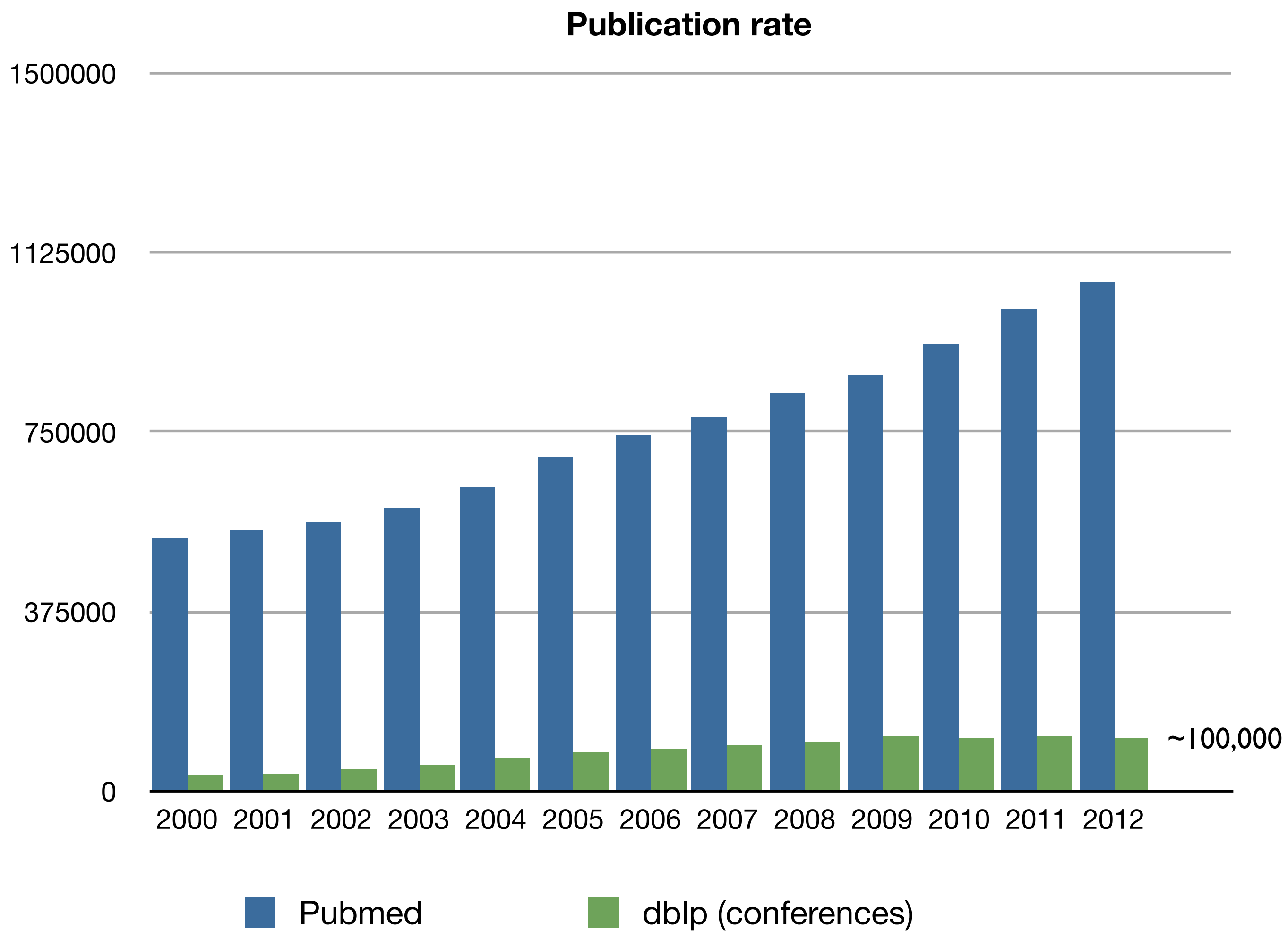
Pubmed
dblp (conferences)

Them?



How many papers should you read if you are a specialist of subject X?

Them?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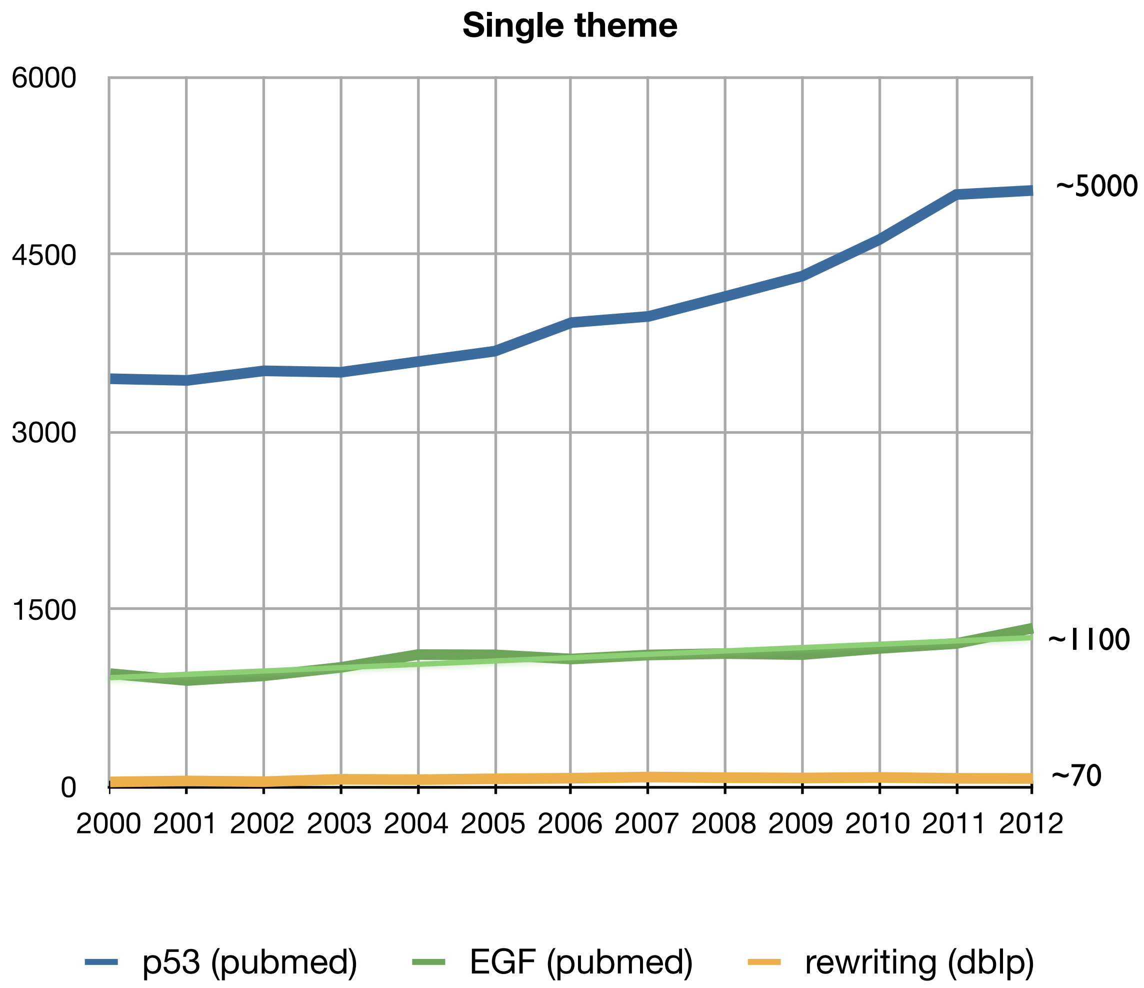
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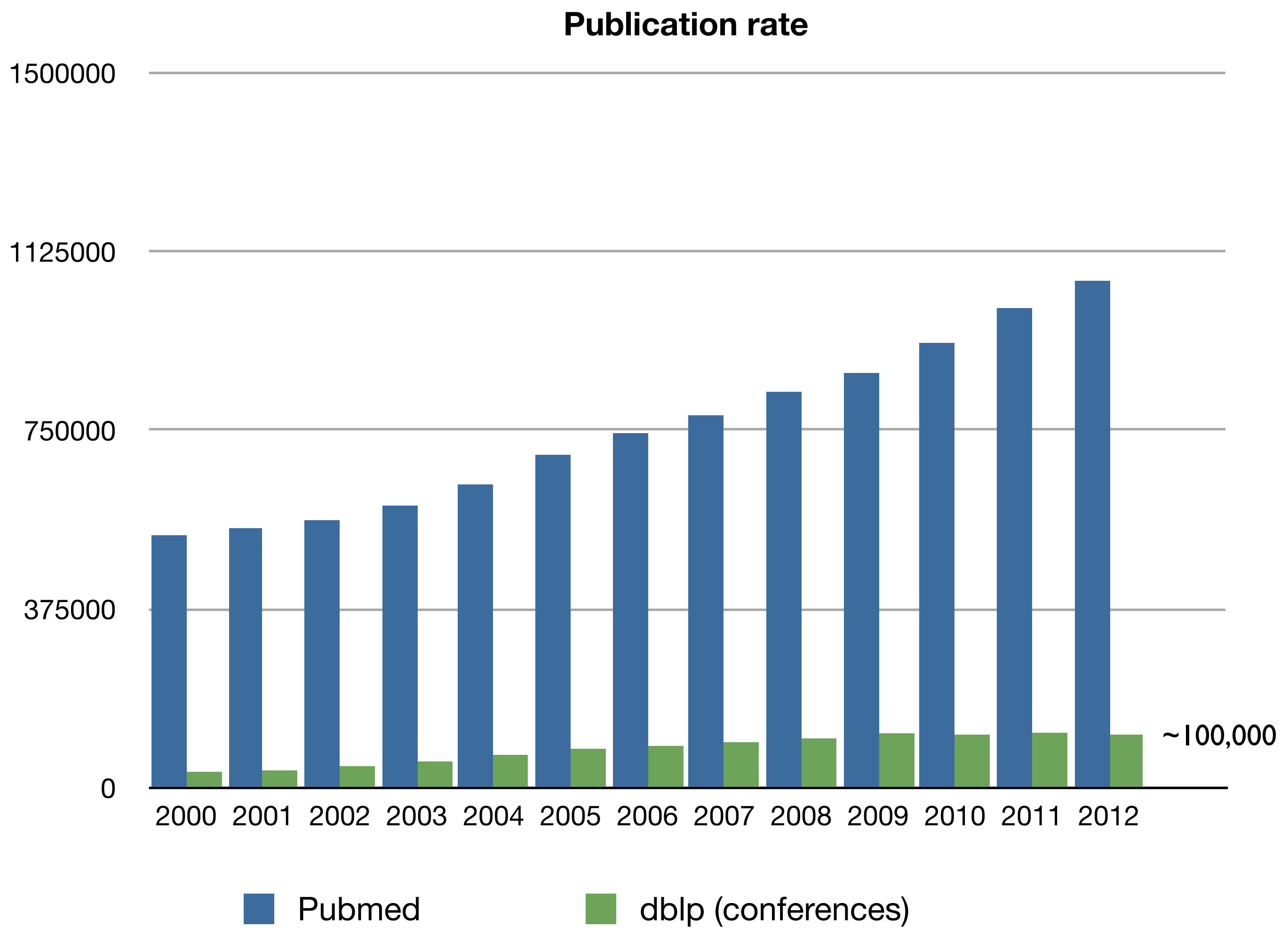
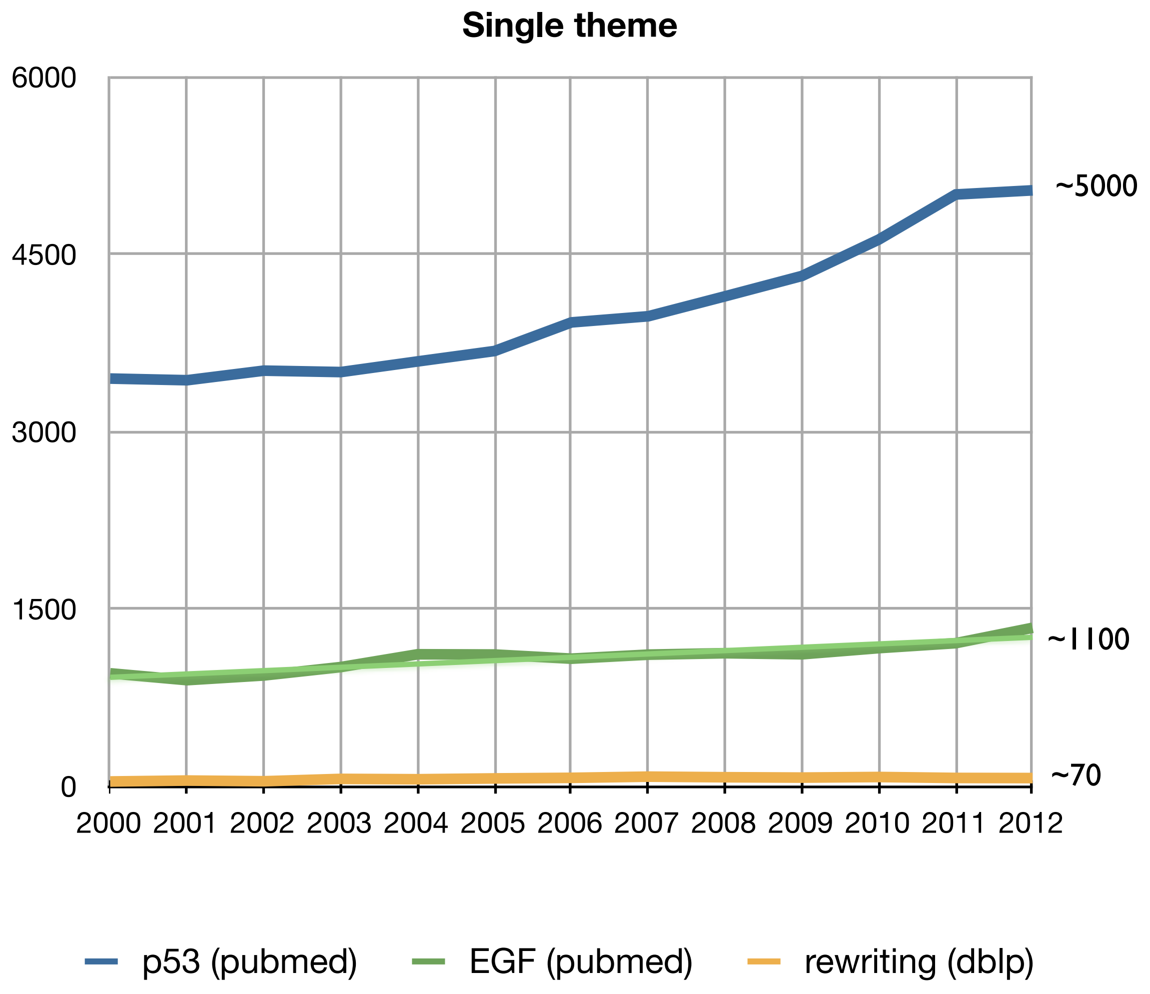
EGF (pubmed)
rewriting (dblp)

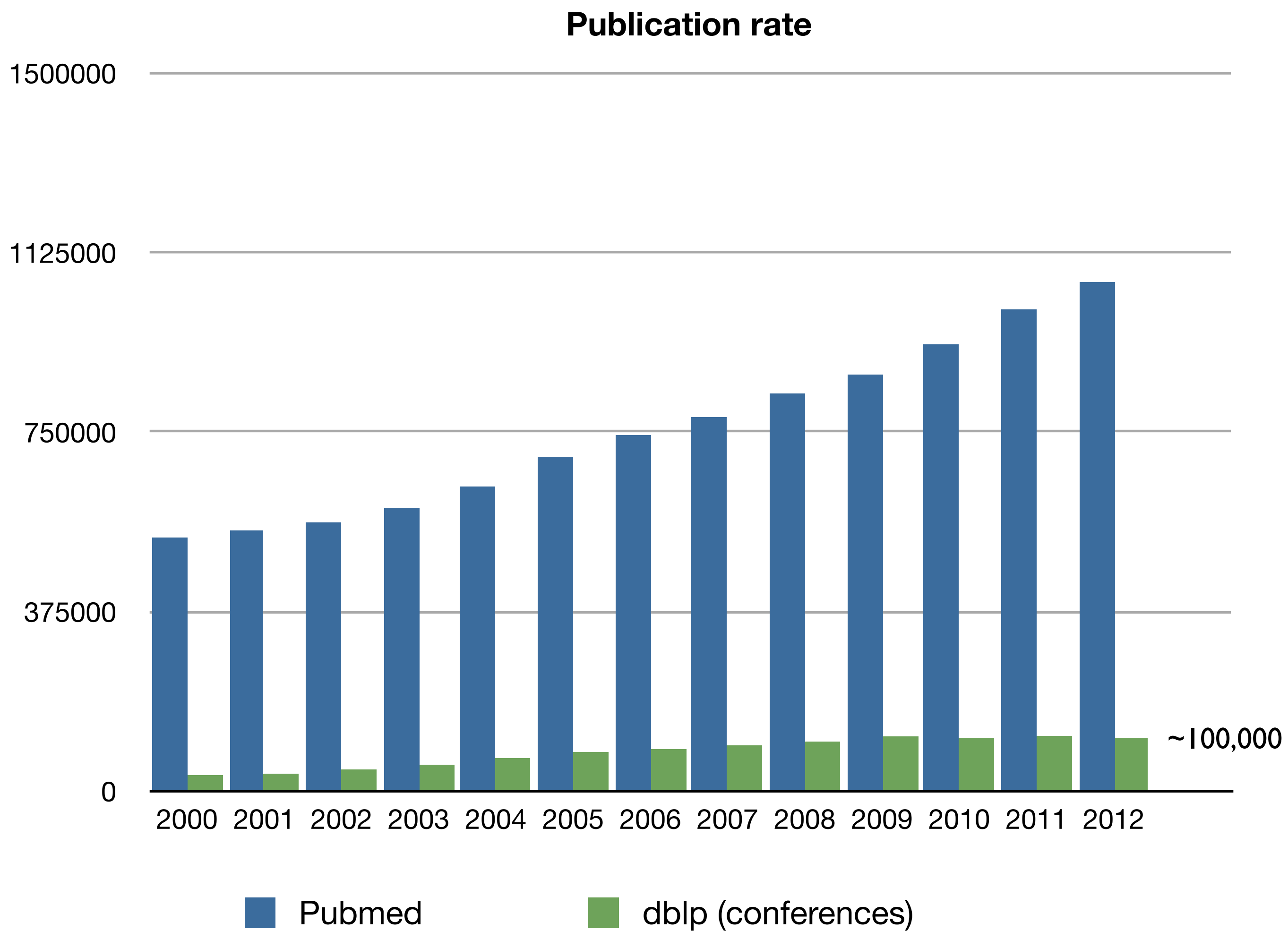
Them?

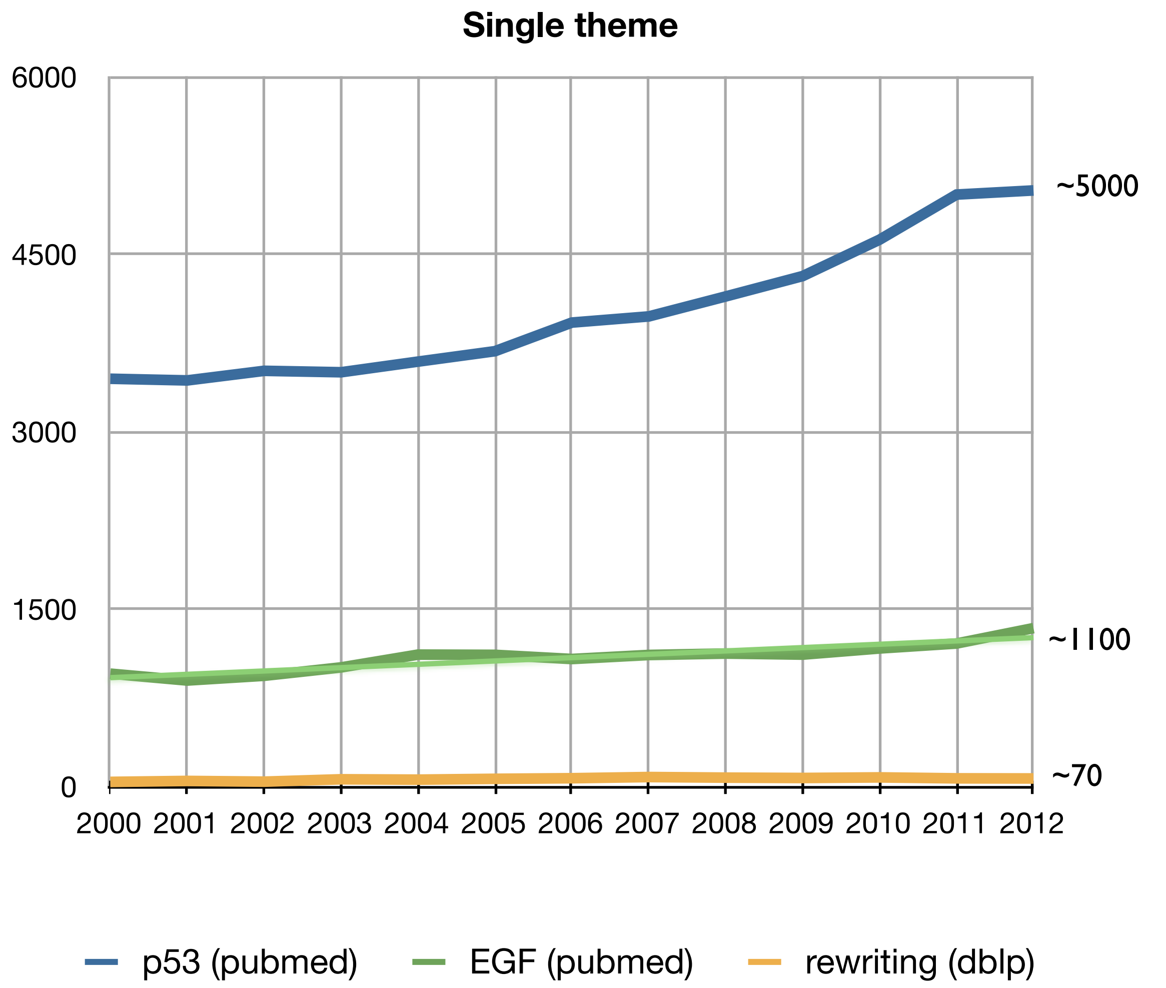




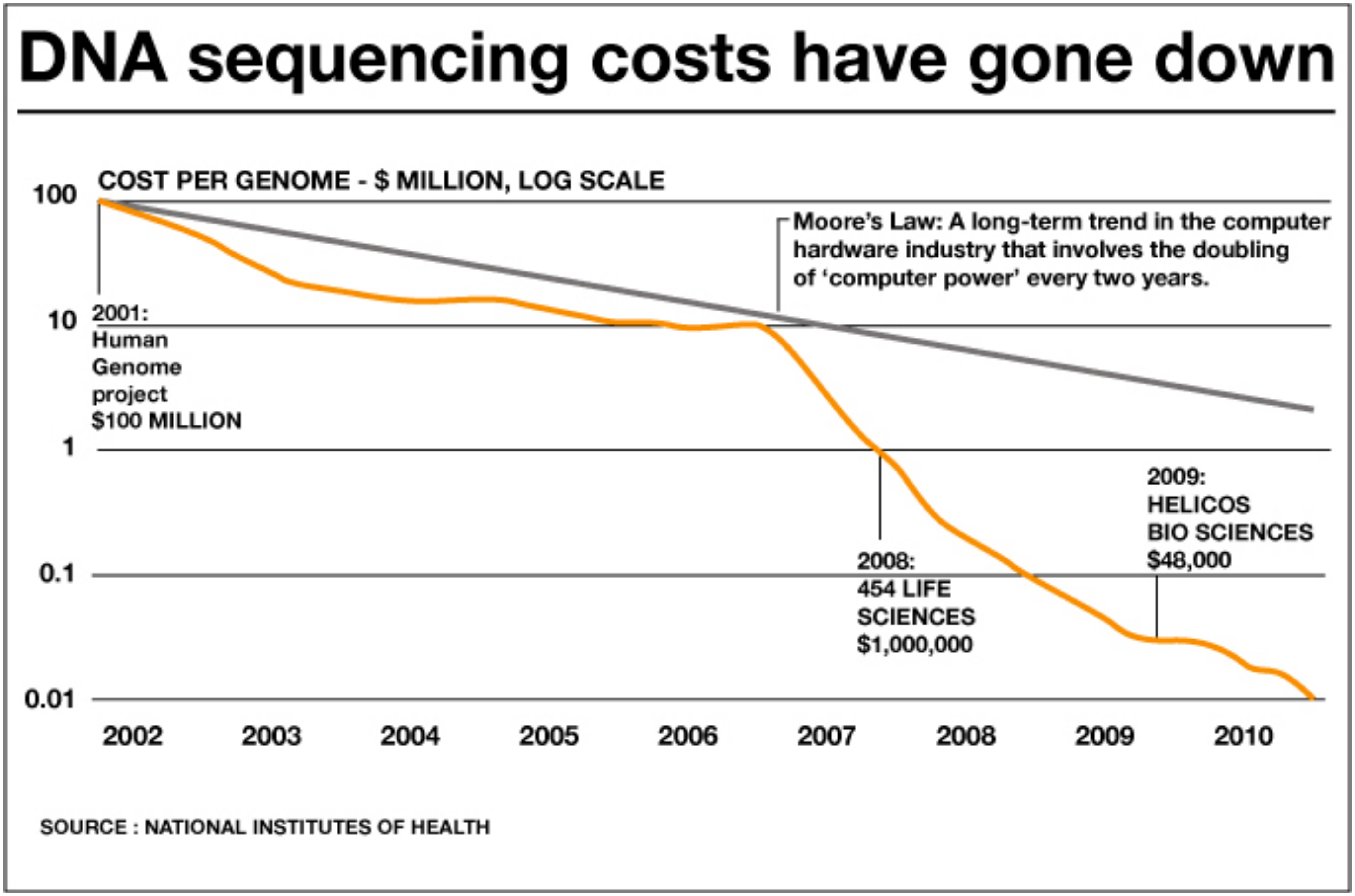
Budget? (USA)

Them?





Budget 2012 of NIH : 31 billion $ (~ total budget of France research!)
Budget 2012 of NIST : 750 million $
(source: nih.giv and nist.gov)



DNA sequencing costs have gone down

COST PER GENOME - $ MILLION, LOG SCALE

Moore's Law: A long-term trend in the computer hardware industry that involves the doubling of 'computer power' every two years.

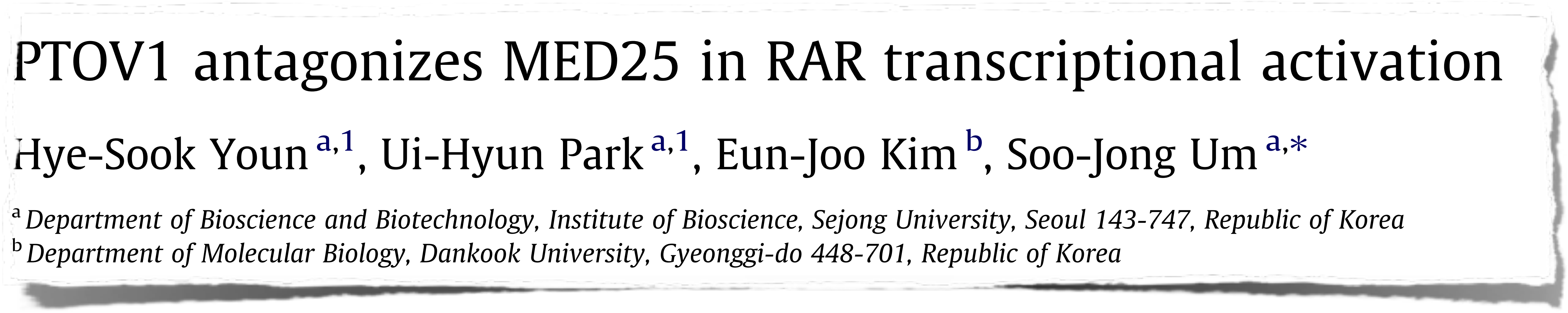
2001: Human Genome project $100 MILLION

2008: 454 LIFE SCIENCES $1,000,000

2009: HELICOS BIO SCIENCES $48,000

SOURCE : NATIONAL INSTITUTES OF HEALTH

No theorems, only facts...

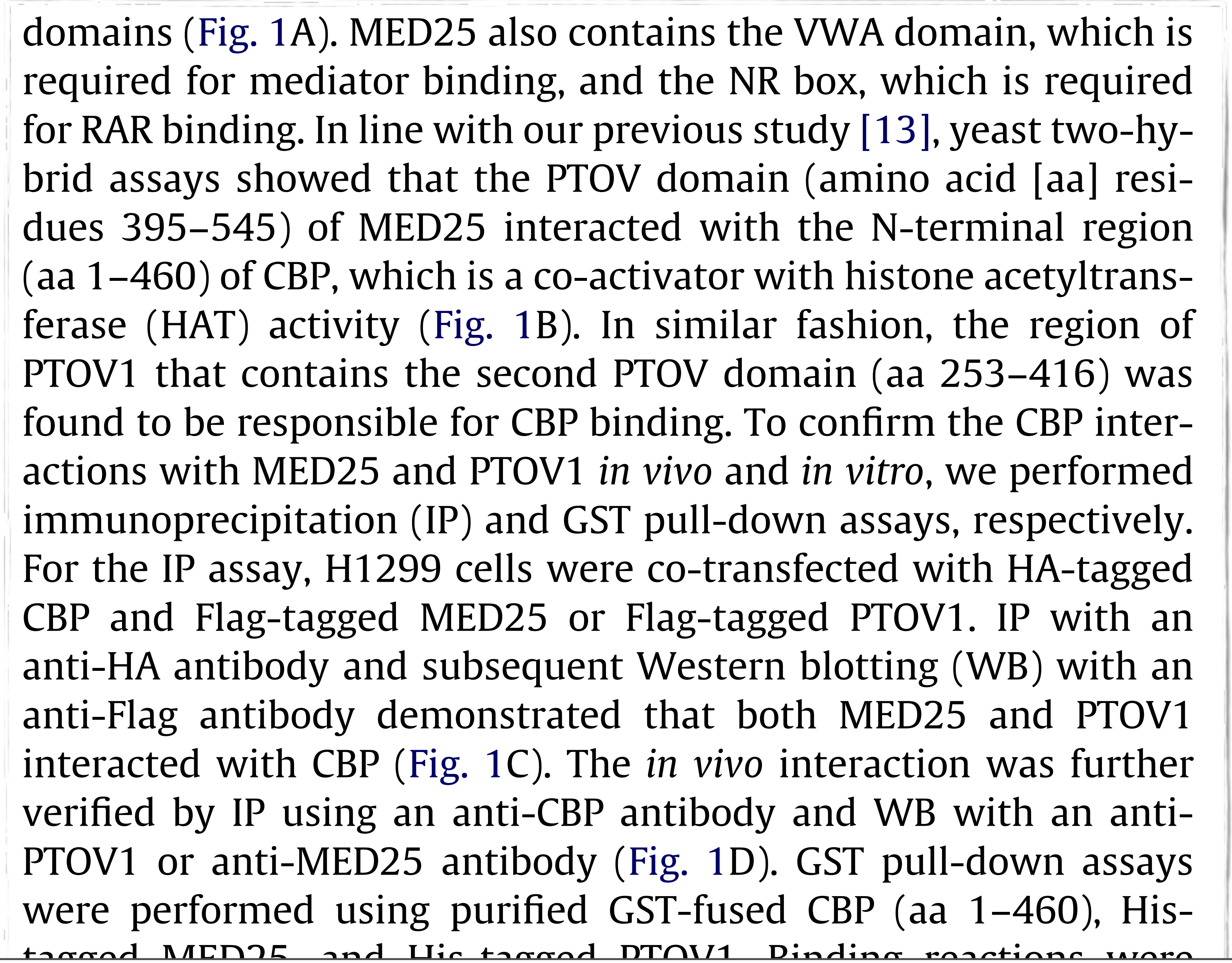


PTOV1 antagonizes MED25 in RAR transcriptional activation

Hye-Sook Youn [a,1], Ui-Hyun Park [a,1], Eun-Joo Kim [b], Soo-Jong Um [a,*]

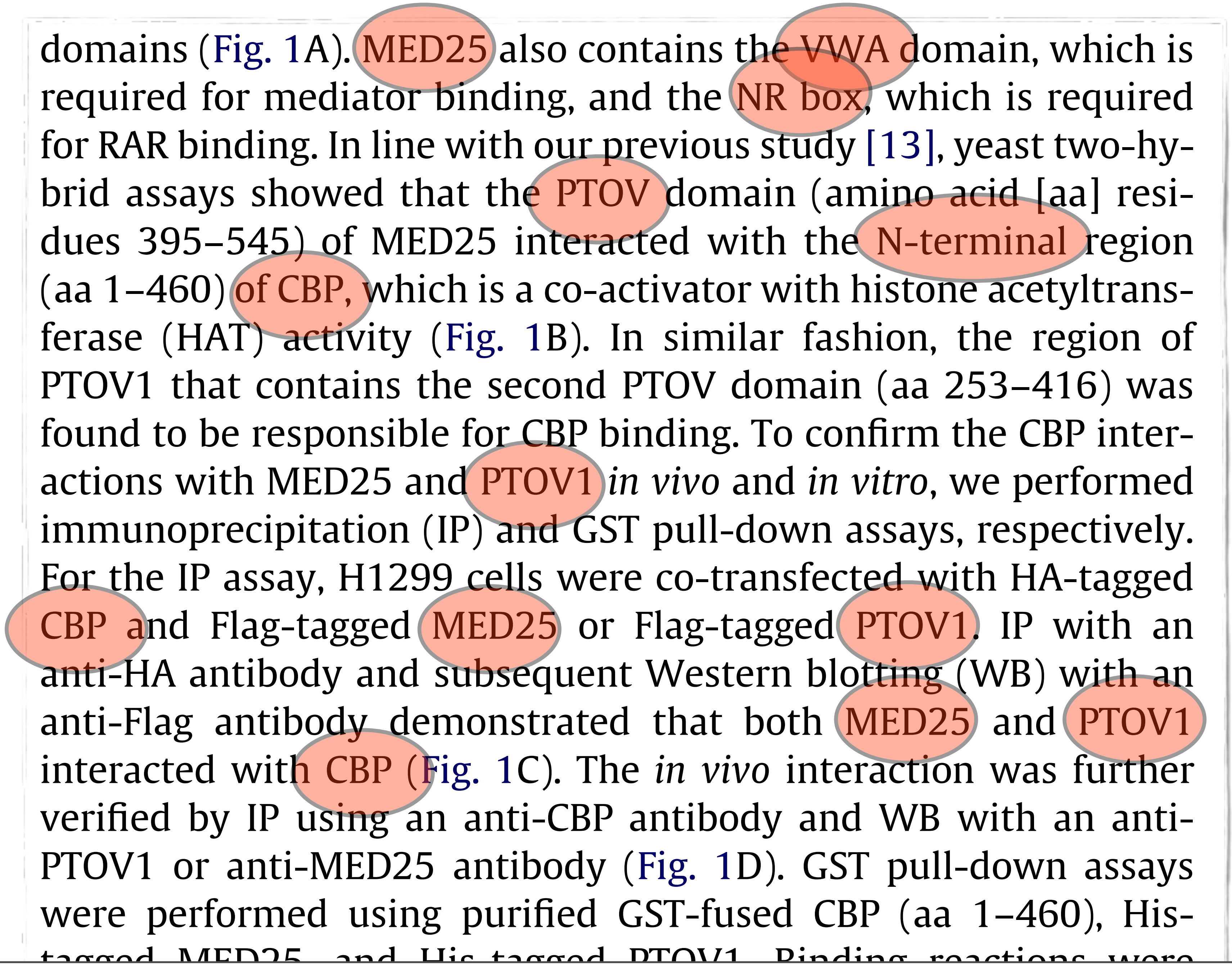
[a] *Department of Bioscience and Biotechnology, Institute of Bioscience, Sejong University, Seoul 143-747, Republic of Korea*
[b] *Department of Molecular Biology, Dankook University, Gyeonggi-do 448-701, Republic of Korea*

No theorems, only facts...



domains (Fig. 1A). MED25 also contains the VWA domain, which is required for mediator binding, and the NR box, which is required for RAR binding. In line with our previous study [13], yeast two-hybrid assays showed that the PTOV domain (amino acid [aa] residues 395–545) of MED25 interacted with the N-terminal region (aa 1–460) of CBP, which is a co-activator with histone acetyltransferase (HAT) activity (Fig. 1B). In similar fashion, the region of PTOV1 that contains the second PTOV domain (aa 253–416) was found to be responsible for CBP binding. To confirm the CBP interactions with MED25 and PTOV1 *in vivo* and *in vitro*, we performed immunoprecipitation (IP) and GST pull-down assays, respectively. For the IP assay, H1299 cells were co-transfected with HA-tagged CBP and Flag-tagged MED25 or Flag-tagged PTOV1. IP with an anti-HA antibody and subsequent Western blotting (WB) with an anti-Flag antibody demonstrated that both MED25 and PTOV1 interacted with CBP (Fig. 1C). The *in vivo* interaction was further verified by IP using an anti-CBP antibody and WB with an anti-PTOV1 or anti-MED25 antibody (Fig. 1D). GST pull-down assays were performed using purified GST-fused CBP (aa 1–460), His-tagged MED25, and His-tagged PTOV1. Binding reactions were

No theorems, only facts...



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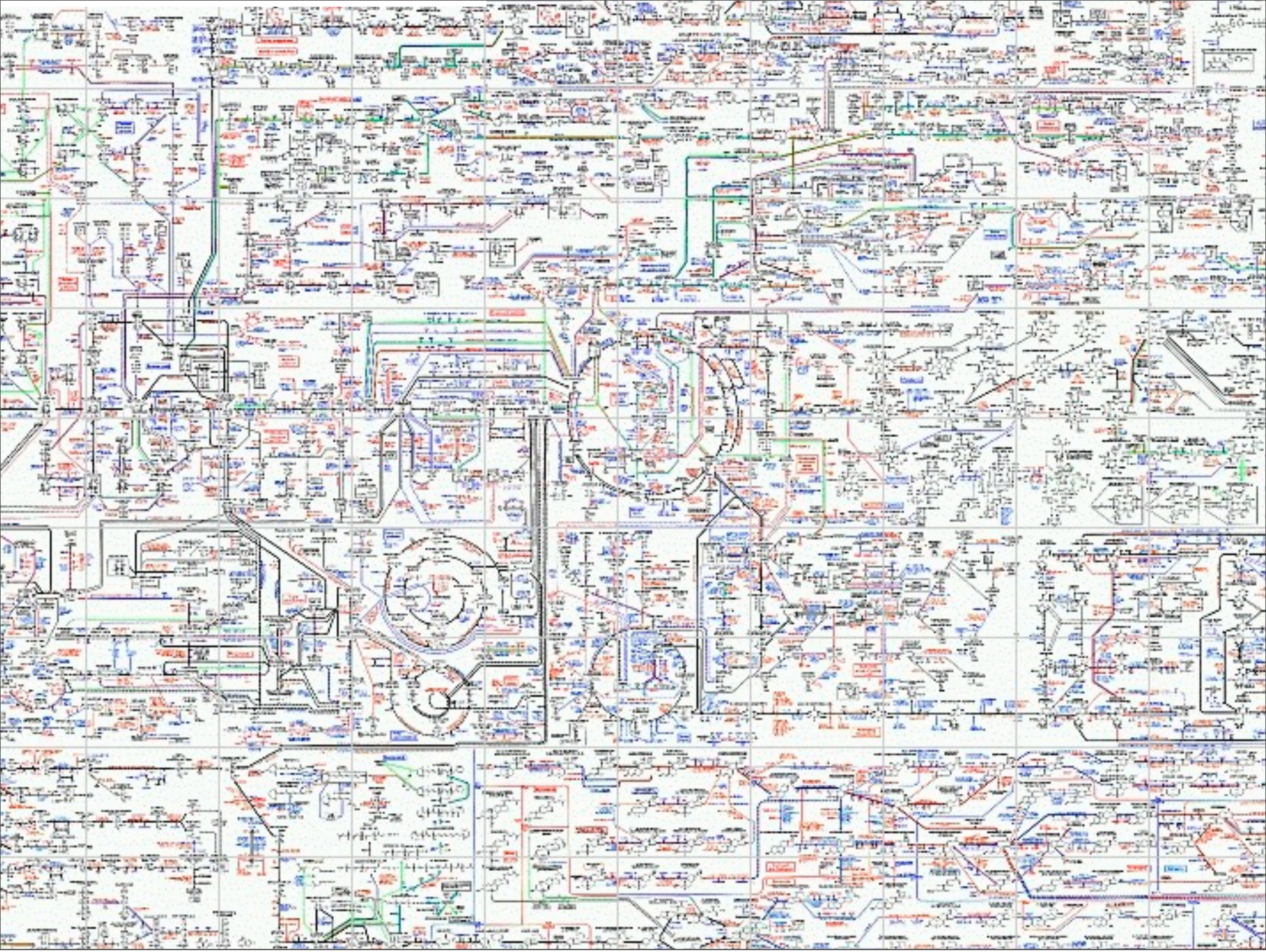
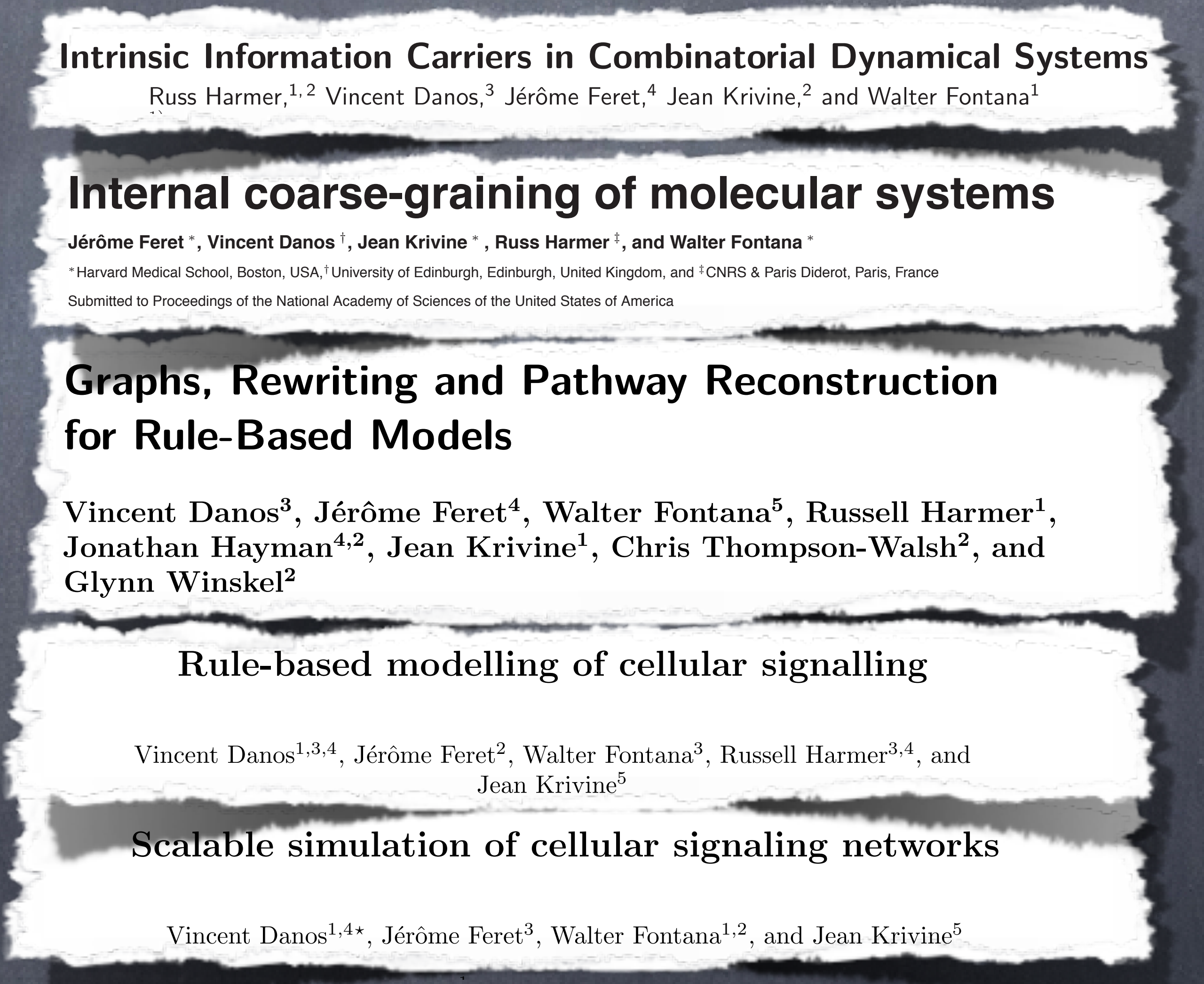


What we would like

- Translate facts (in English) into *formal* rules
- Use machines to connect related facts (negative knowledge, redundancy...)
- Build models from rules and simulate them (stochastic simulation, ODEs generation)

What we can do…

- Abstract interpretation
- Graph rewriting
- Stochasticity/CTMC



Intrinsic Information Carriers in Combinatorial Dynamical Systems

Russ Harmer,[1, 2] Vincent Danos,[3] Jérôme Feret,[4] Jean Krivine,[2] and Walter Fontana[1]

Internal coarse-graining of molecular systems

Jérôme Feret *, Vincent Danos †, Jean Krivine * , Russ Harmer ‡, and Walter Fontana *

*Harvard Medical School, Boston, USA,† University of Edinburgh, Edinburgh, United Kingdom, and ‡CNRS & Paris Diderot, Paris, France

Submitted to Proceedings of the National Academy of Sciences of the United States of America

Graphs, Rewriting and Pathway Reconstruction for Rule-Based Models

Vincent Danos[3], Jérôme Feret[4], Walter Fontana[5], Russell Harmer[1], Jonathan Hayman[4,2], Jean Krivine[1], Chris Thompson-Walsh[2], and Glynn Winskel[2]

Rule-based modelling of cellular signalling

Vincent Danos[1,3,4], Jérôme Feret[2], Walter Fontana[3], Russell Harmer[3,4], and Jean Krivine[5]

Scalable simulation of cellular signaling networks

Vincent Danos[1,4⋆], Jérôme Feret[3], Walter Fontana[1,2], and Jean Krivine[5]

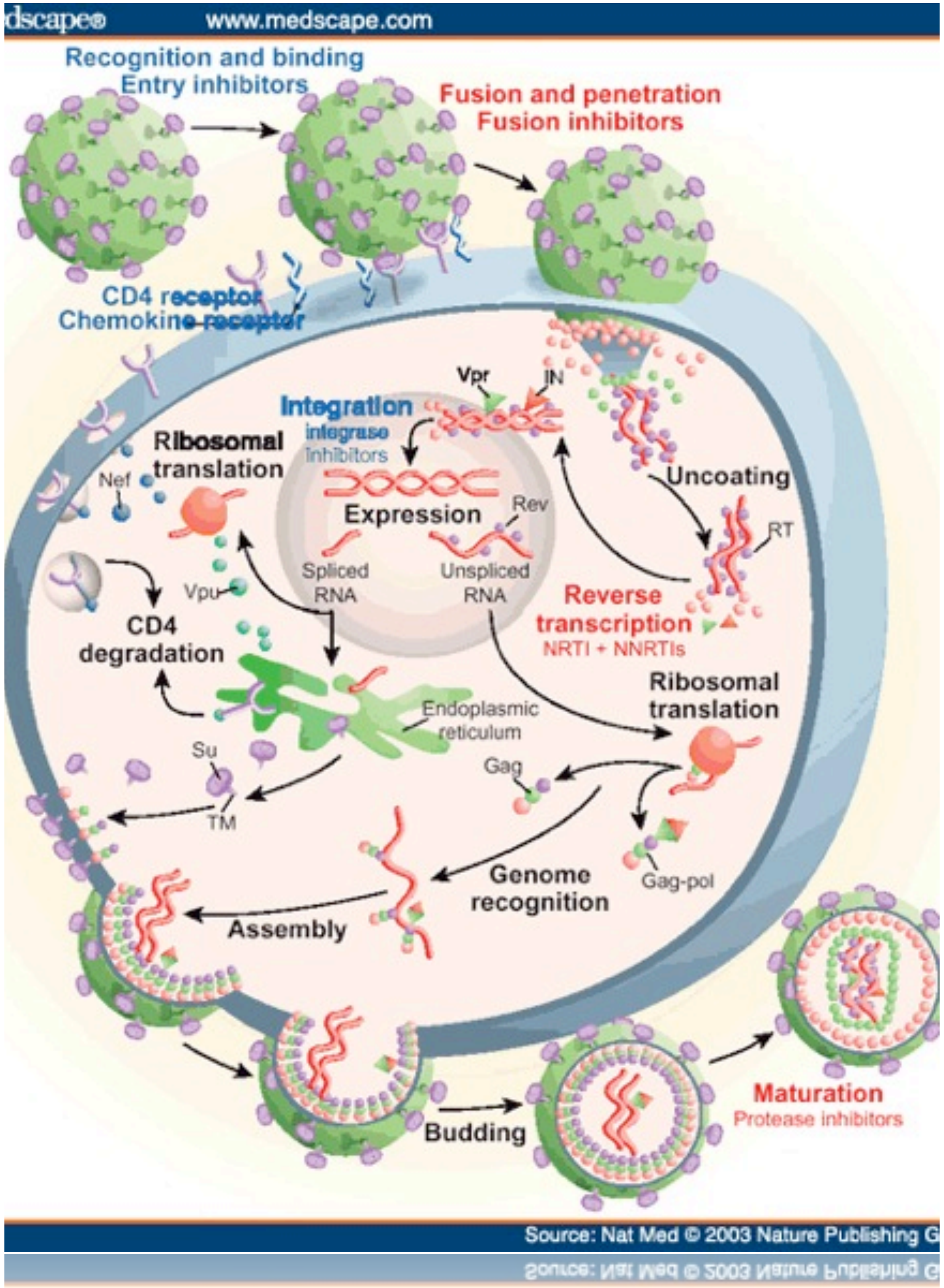
KaSim 3.4

Representation issue

“A model should be a data structure that contains a transparent, formal, and executable representation of the facts it rests upon”

Fontana, POPL’08

Can we do this?



Source: Nat Med © 2003 Nature Publishing G

Operational semantics for the biologist!

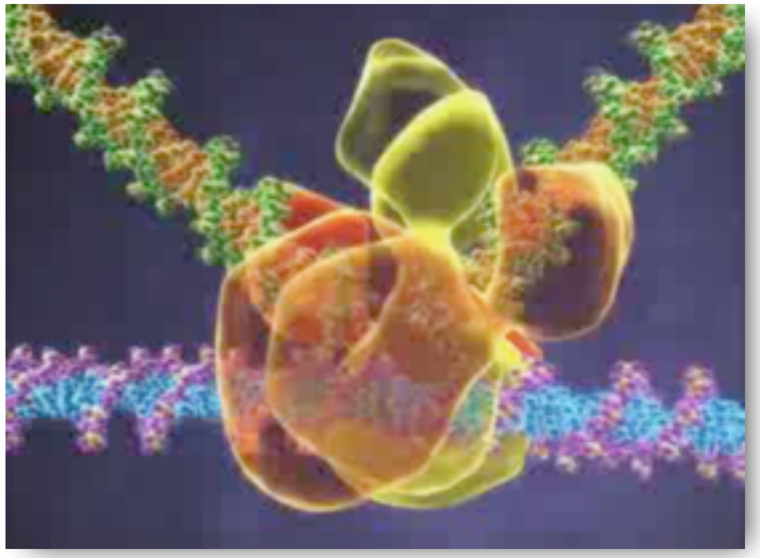
From 2002 International AIDS Conference in Barcelona, GlaxoSmithKline commissioned movie on the life cycle of HIV

Operational semantics for the biologist!

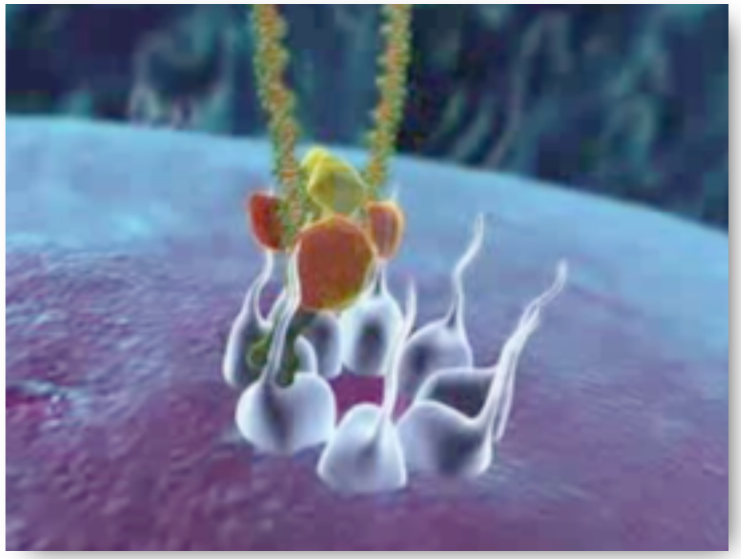
From 2002 International AIDS Conference in Barcelona, GlaxoSmithKline commissioned movie on the life cycle of HIV

Cellular machinery

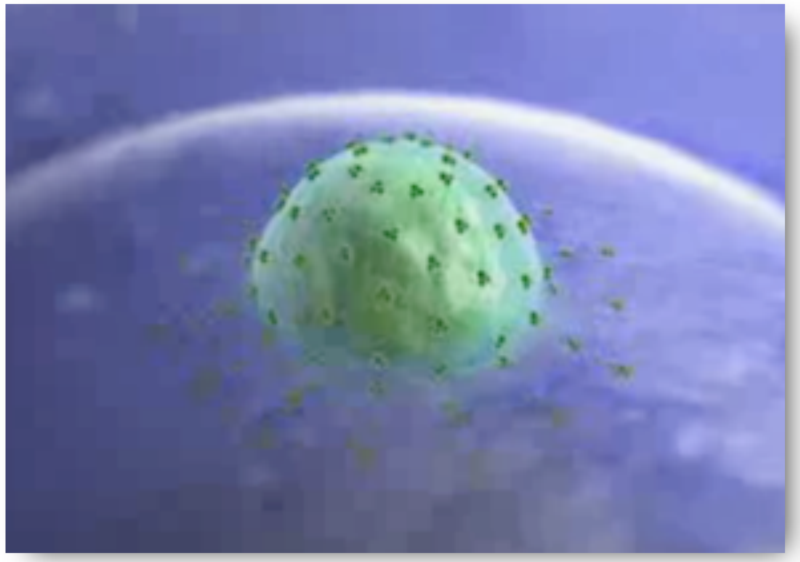
Protein-protein interaction



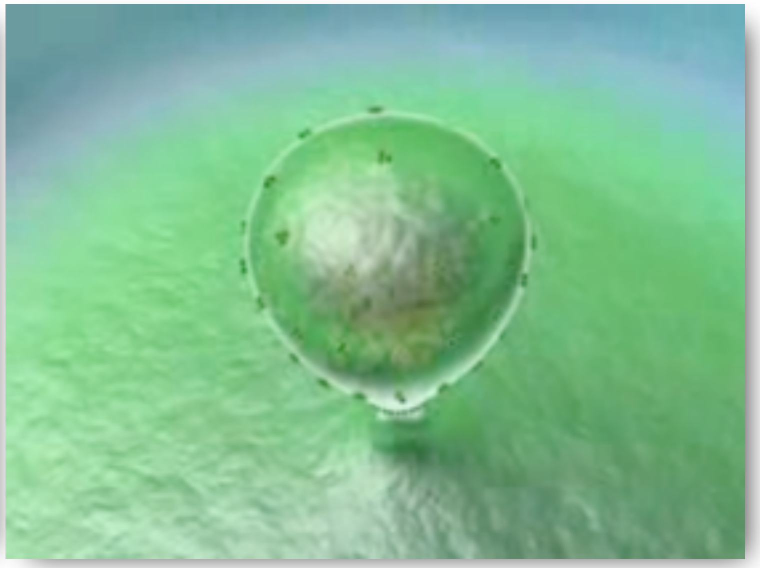
Protein-DNA interaction



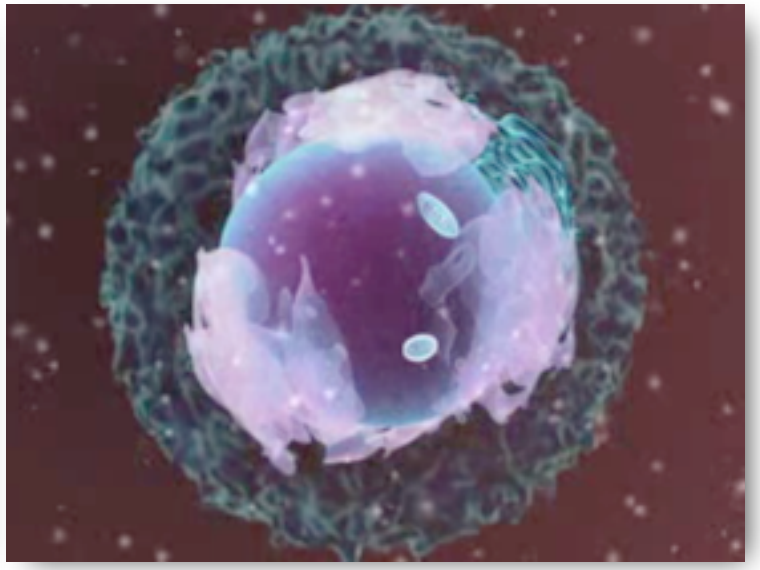
Diffusion



Membrane fusion



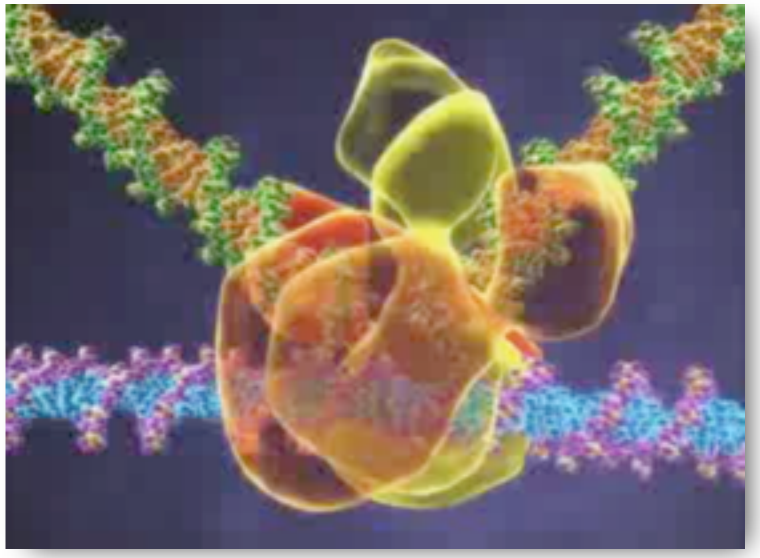
Membrane fission



Static compartments

Cellular machinery

Protein-protein interaction



Protein-DNA interaction

Diffusion

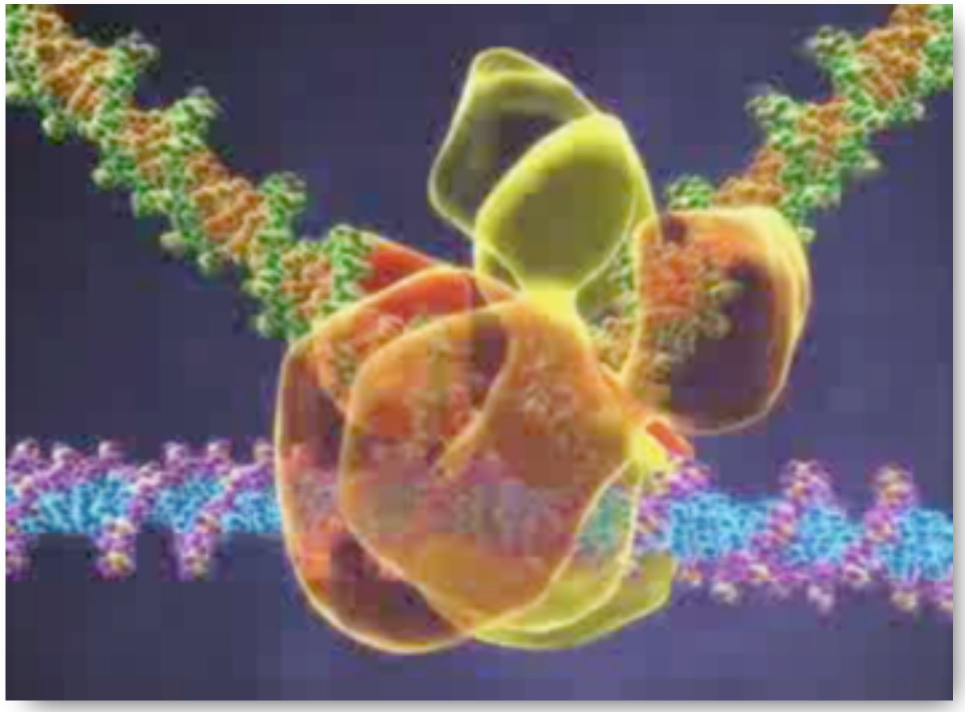
Membrane fusion

Membrane fission

Static compartments

A language factory...

- C0: forming molecules *untyped basic reactions*
- C1: naming molecules *names as a refinements*
- C2: placing molecules *compartments*
- C3: moving molecules *the diffusion problem*



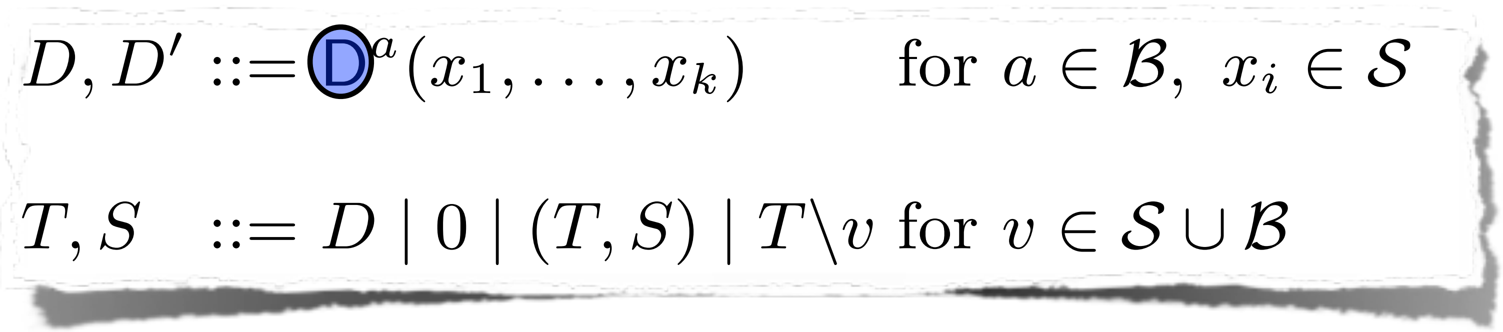
C0: Forming molecules

Terms

$$D, D' ::= \mathsf{D}^a(x_1, \ldots, x_k) \qquad \text{for } a \in \mathcal{B},\ x_i \in \mathcal{S}$$

$$T, S \quad ::= D \mid 0 \mid (T, S) \mid T\backslash v \text{ for } v \in \mathcal{S} \cup \mathcal{B}$$

Terms



$$D, D' ::= \textcircled{\mathsf{D}}^a(x_1, \ldots, x_k) \qquad \text{for } a \in \mathcal{B},\ x_i \in \mathcal{S}$$

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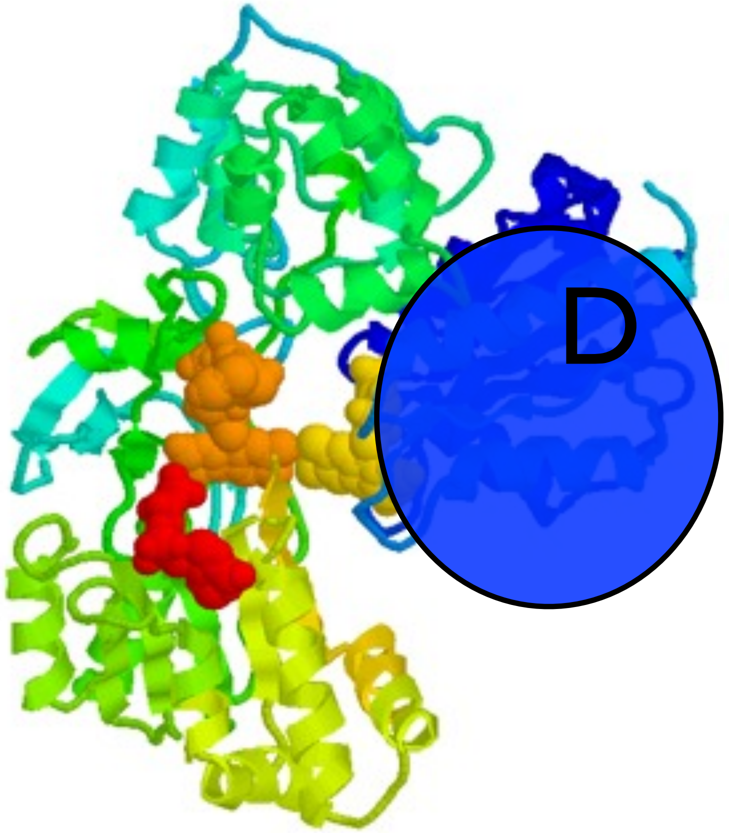
Terms

$$\begin{aligned} D, D' &::= \textcircled{D}^{a}(x_1, \ldots, x_k) && \text{for } a \in \mathcal{B},\ x_i \in \mathcal{S} \\ T, S &::= D \mid 0 \mid (T, S) \mid T \backslash v && \text{for } v \in \mathcal{S} \cup \mathcal{B} \end{aligned}$$



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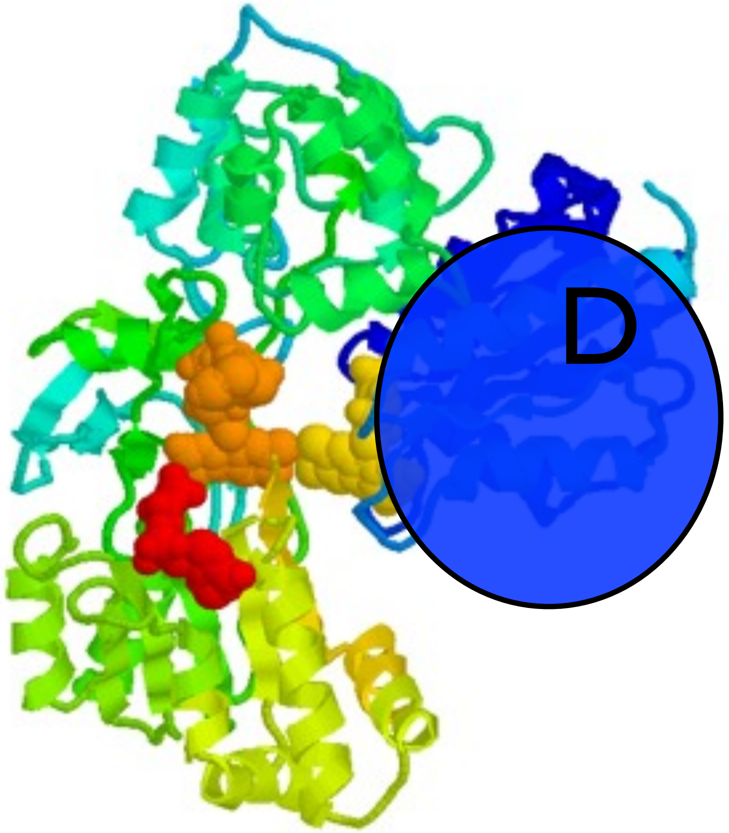

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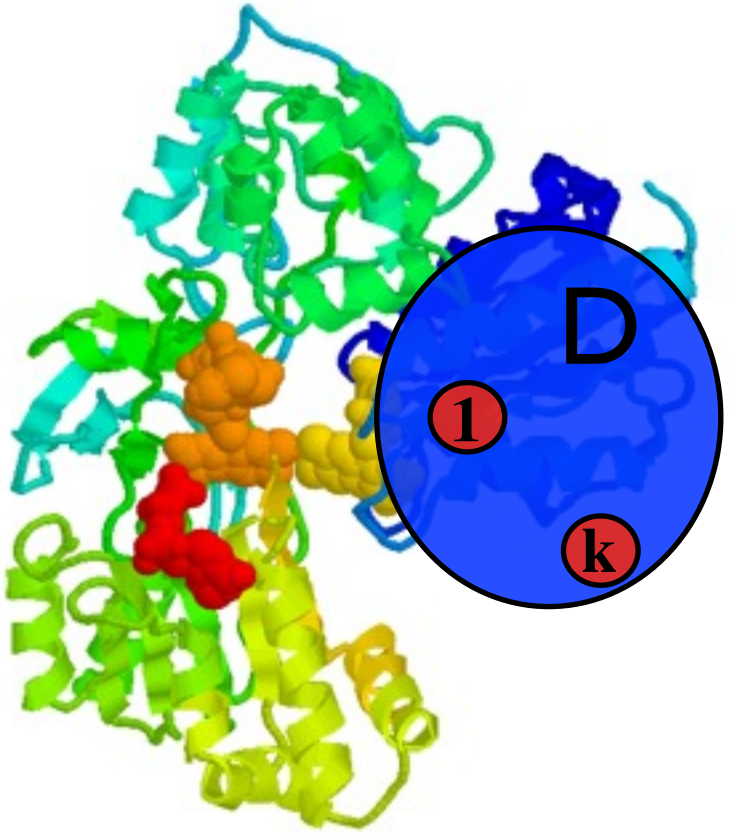

Terms

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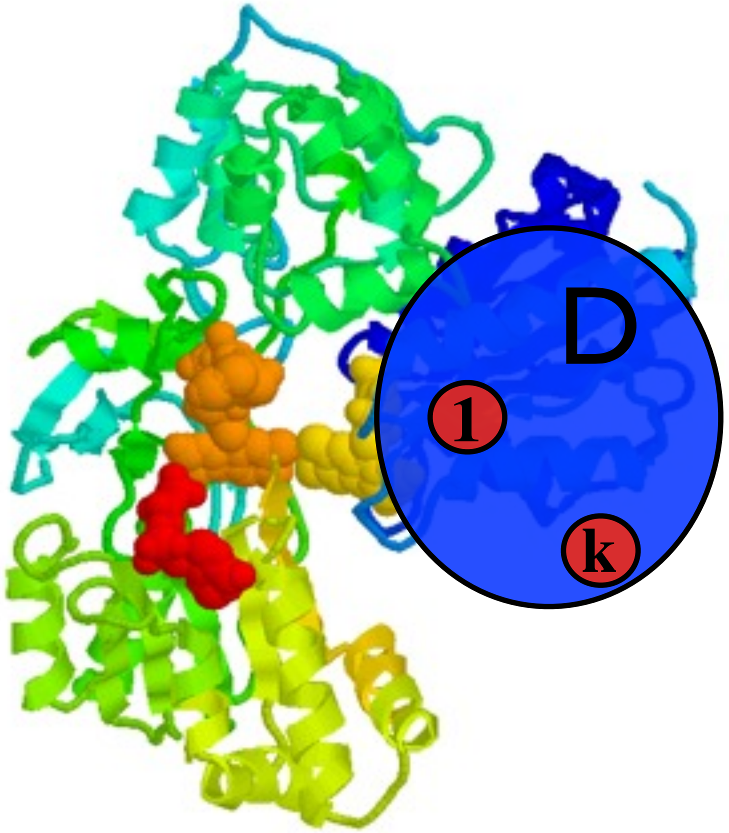
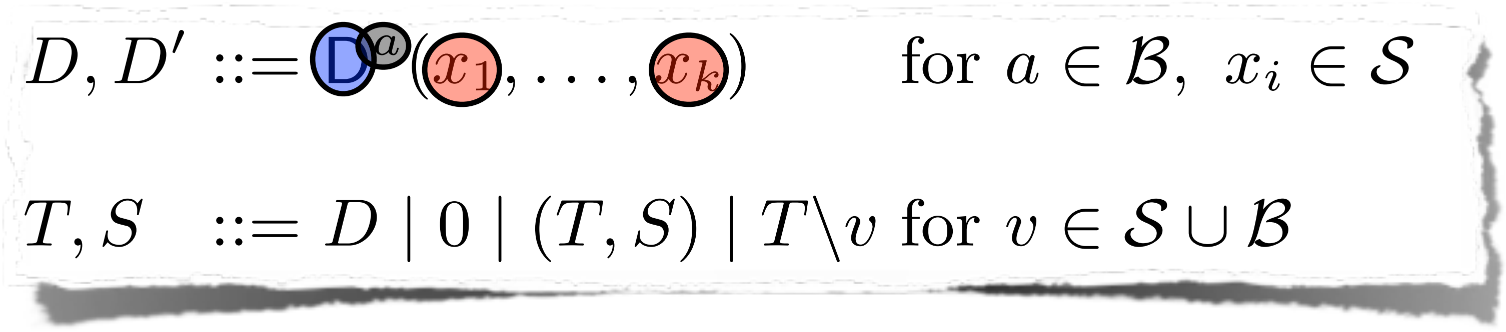
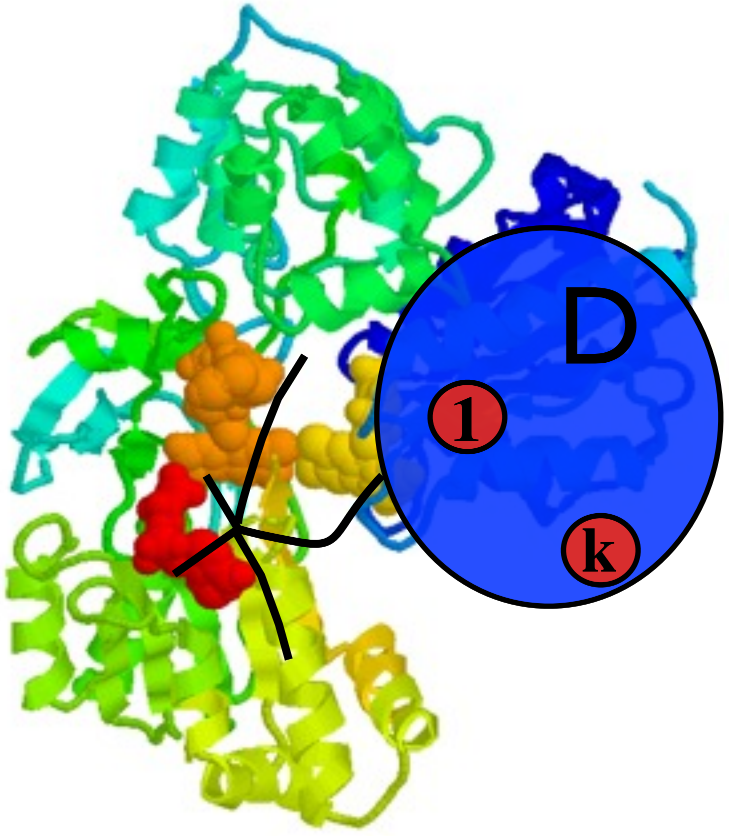


Terms



$D, D' ::= \mathsf{D}^{a}(x_1, \ldots, x_k)$ for $a \in \mathcal{B},\ x_i \in \mathcal{S}$

$T, S ::= D \mid 0 \mid (T, S) \mid T\backslash v$ for $v \in \mathcal{S} \cup \mathcal{B}$



Terms

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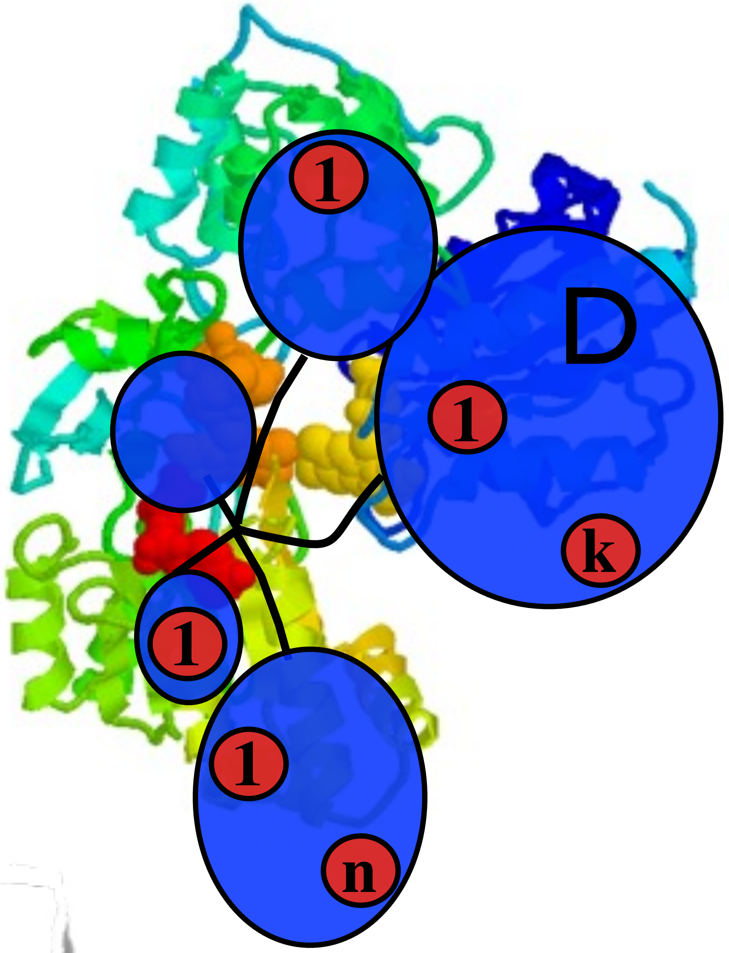


$$\begin{aligned}
(S, T) &\equiv (T, S) \\
(T, S), T' &\equiv T, (S, T') \\
T, 0 &\equiv T \\
T\backslash u &\equiv T \quad u \notin fn(T) \\
(T\backslash u)\backslash v &\equiv (T\backslash v)\backslash u \\
T\backslash u &\equiv (T\{v/u\})\backslash v \quad v \notin fn(T) \\
T\backslash u, S &\equiv (T, S)\backslash u \quad u \notin fn(S)
\end{aligned}$$

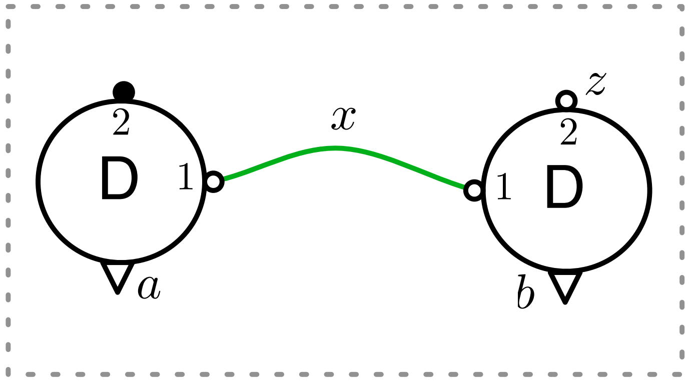
Graphical notation

$$\begin{aligned} \mathit{fn}\,(\mathsf{D}^a(x_1,\ldots,x_k)) &= \textstyle\bigcup_i x_i \cup \{a\} \\ \mathit{fn}(0) &= \emptyset \\ \mathit{fn}(T,S) &= \mathit{fn}(T) \cup \mathit{fn}(S) \\ \mathit{fn}(T\backslash v) &= \mathit{fn}(T) - \{v\} \end{aligned}$$

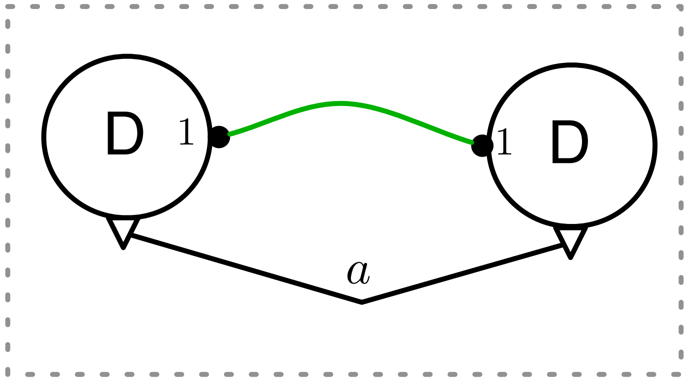
free names

bound names

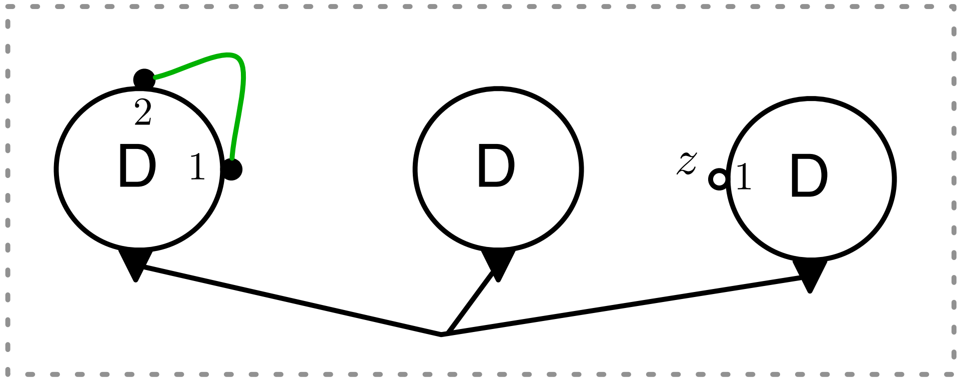
shared names



$T = \left(\mathsf{D}^a(x,y), \mathsf{D}^b(x,z)\right) \backslash y$



$S = (\mathsf{D}^a(x), \mathsf{D}^a(x)) \backslash x$



$U = (\mathsf{D}^a(x,x), \mathsf{D}^a(z), \mathsf{D}^a()) \backslash a \backslash x$

Dynamics

Contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet]\backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet]\,\{u/v\} \quad u, v \in \mathcal{B} \cup \mathcal{S}$$

Context free rewriting:

$$\frac{r = \langle T, S\rangle \in \mathcal{R} \quad T' \equiv \mathbb{C}[T] \quad S' \equiv \mathbb{C}[S]}{T' \to_r S'}$$

Dynamics

Contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet]\backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet]\,\{u/v\} \qquad u, v \in \mathcal{B} \cup \mathcal{S}$$

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$$\frac{r = \langle T, S\rangle \in \mathcal{R} \quad T' \equiv \mathbb{C}[T] \quad S' \equiv \mathbb{C}[S]}{T' \rightarrow_r S'}$$

A rule

Dynamics

Contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet]\backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet]\,\{u/v\} \quad u, v \in \mathcal{B} \cup \mathcal{S}$$

Context free rewriting:

$$\frac{r = \langle T, S\rangle \in \mathcal{R} \quad T' \equiv \mathbb{C}[T] \quad S' \equiv \mathbb{C}[S]}{T' \rightarrow_r S'}$$

A rule A match for T in T’

Dynamics

Contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet]\backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet]\,\{u/v\} \quad u, v \in \mathcal{B} \cup \mathcal{S}$$

Context free rewriting:

$$\frac{r = \langle T, S \rangle \in \mathcal{R} \quad T' \equiv \mathbb{C}[T] \quad S' \equiv \mathbb{C}[S]}{T' \rightarrow_r S'}$$

An r-generated transition

A rule

A match for T in T'

Generators

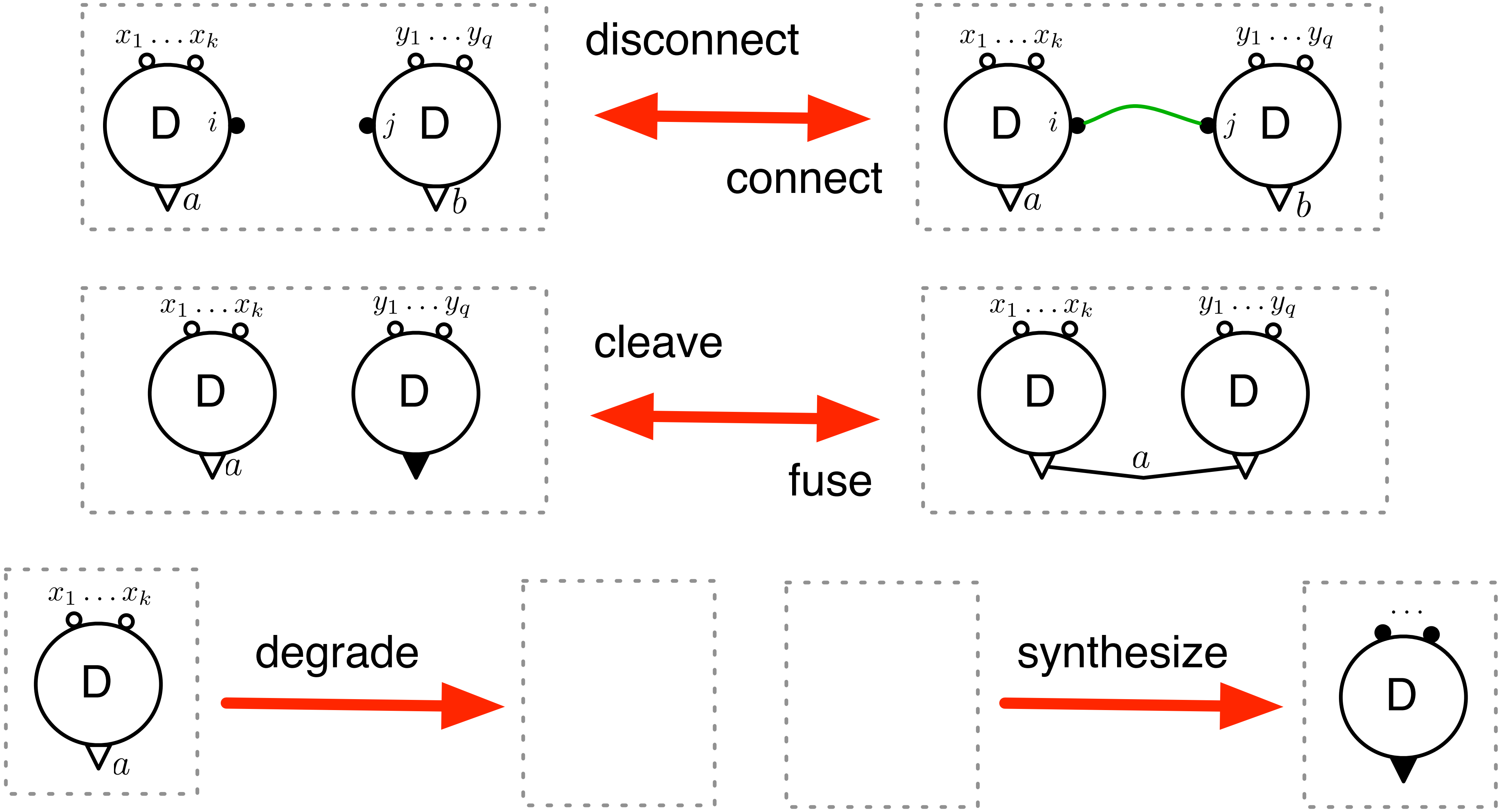
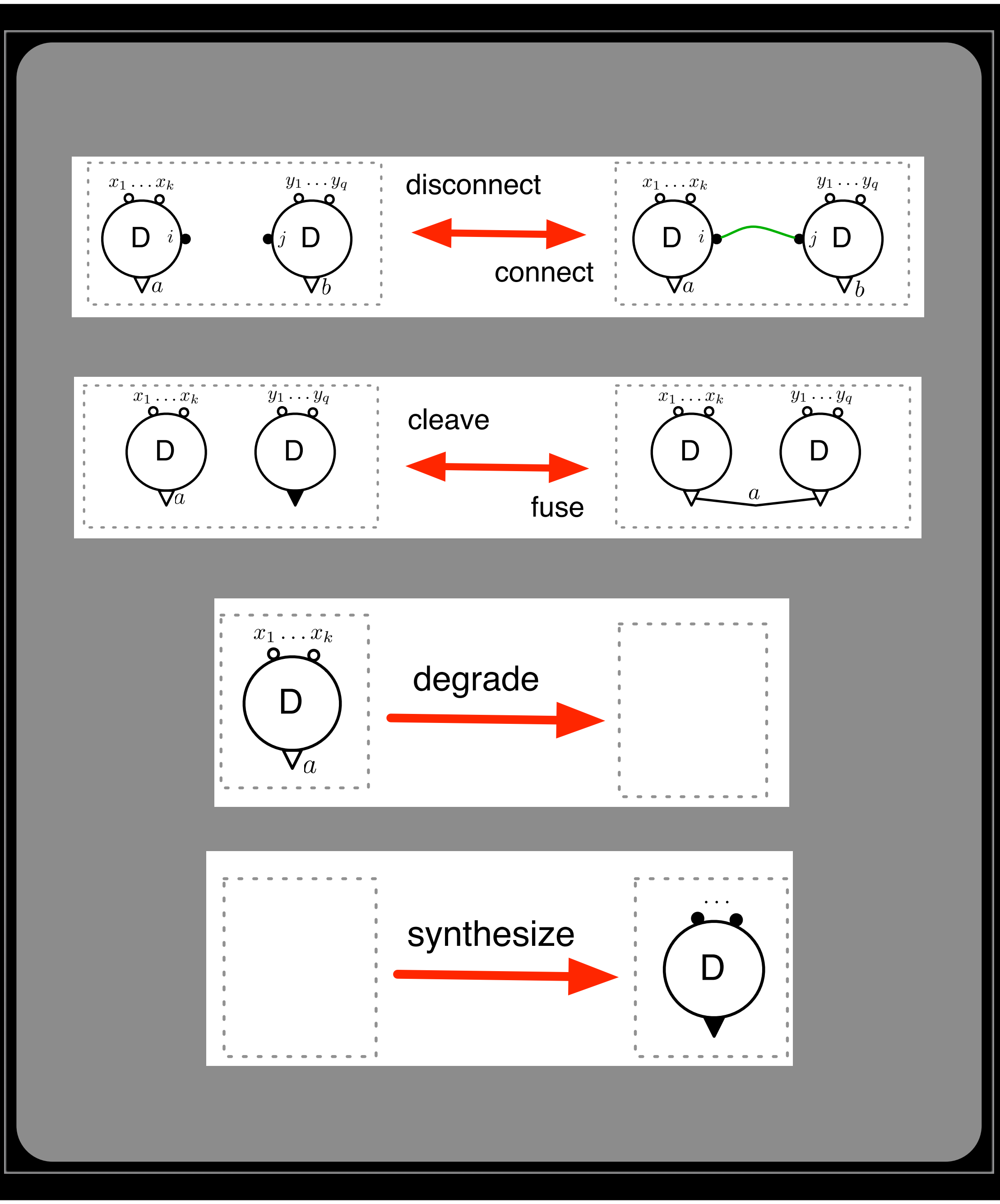
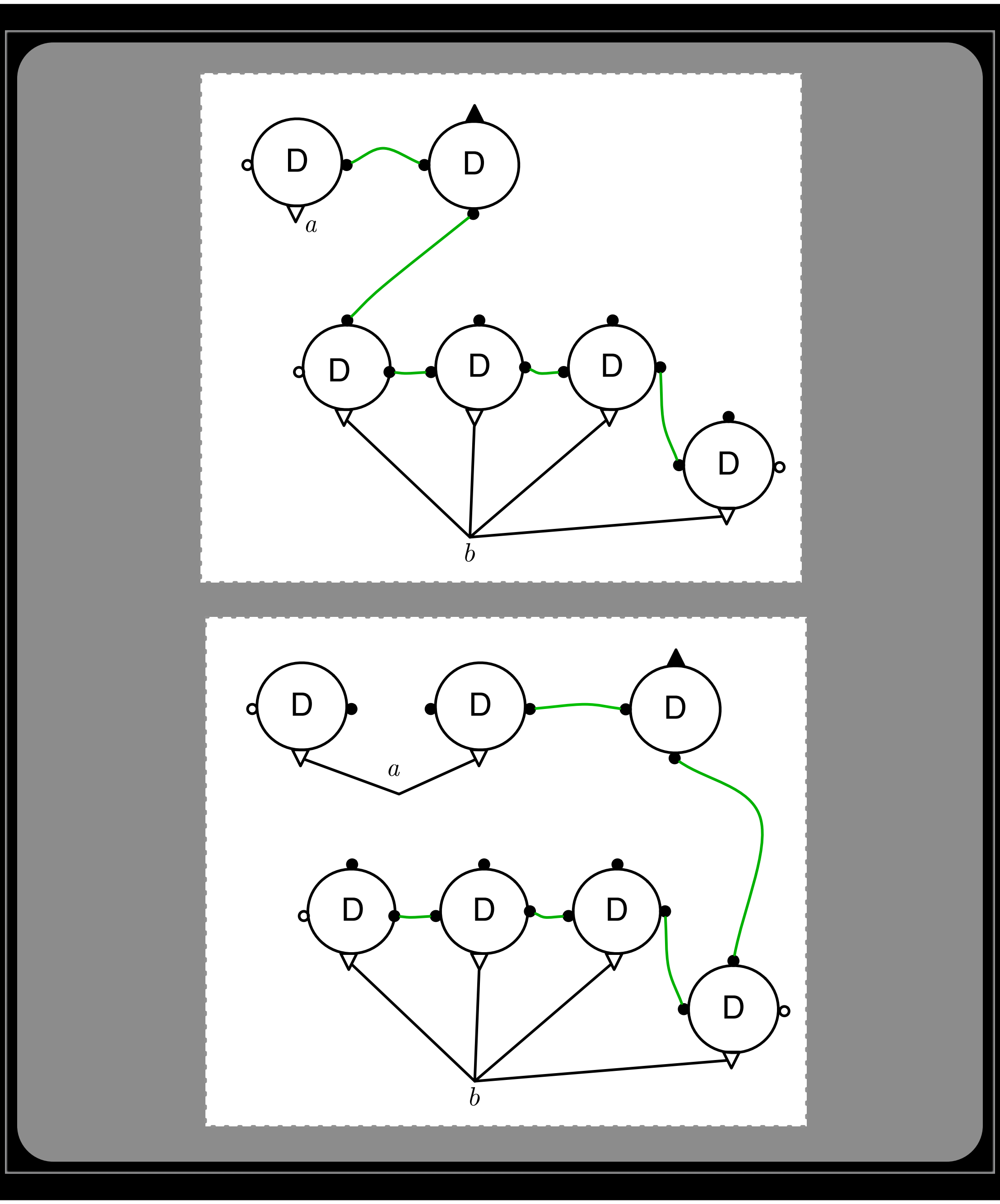


Fig. 1: Generators for $\mathcal{C}_0$.

Generating rules

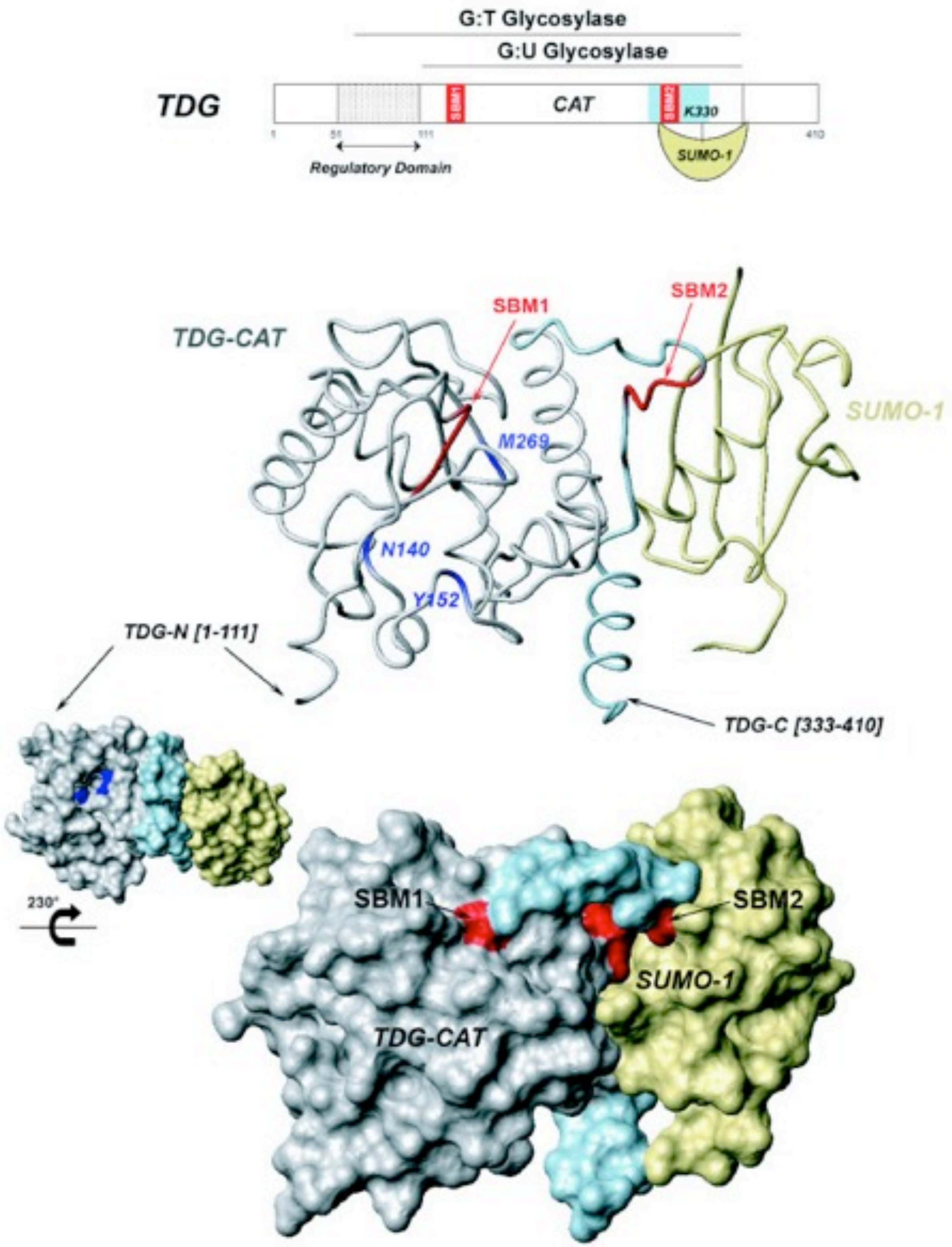


Generators toolbox



A rule of the model

(using compose and refine)



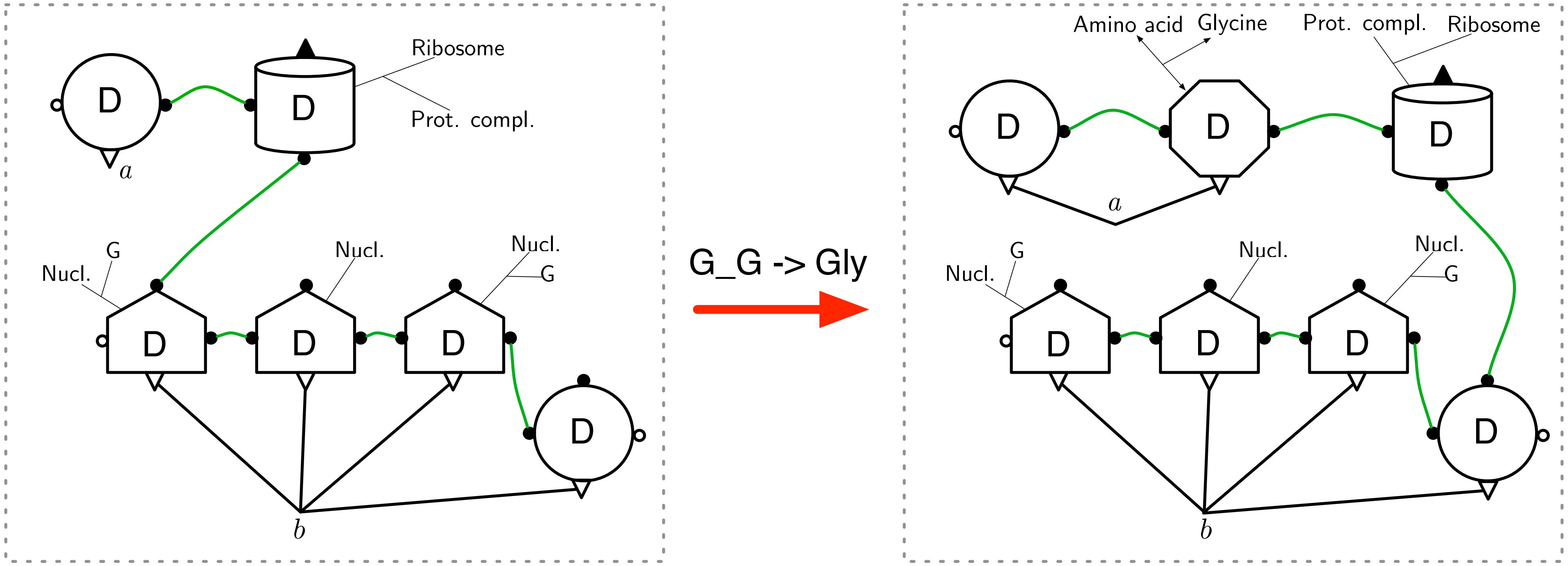
C1: Naming molecules

Names as refinements

$$\begin{array}{lll}
D, D' ::= \mathsf{D}^a_m(x_1, \ldots, x_k) & a \in \mathcal{B},\ m \in \mathcal{M},\ x_i \in \mathcal{S} & \text{(domains)} \\
I, J ::= \mathsf{Info}_m & \mathsf{info} \in \mathcal{I},\ m \in \mathcal{M} & \text{(info)} \\
T, S ::= 0 \mid D \mid I \mid (T, S) \mid T \backslash v & \text{for } v \in \mathcal{S} \cup \mathcal{B} \cup \mathcal{M} & \text{(named terms)}
\end{array}$$

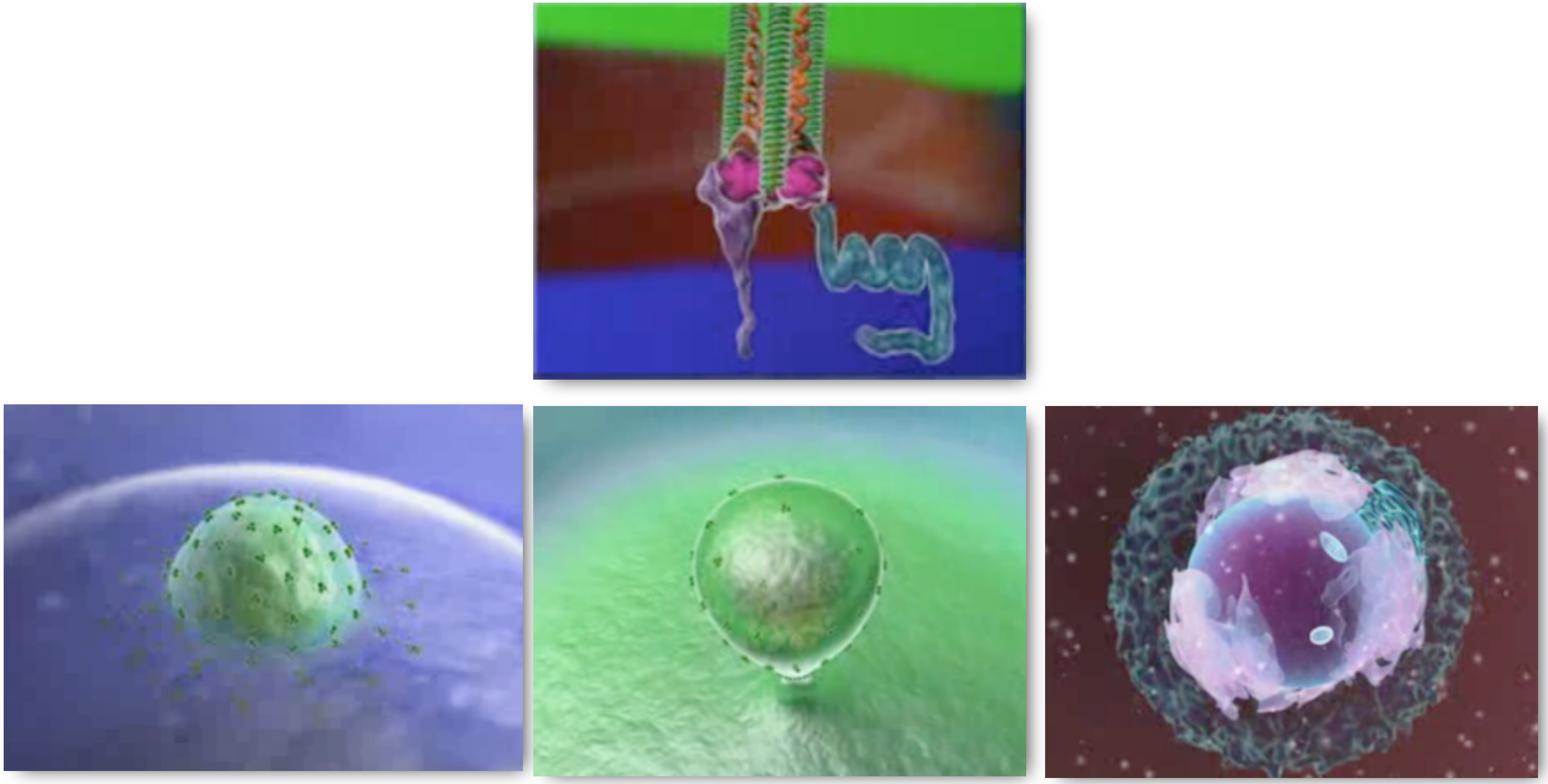
$\mathsf{D}^a_m(x)$	A domain
$\mathsf{D}^a_m(x), \mathsf{Tyrosine}_m$	A Tyrosine domain
$\mathsf{D}^a_m(x), \mathsf{Tyr}_m, \mathsf{phos}_m$	A pho'ylated Tyrosine domain

Partial information!



$$(\text{Concretize})\ \mathsf{D}^a_m(x_1,\ldots,x_k) \to \mathsf{D}^a_m(x_1,\ldots,x_k), \mathsf{Info}_m$$

$$(\text{Abstract})\quad \mathsf{D}^a_m(x_1,\ldots,x_k), \mathsf{Info}_m \to \mathsf{D}^a_m(x_1,\ldots,x_k)$$



C2: Placing molecules

Terms

$$T, S ::= \cdots \mid \mathsf{C}_m(T) \mid X \quad m \in \mathcal{M},\ X \in \mathcal{V} \text{ (local terms)}$$

$$P, Q ::= (T \parallel P) \mid P \backslash v \quad v \in \mathcal{M} \cup \mathcal{S} \cup \mathcal{B} \quad \text{(wide terms)}$$

Terms

Compartments

$$T, S ::= \cdots \mid \mathsf{C}_m(T) \mid X \quad m \in \mathcal{M},\; X \in \mathcal{V} \text{ (local terms)}$$

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Terms

Compartments Variables

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Terms

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Membrane patch!

Terms

Compartments   Variables

$$T, S ::= \cdots \mid \mathsf{C}_m(T) \mid X \quad m \in \mathcal{M},\ X \in \mathcal{V} \text{ (local terms)}$$

$$P, Q ::= (T \parallel P) \mid P\backslash v \quad v \in \mathcal{M} \cup \mathcal{S} \cup \mathcal{B} \quad \text{(wide terms)}$$

Membrane patch!

$$\begin{aligned}
\mathsf{C}_m(T) &\equiv \mathsf{C}_m(T') && \text{if } T \equiv T' \\
\mathsf{C}_m(T\backslash u) &\equiv \mathsf{C}_m(T)\backslash u && \text{if } u \neq m \\
T\backslash u \parallel P &\equiv (T \parallel P)\backslash u && u \notin fn(P) \\
T \parallel P\backslash u &\equiv (T \parallel P)\backslash u && u \notin fn(T)
\end{aligned}$$

Terms

Compartments

Variables

$$T, S ::= \cdots \mid \mathsf{C}_m(T) \mid X \quad m \in \mathcal{M},\ X \in \mathcal{V} \ \text{(local terms)}$$

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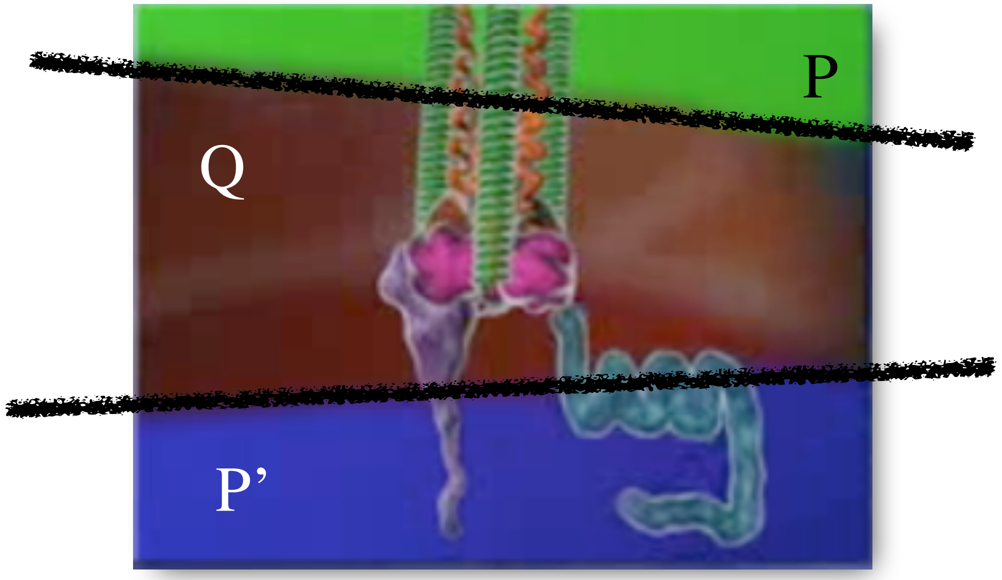
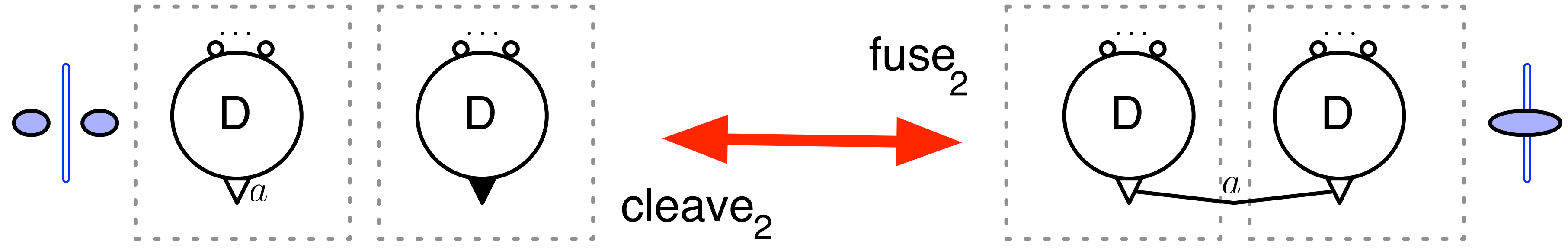
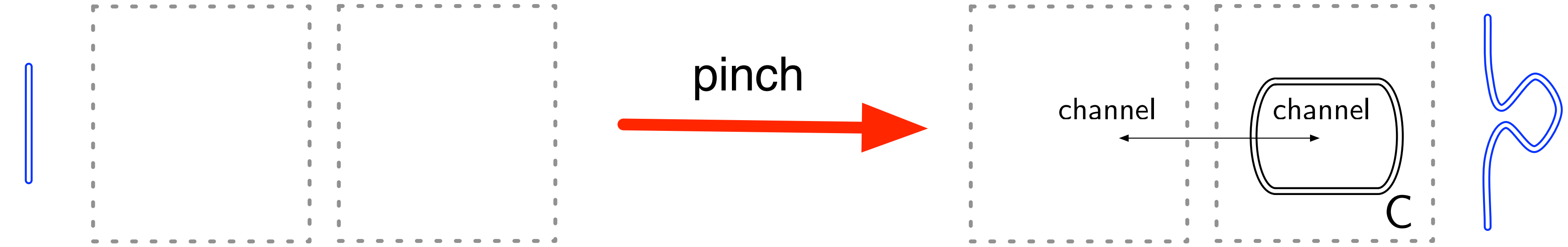


Generators 1/2

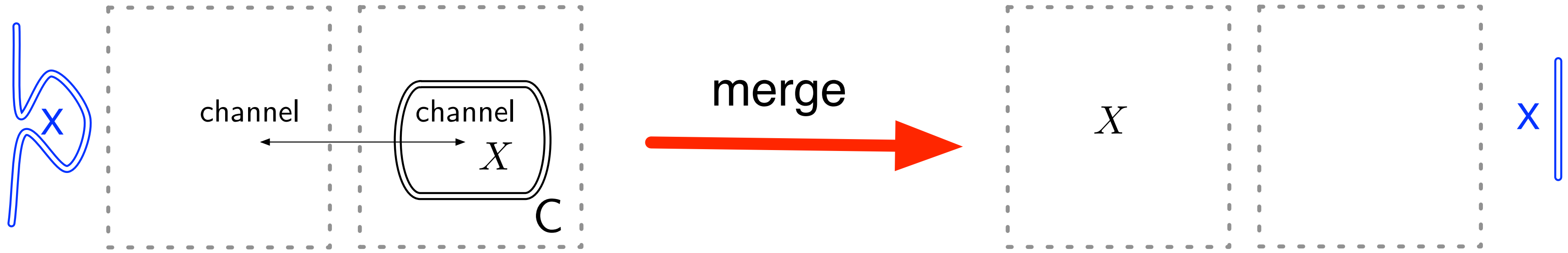
Informal Left hand side Right hand side Informal



$$\mathsf{D}^a(x_1,\ldots,x_k) \parallel \mathsf{D}^b(y_1,\ldots,y_q)\backslash b \to \mathsf{D}^a(x_1,\ldots,x_k) \parallel \mathsf{D}^a(y_1,\ldots,y_q)$$

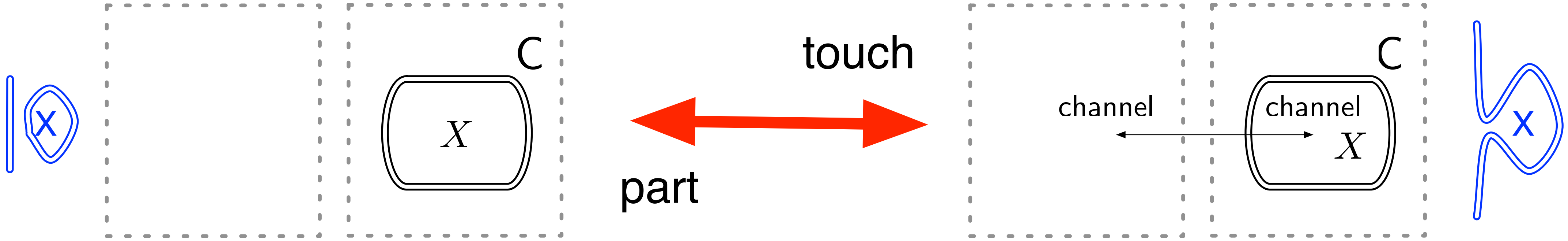


$$0 \parallel 0 \to (\mathsf{channel}_m \parallel \mathsf{C}(\mathsf{channel}_m))\backslash m$$

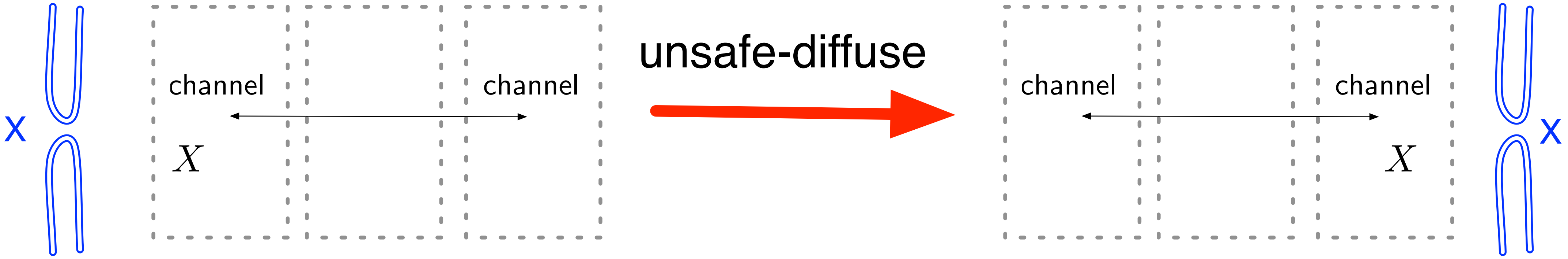


$$(\mathsf{channel}_m \parallel \mathsf{C}(\mathsf{channel}_m, X))\backslash m \to X \parallel 0$$

Generators 2/2

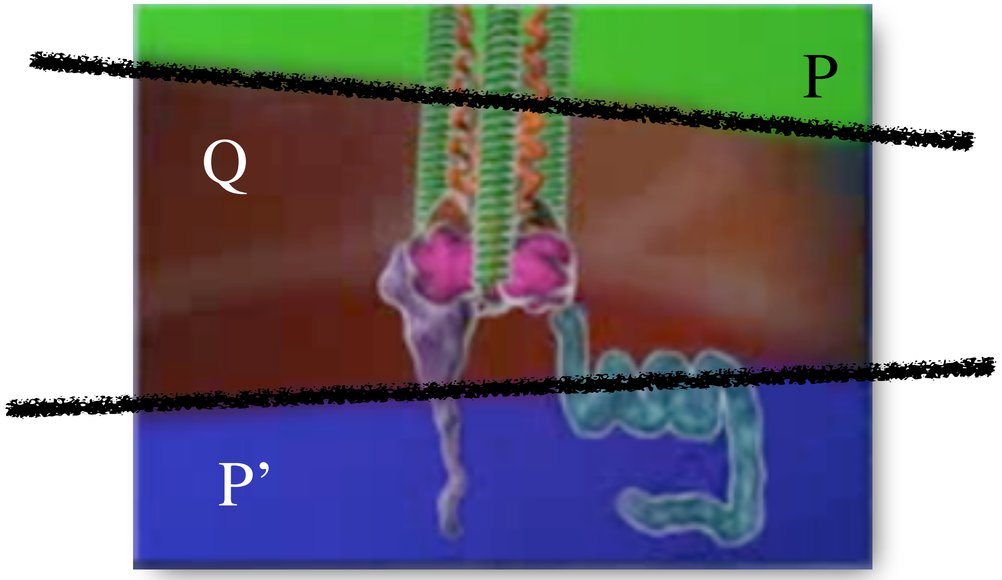


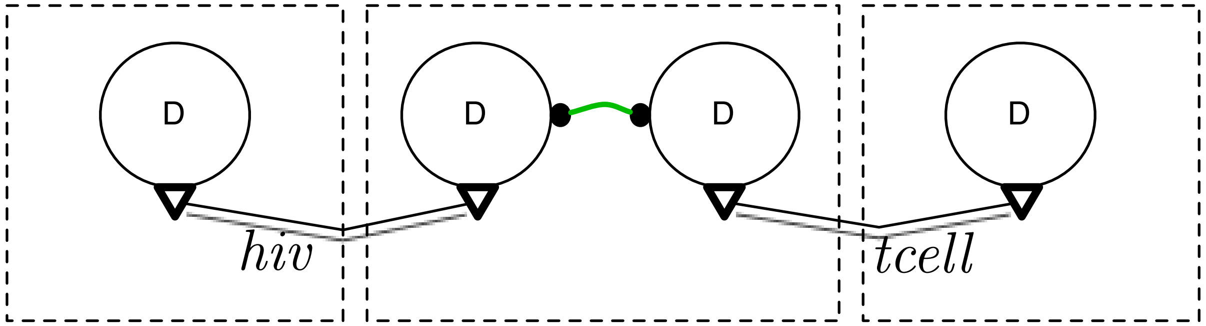
$$0 \parallel \text{C}(X) \to (\text{channel}_m \parallel \text{C}(\text{channel}_m, X))\backslash m$$



$$(X, \text{channel}_m \parallel 0 \parallel \text{channel}_m)\backslash m \to (\text{channel}_m \parallel 0 \parallel \text{channel}_m, X)\backslash m$$

Pattern matching issue





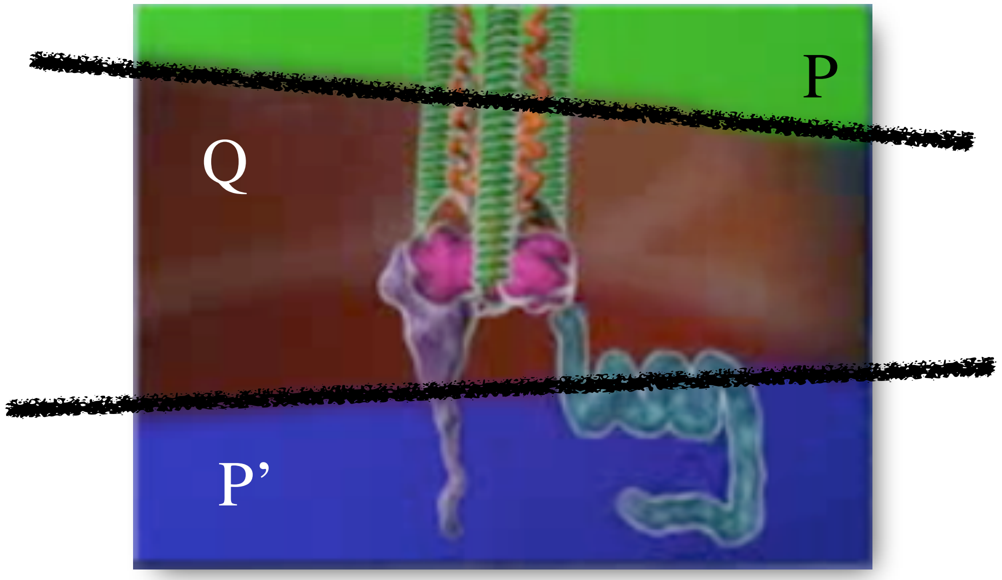
$$\mathsf{D}^{hiv}_{m}() \parallel (\mathsf{D}^{hiv}_{n}(x), \mathsf{D}^{tcell}_{o}(x))\backslash x \parallel \mathsf{D}^{tcell}_{p}()$$

HIV membrane

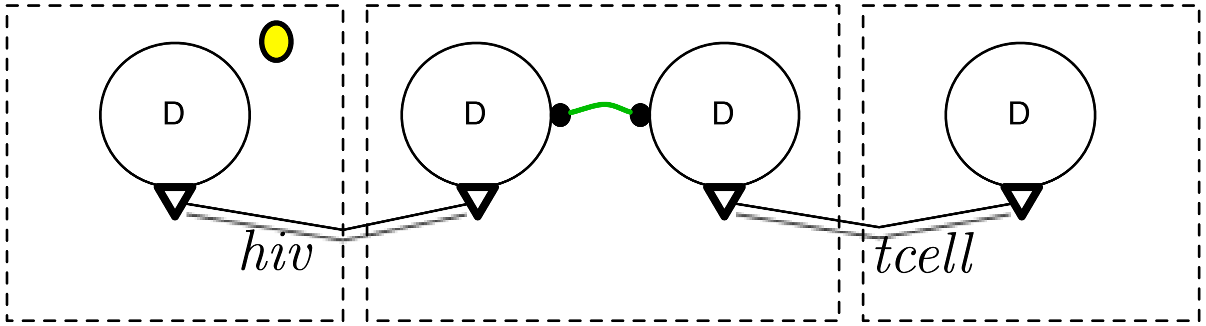
T-cell membrane

Define contexts with n holes that preserve projective distance...

Pattern matching issue



Proj. dist



$$\mathsf{D}^{hiv}_{m}() \parallel (\mathsf{D}^{hiv}_{n}(x), \mathsf{D}^{tcell}_{o}(x))\backslash x \parallel \mathsf{D}^{tcell}_{p}()$$

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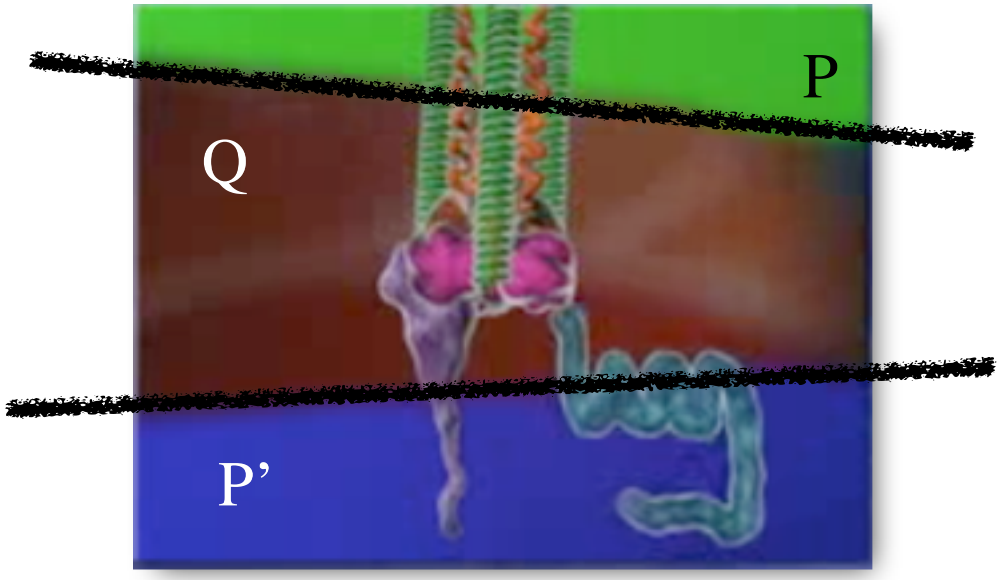

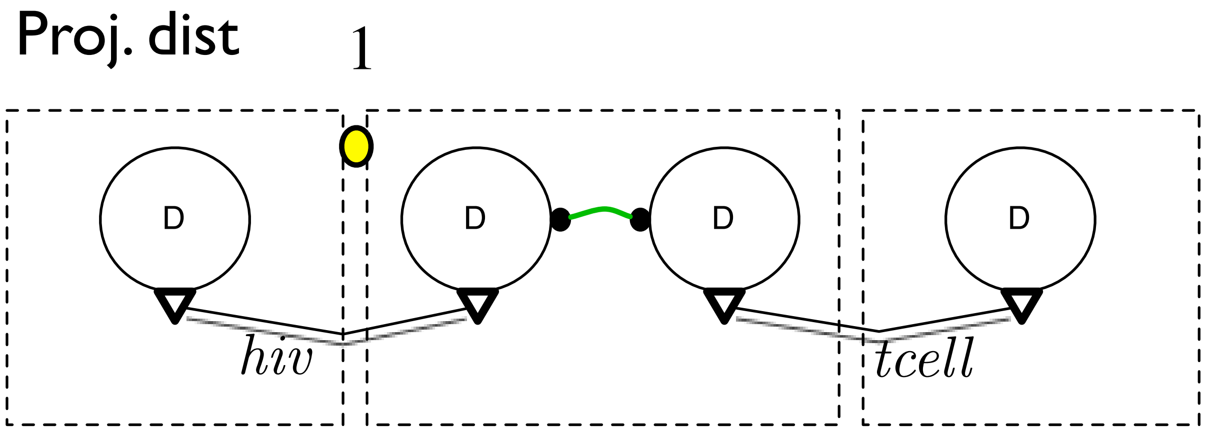

$$\mathsf{D}^{hiv}_{m}() \;\|\; (\mathsf{D}^{hiv}_{n}(x), \mathsf{D}^{tcell}_{o}(x))\backslash x \;\|\; \mathsf{D}^{tcell}_{p}()$$

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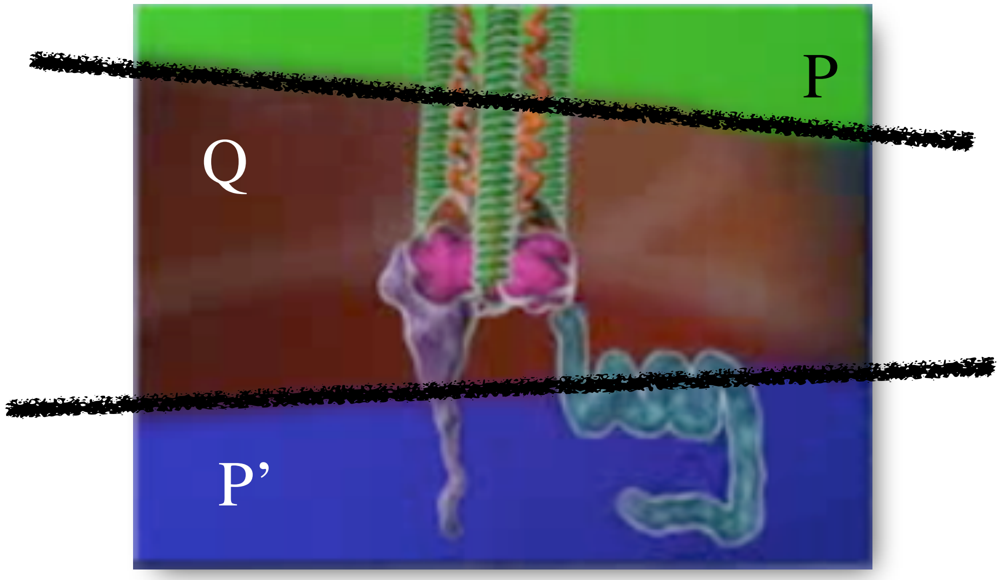

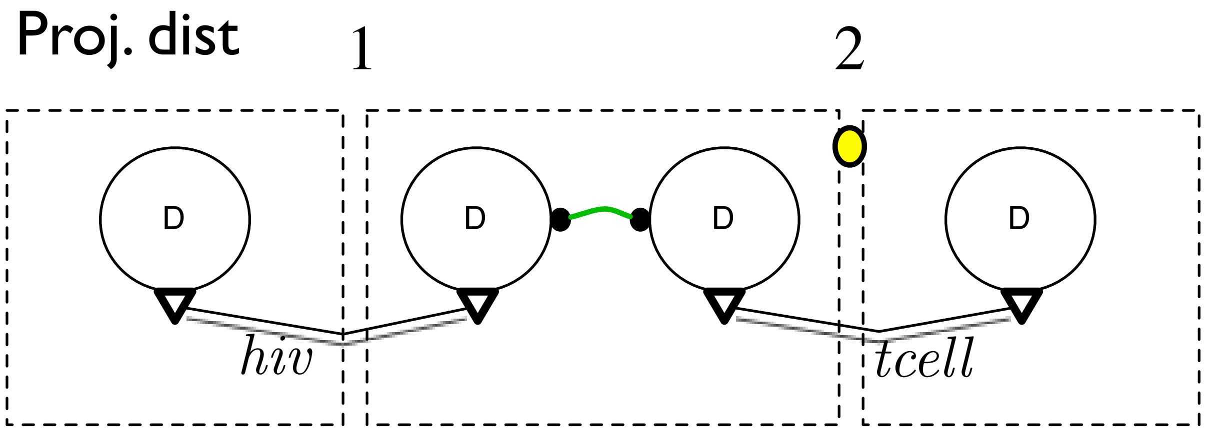

$$\mathrm{D}^{hiv}_{m}() \parallel (\mathrm{D}^{hiv}_{n}(x), \mathrm{D}^{tcell}_{o}(x))\backslash x \parallel \mathrm{D}^{tcell}_{p}()$$

HIV membrane

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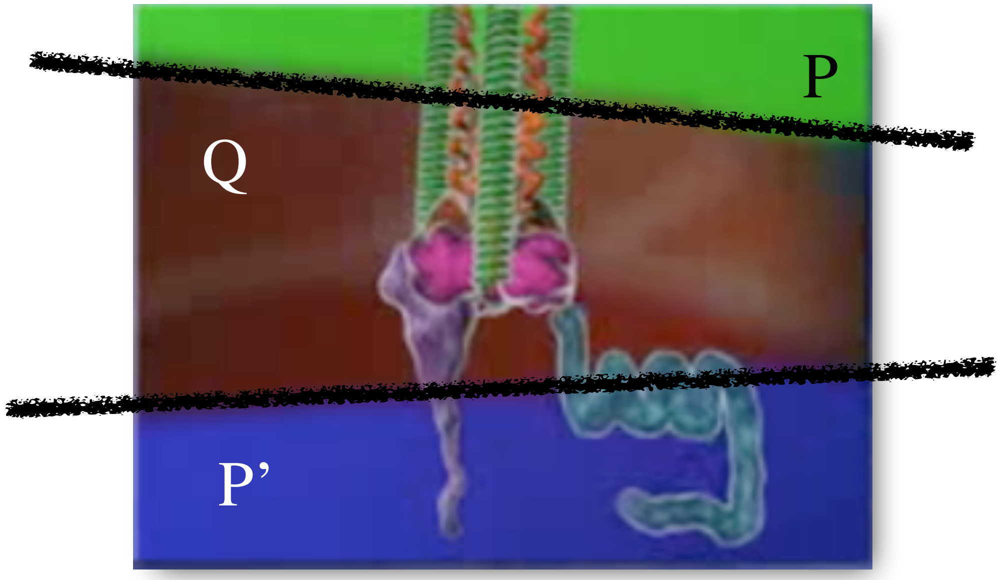
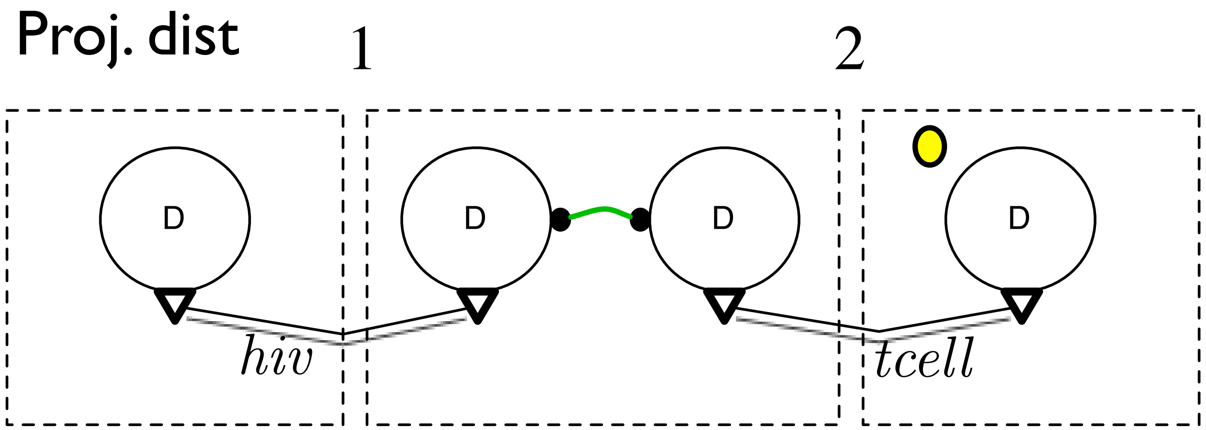
Define contexts with n holes that preserve projective distance...

Pattern matching issue





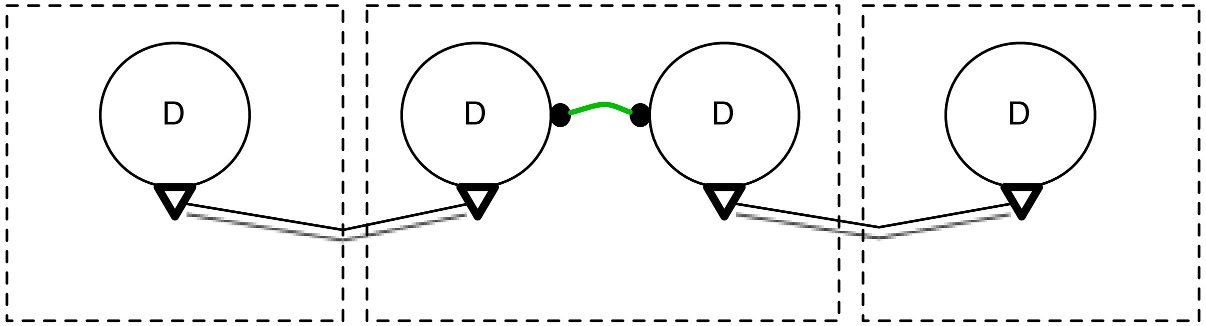
$$\mathsf{D}^{hiv}_{m}() \,\|\, (\mathsf{D}^{hiv}_{n}(x), \mathsf{D}^{tcell}_{o}(x))\backslash x \,\|\, \mathsf{D}^{tcell}_{p}()$$

HIV membrane

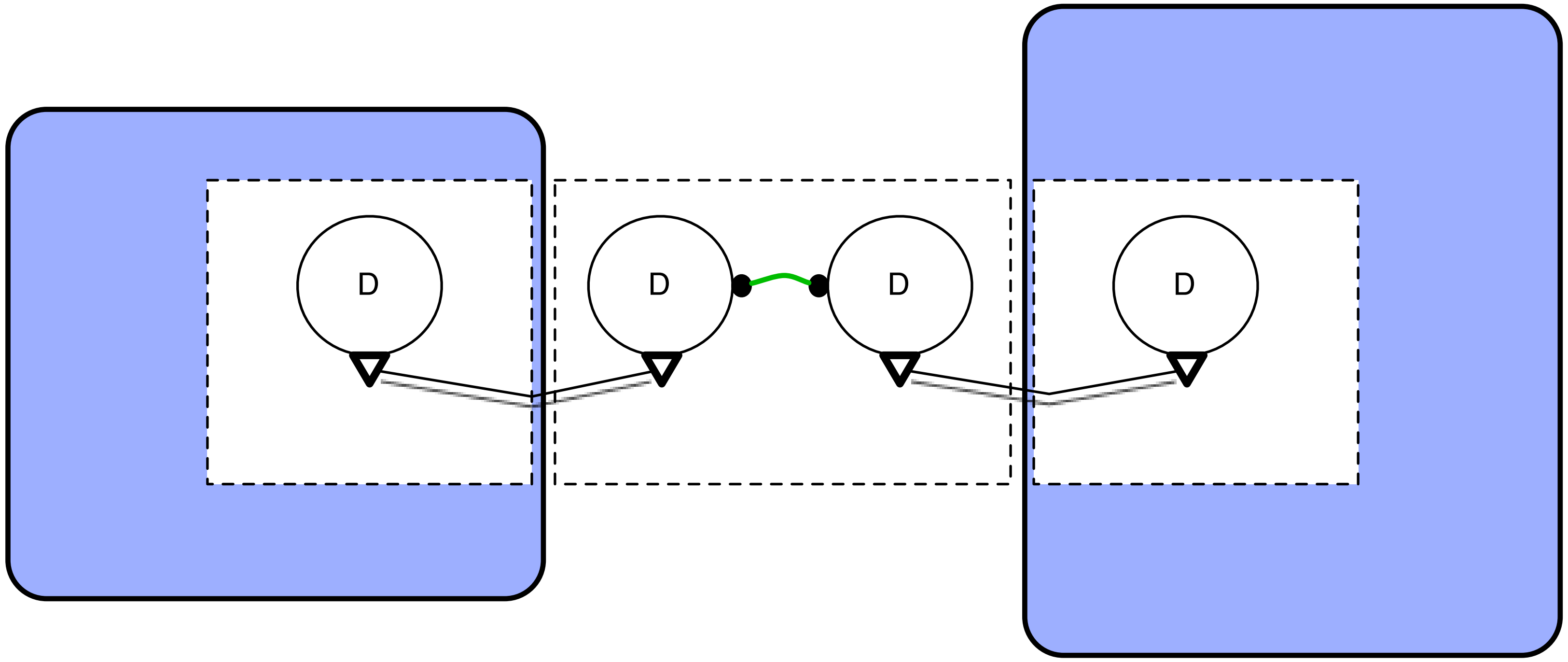
T-cell membrane

Define contexts with n holes that preserve projective distance...

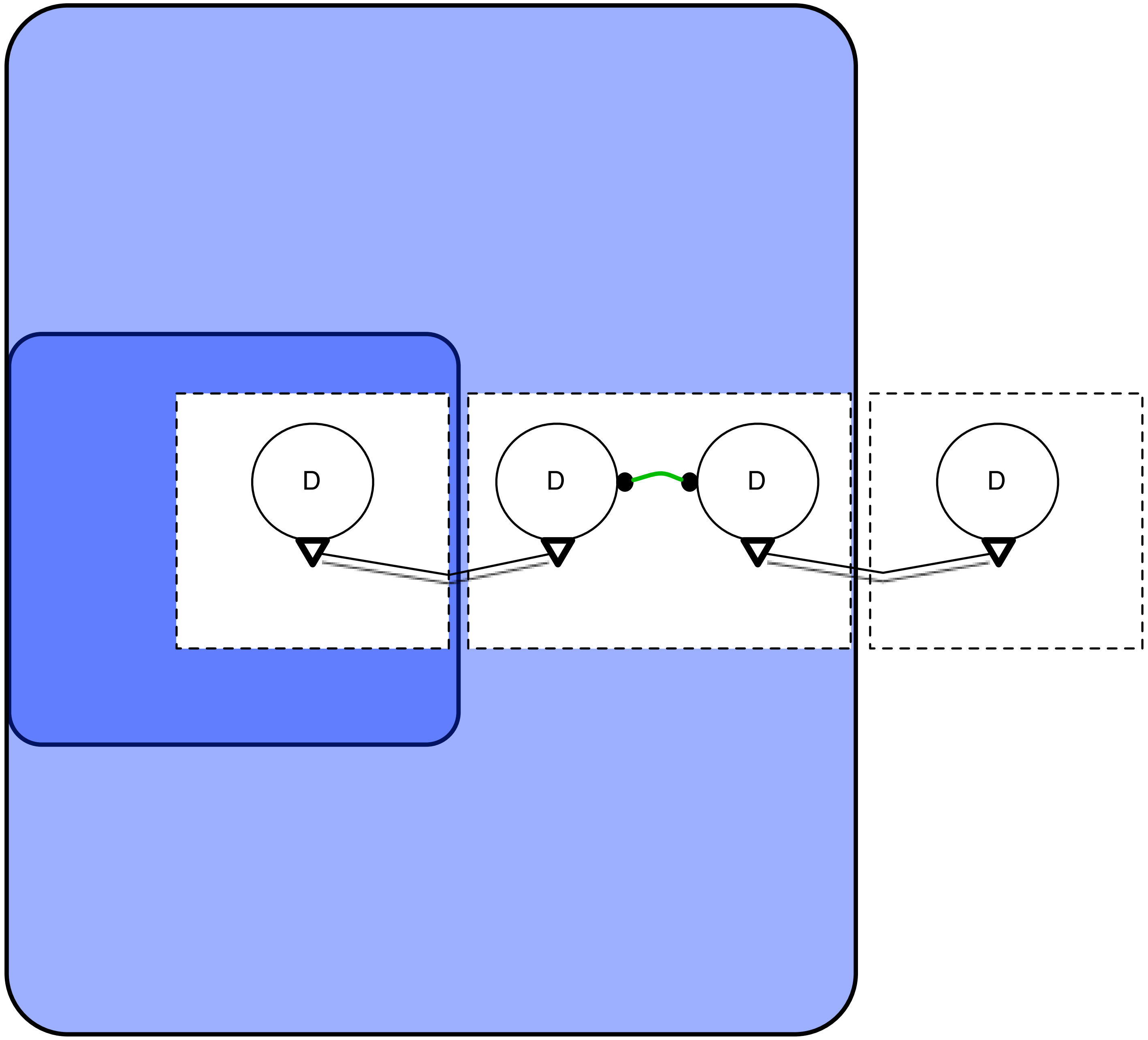
Valid contexts with 3 holes...



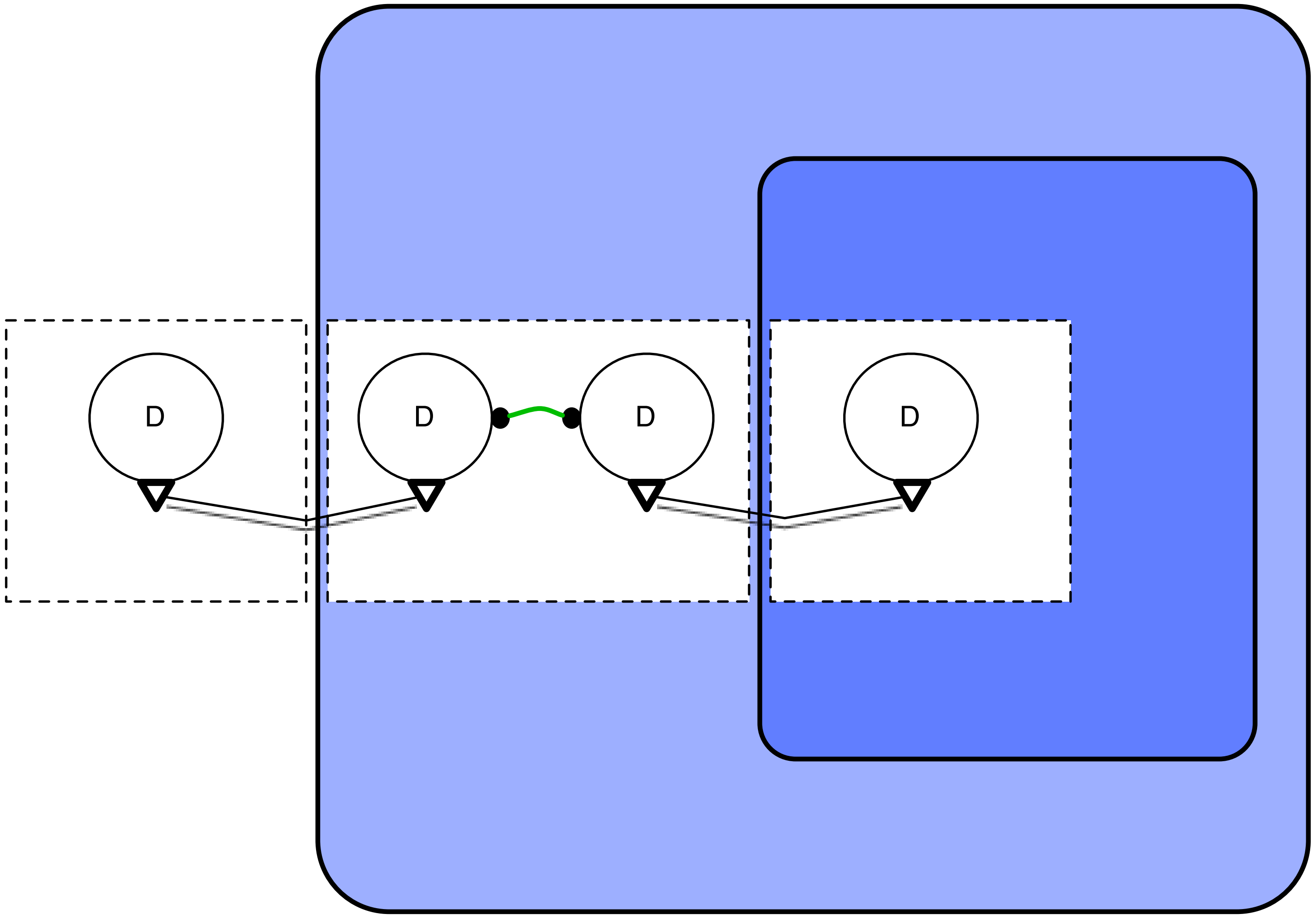
Valid contexts with 3 holes...



Valid contexts with 3 holes...



Valid contexts with 3 holes...



Extension relation

$$\text{(ax.)} \quad \frac{|\sigma| = \mathcal{V}(T)}{T \hookrightarrow_{\bullet} \langle \mathbb{C}[\bullet], \sigma \rangle} \qquad \frac{P \hookrightarrow_{\pi} \langle T_{\bullet}, \sigma \rangle \quad m \text{ fresh} \quad \llparenthesis \cdot \pi \cdot \rrparenthesis \not\to \bot}{P \hookrightarrow_{\llparenthesis \pi \rrparenthesis} \langle \mathsf{C}_m(T_{\bullet}), \sigma \rangle} \quad \text{(wrap)}$$

$$\frac{P \hookrightarrow_{\pi_0} \langle T_{\bullet}, \sigma \rangle \quad Q \hookrightarrow_{\pi_1} \langle S_{\bullet}, \sigma' \rangle \quad \pi_0 \cdot \pi_1 \not\to \bot}{P \parallel Q \hookrightarrow_{\pi_0 \pi_1} \langle \mathbb{C}[T_{\bullet}, S_{\bullet}], \sigma; \sigma' \rangle} \quad \text{(comp)}$$

Local contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet] \backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet] \{u/v\}$$

Compatibility relation:

$$\bullet \cdot \llparenthesis \cdot \llparenthesis \to \bot \qquad \rrparenthesis \cdot \rrparenthesis \cdot \bullet \to \bot \qquad \rrparenthesis \cdot \llparenthesis \to \bot$$

$$\bullet \cdot \bullet \to \bot \qquad \bullet \cdot \llparenthesis \cdot \bullet \cdot \rrparenthesis \cdot \bullet \to \bot \qquad \bot \cdot \pi \to \bot \qquad \pi \cdot \bot \to \bot$$

Extension relation

(ax.) $$\frac{|\sigma| = \mathcal{V}(T)}{T \hookrightarrow_{\bullet} \langle \mathbb{C}[\bullet], \sigma \rangle}$$

$$\frac{P \hookrightarrow_{\pi} \langle T_{\bullet}, \sigma \rangle \quad m \text{ fresh} \quad \llparenthesis \cdot \pi \cdot \rrparenthesis \not\to \bot}{P \hookrightarrow_{\llparenthesis \pi \rrparenthesis} \langle \mathsf{C}_m(T_{\bullet}), \sigma \rangle}$$ (wrap)

$$\frac{P \hookrightarrow_{\pi_0} \langle T_{\bullet}, \sigma \rangle \quad Q \hookrightarrow_{\pi_1} \langle S_{\bullet}, \sigma' \rangle \quad \pi_0 \cdot \pi_1 \not\to \bot}{P \parallel Q \hookrightarrow_{\pi_0 \pi_1} \langle \mathbb{C}[T_{\bullet}, S_{\bullet}], \sigma; \sigma' \rangle}$$ (comp)

Term abstraction! $\mathit{\Pi} \overset{def}{=} \{\llparenthesis, \rrparenthesis, \bullet, \bot\}$

Local contexts:

$$\mathbb{C}[\bullet] ::= \bullet \mid \mathbb{C}[\bullet]\backslash u \mid \mathbb{C}[\bullet], T \mid \mathbb{C}[\bullet]\,\{u/v\}$$

Compatibility relation:

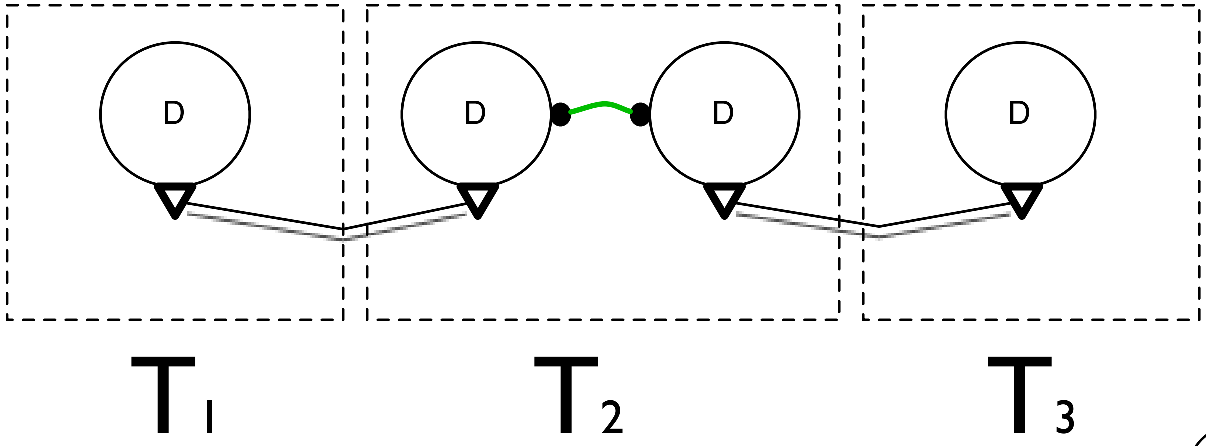
$\bullet \cdot \llparenthesis \cdot \llparenthesis \to \bot$ $\quad$ $\rrparenthesis \cdot \rrparenthesis \cdot \bullet \to \bot$ $\quad$ $\rrparenthesis \cdot \llparenthesis \to \bot$

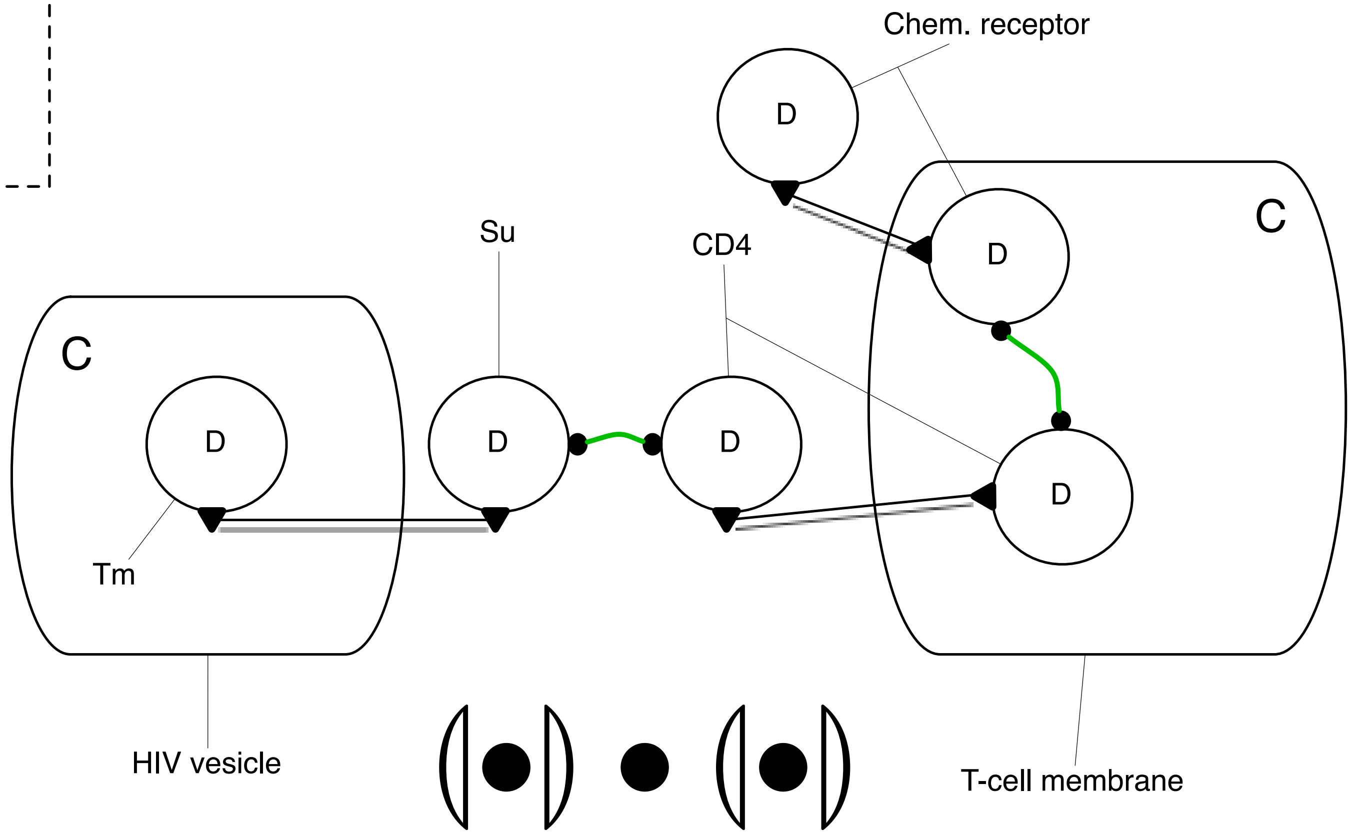
$\bullet \cdot \bullet \to \bot$ $\quad$ $\bullet \cdot \llparenthesis \cdot \bullet \cdot \rrparenthesis \cdot \bullet \to \bot$ $\quad$ $\bot \cdot \pi \to \bot$ $\quad$ $\pi \cdot \bot \to \bot$

Valid wide matches

Definition 4 (Matches). *A wide context* $\mathbb{C}^n[\bullet, \ldots, \bullet]$ *with exactly* n *holes and a parameter assignation list* σ *form a* match $\langle \mathbb{C}^n, \sigma \rangle$ *for a wide term* $P = T_1 \parallel \cdots \parallel T_n$ *in* S *if and only if:*

$$P \hookrightarrow_\pi \langle \mathbb{C}^n, \sigma \rangle \quad \textit{and} \quad \mathbb{C}^n[T_1, \ldots, T_n]\sigma \equiv S$$





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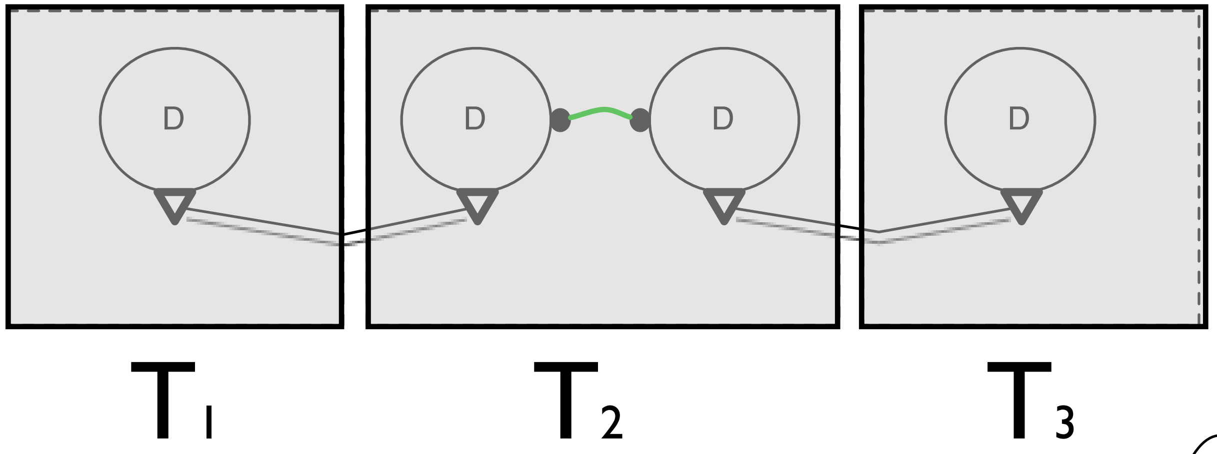

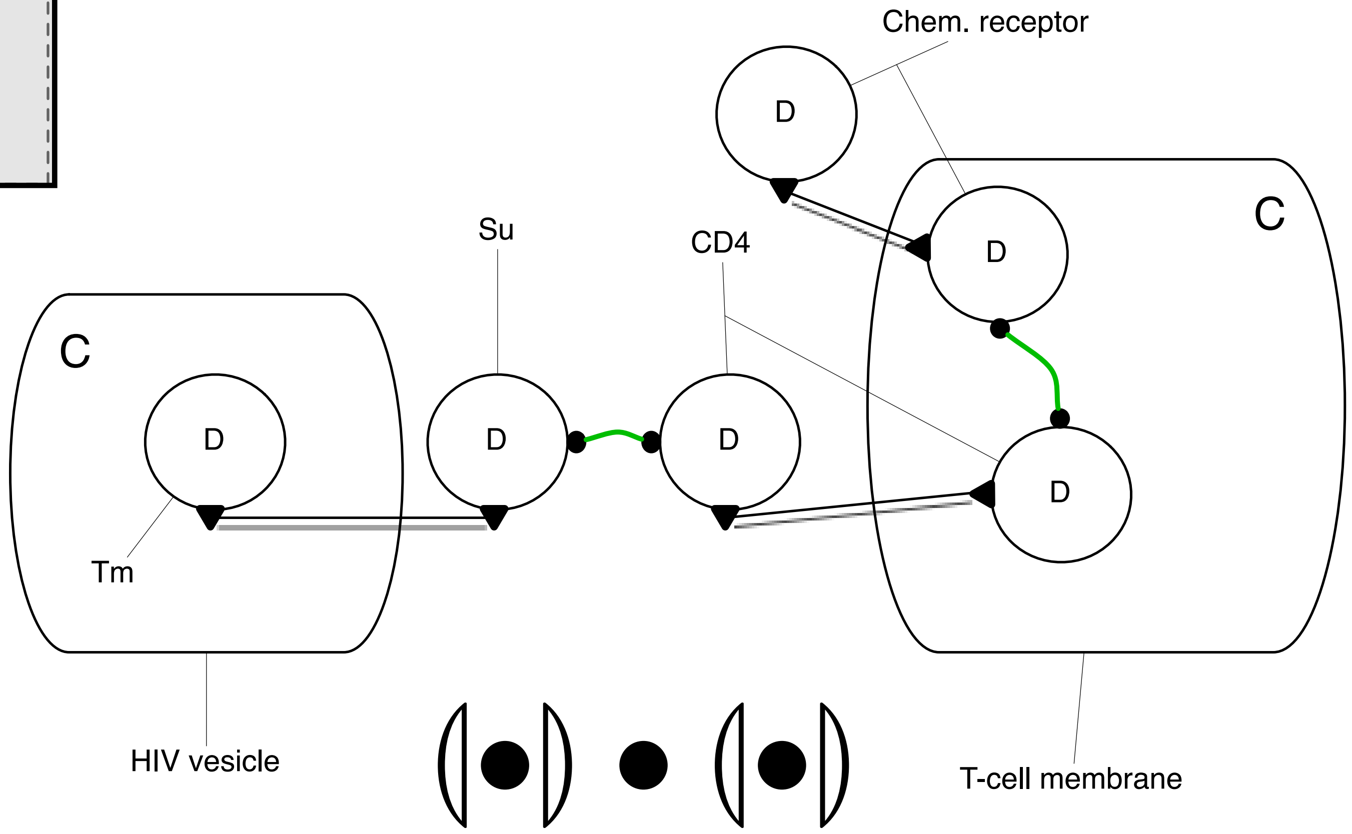

$$(\!|\bullet|\!) \bullet (\!|\bullet|\!)$$

Valid wide matches

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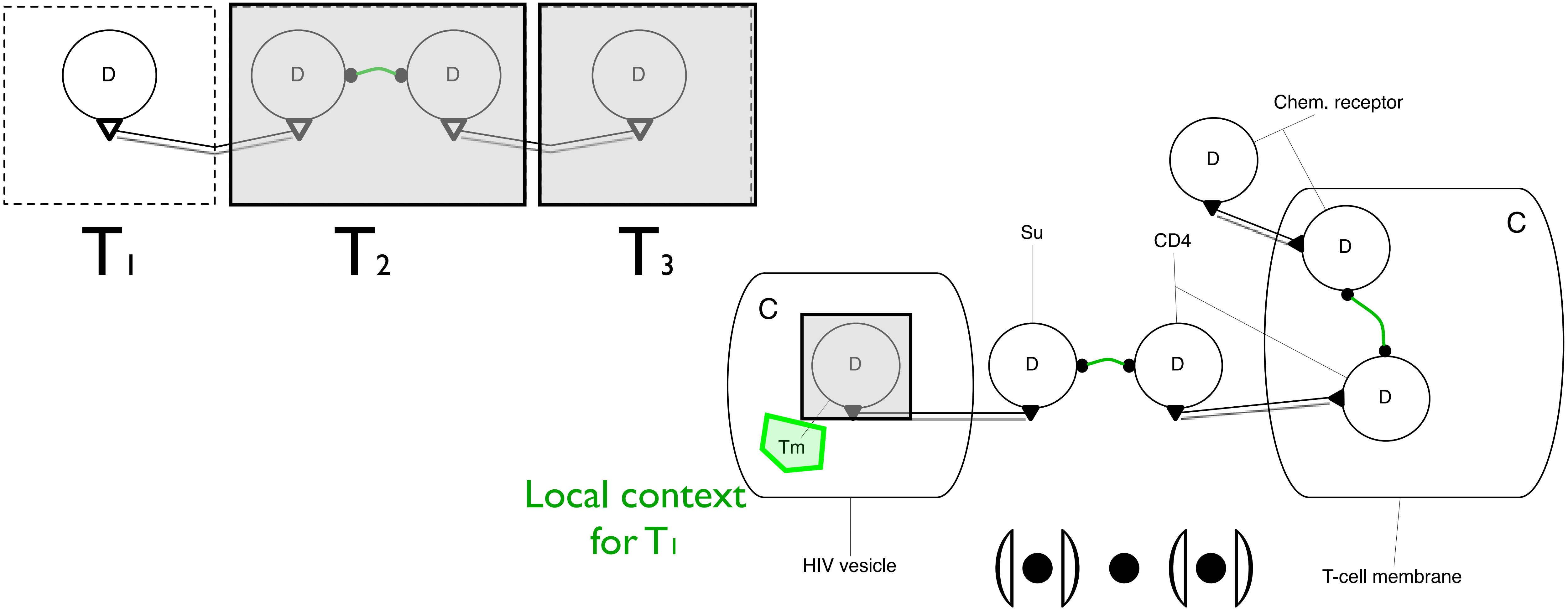

Valid wide matches

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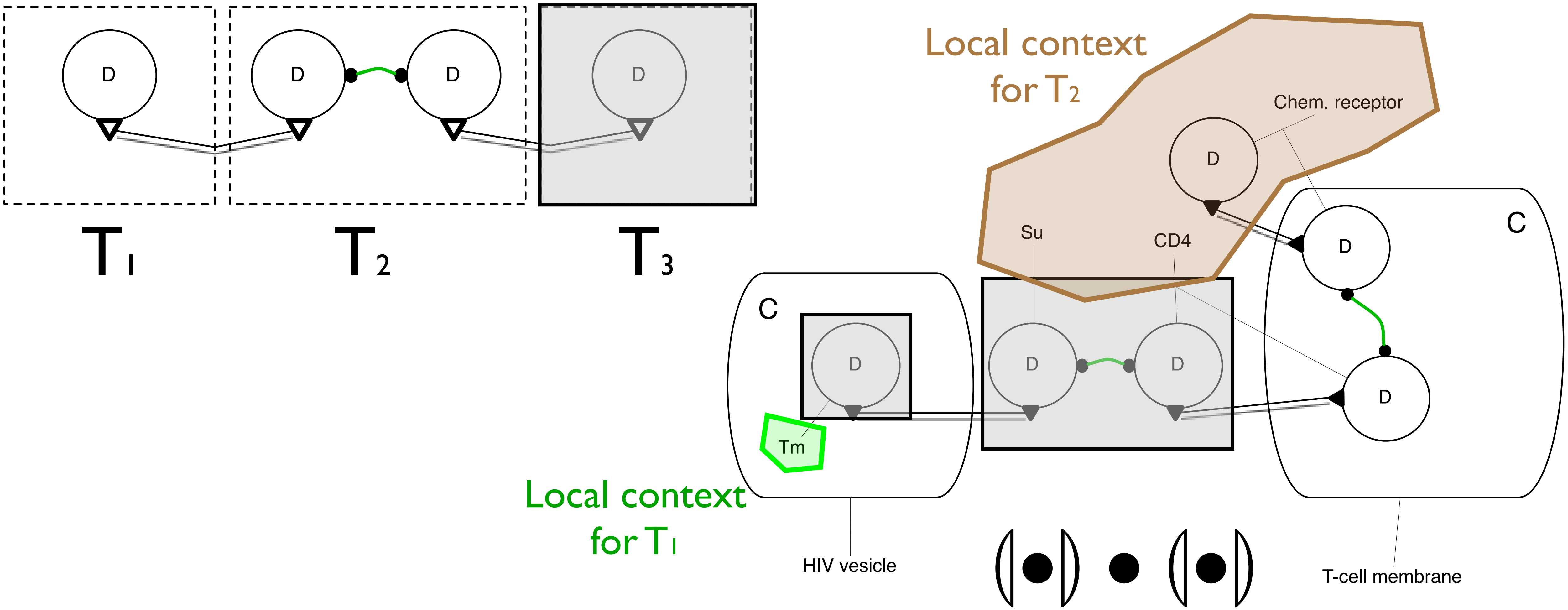

Valid wide matches

Definition 4 (Matches). *A wide context* $\mathbb{C}^n[\bullet,\dots,\bullet]$ *with exactly* n *holes and a parameter assignation list* σ *form a* match $\langle \mathbb{C}^n, \sigma \rangle$ *for a wide term* $P = T_1 \parallel \cdots \parallel T_n$ *in* S *if and only if:*

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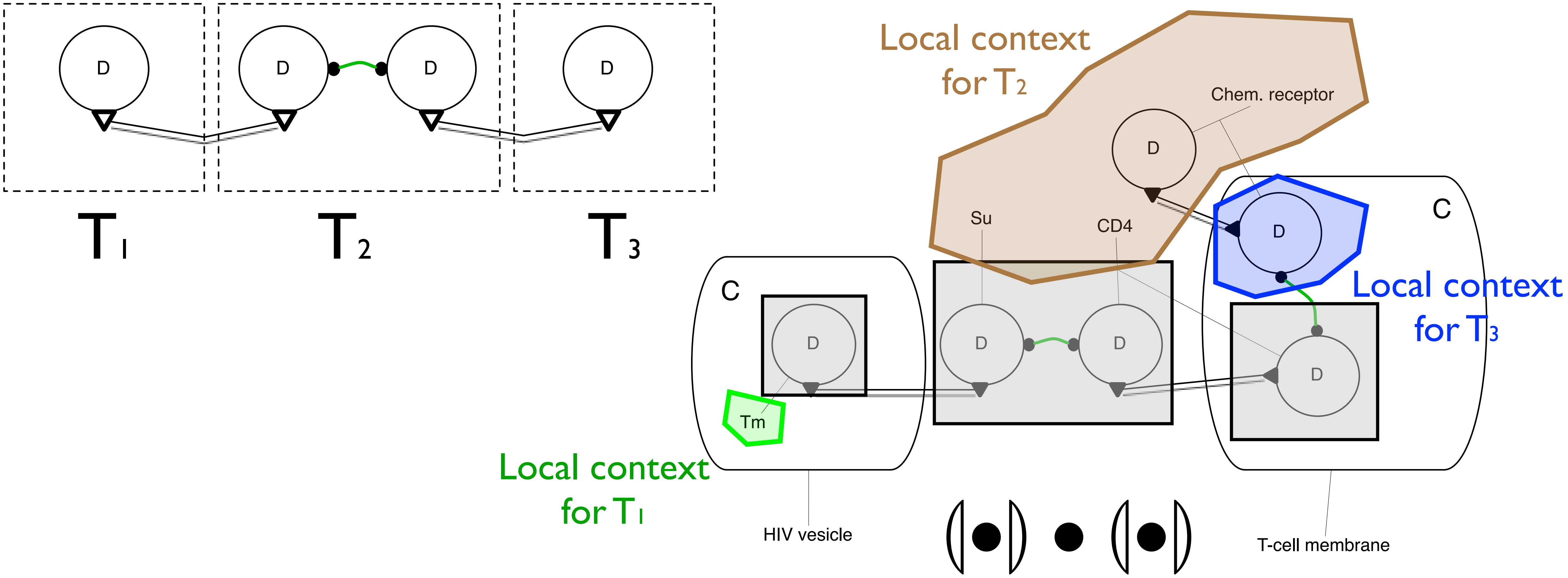
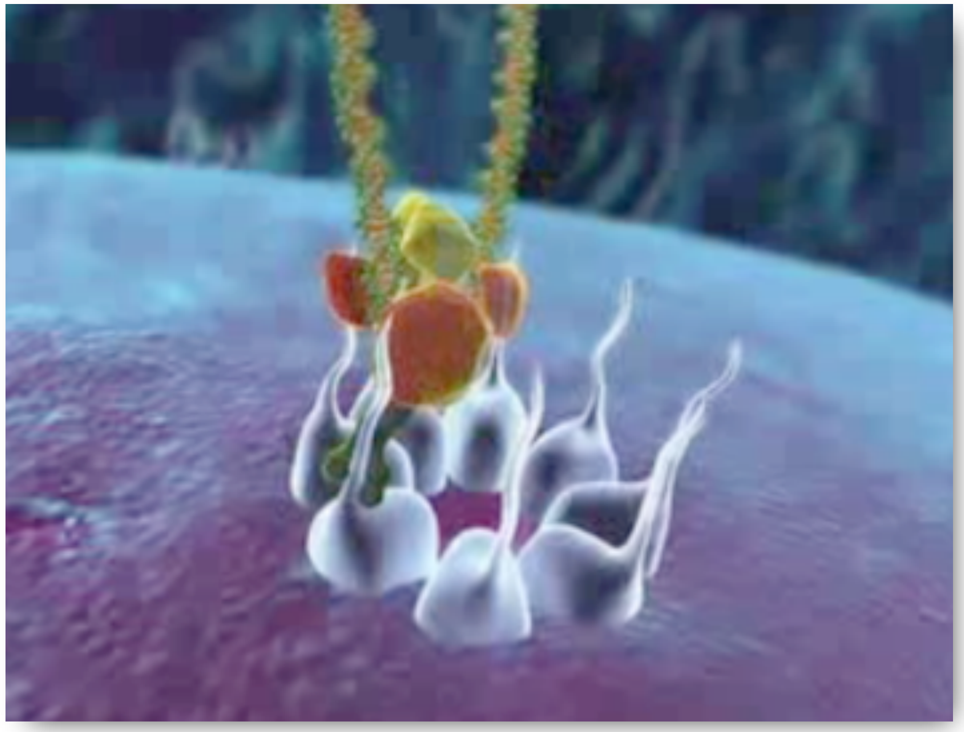


Results

Theorem 1 (Soundness). *Let* $\langle \mathbb{C}^n[\bullet, \ldots, \bullet], \sigma \rangle$ *be a match for a wide term* P *in a local term* T*. For all disjoint local term occurrences* $S, S' \in P$*, we have* $\Delta_{S,S'}(P) = \Delta_{S,S'}(T)$*.*

Theorem 2 (Completeness). *Let* $P = T_1 \parallel \cdots \parallel T_n$ *be a wide term and* $\mathbb{C}^n[\bullet, \ldots, \bullet]$ *be a generic context with exactly* n *holes. Let also* $T \equiv \mathbb{C}^n[T_1, \ldots, T_n]\sigma$ *for some parameter assignation* σ*. If for all* $i, j \leq n$ *one has* $\Delta_{T_i,T_j}(P) = \Delta_{T_i,T_j}(T)$*, then* $P \hookrightarrow_\pi \langle \mathbb{C}^n, \sigma \rangle$ *is derivable, for some* $\pi \in (\Pi \setminus \{\perp\})^*$*.*



C3: Moving molecules

Terms

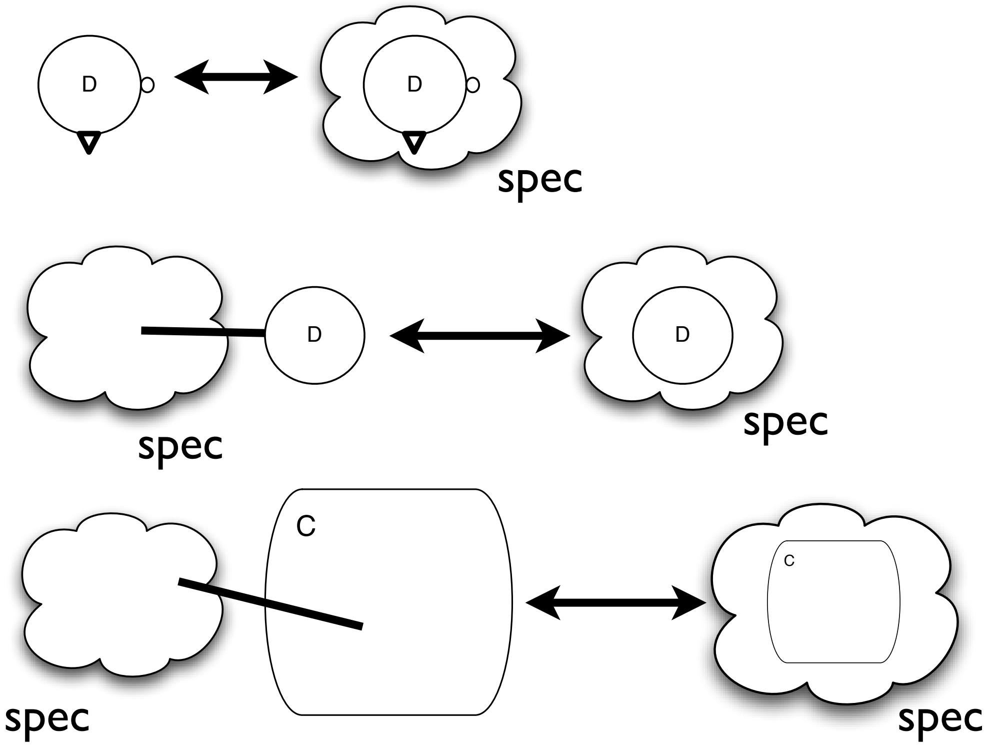
$$\begin{array}{lll} T, S & ::= \ldots & \text{(local terms)} \\ G, H & ::= T \mid \mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \mid (G, H) & \text{(global terms)} \\ P, Q & ::= G \mid (P \parallel Q) \mid \ldots & \text{(wide terms)} \end{array}$$

$$\frac{}{\mathsf{D}^{a}(x_1, \ldots, x_k) \equiv \mathsf{spec}^{\{a\}}_{\{x_1, \ldots, x_k\}}(\mathsf{D}^{a}(x_1, \ldots, x_k))}$$

$$\frac{\mathit{fn}(D) \cap (\mathsf{B} \cup \mathsf{S}) \neq \emptyset \quad \mathsf{B}' = \mathsf{B} \cup (\mathit{fn}(D) \cap \mathcal{B}) \quad \mathsf{S}' = \mathsf{S} \cup (\mathit{fn}(D) \cap \mathcal{S})}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T), D \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T, D)}$$

$$\frac{\mathit{fn}(T') \cap (\mathsf{B} \cup \mathsf{S}) \neq \emptyset \quad \mathsf{B}' = \mathsf{B} \cup (\mathit{fn}(T') \cap \mathcal{B}) \quad \mathsf{S}' = \mathsf{S} \cup (\mathit{fn}(T') \cap \mathcal{S})}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T), \mathsf{C}(T') \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T, \mathsf{C}(T'))}$$

$$\frac{u \in \mathcal{B} \cup \mathcal{S} \quad \mathsf{B}' \overset{def}{=} \mathsf{B} - \{u\} \quad \mathsf{S}' \overset{def}{=} \mathsf{S} - \{u\}}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \backslash u \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T \backslash u)} \qquad \frac{T \equiv T'}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \equiv \mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T')}$$



Terms

open names

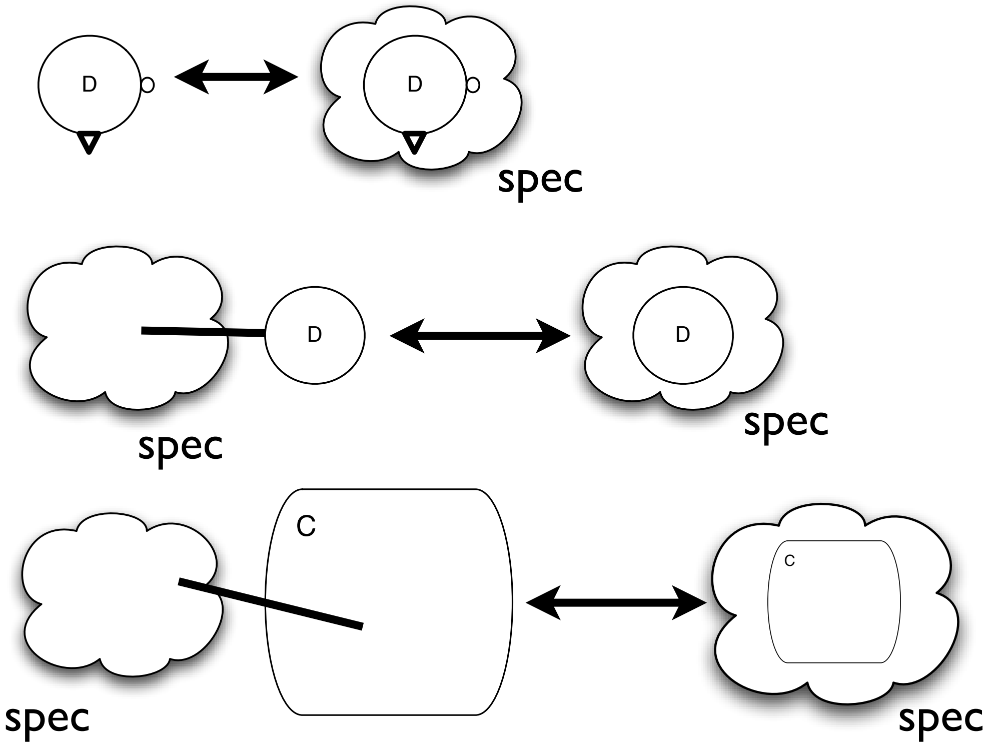
$$\begin{array}{lll} T, S & ::= \dots & \text{(local terms)}\\ G, H & ::= T \mid \mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \mid (G, H) & \text{(global terms)}\\ P, Q & ::= G \mid (P \parallel Q) \mid \dots & \text{(wide terms)} \end{array}$$

$$\frac{}{\mathsf{D}^a(x_1, \dots, x_k) \equiv \mathsf{spec}^{\{a\}}_{\{x_1, \dots, x_k\}}(\mathsf{D}^a(x_1, \dots, x_k))}$$

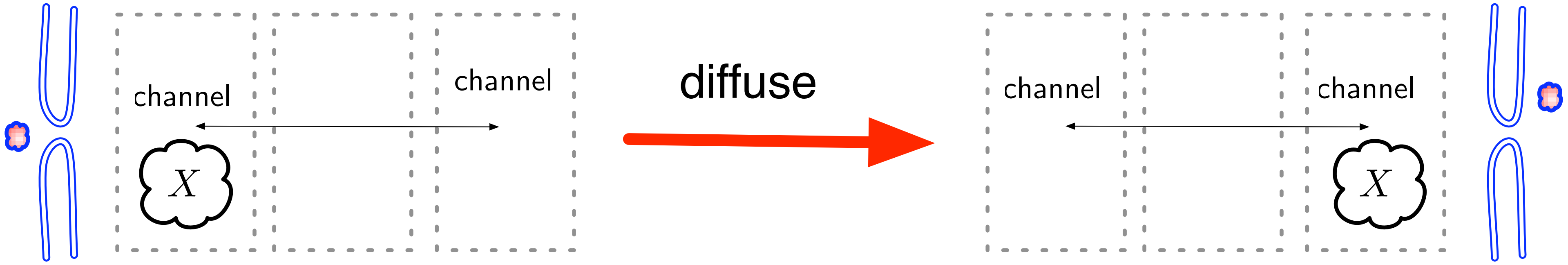
$$\frac{\mathit{fn}(D) \cap (\mathsf{B} \cup \mathsf{S}) \neq \emptyset \quad \mathsf{B}' = \mathsf{B} \cup (\mathit{fn}(D) \cap \mathcal{B}) \quad \mathsf{S}' = \mathsf{S} \cup (\mathit{fn}(D) \cap \mathcal{S})}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T), D \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T, D)}$$

$$\frac{\mathit{fn}(T') \cap (\mathsf{B} \cup \mathsf{S}) \neq \emptyset \quad \mathsf{B}' = \mathsf{B} \cup (\mathit{fn}(T') \cap \mathcal{B}) \quad \mathsf{S}' = \mathsf{S} \cup (\mathit{fn}(T') \cap \mathcal{S})}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T), \mathsf{C}(T') \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T, \mathsf{C}(T'))}$$

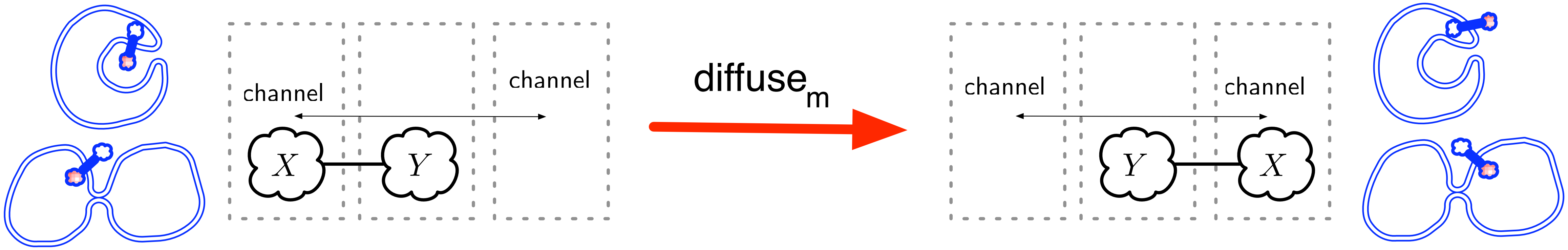
$$\frac{u \in \mathcal{B} \cup \mathcal{S} \quad \mathsf{B}' \overset{def}{=} \mathsf{B} - \{u\} \quad \mathsf{S}' \overset{def}{=} \mathsf{S} - \{u\}}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \backslash u \equiv \mathsf{spec}^{\mathsf{B}'}_{\mathsf{S}'}(T \backslash u)} \qquad \frac{T \equiv T'}{\mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T) \equiv \mathsf{spec}^{\mathsf{B}}_{\mathsf{S}}(T')}$$



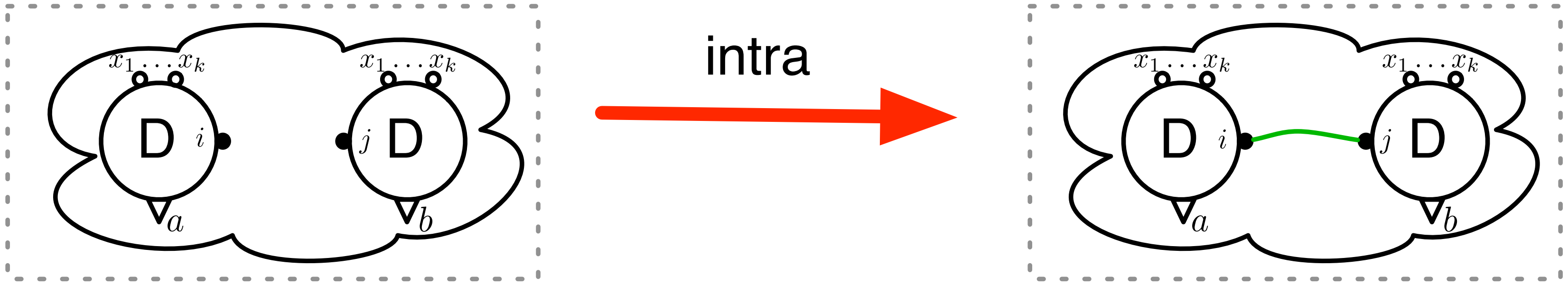
Generators



$$(\mathsf{spec}^{\emptyset}_{\emptyset}(X), \mathsf{channel}_m \parallel 0 \parallel \mathsf{channel}_m)\backslash m \rightarrow (\mathsf{channel}_m \parallel 0 \parallel \mathsf{channel}_m, \mathsf{spec}^{\emptyset}_{\emptyset}(X))\backslash m$$



$$(\mathsf{spec}^{a}_{\emptyset}(X), \mathsf{channel}_m \parallel \mathsf{spec}^{a}_{\emptyset}(Y) \parallel \mathsf{channel}_m)\backslash m\backslash a \rightarrow (\mathsf{channel}_m \parallel \mathsf{spec}^{a}_{\emptyset}(Y) \parallel \mathsf{channel}_m, \mathsf{spec}^{a}_{\emptyset}(X))\backslash m\backslash a$$



$$\mathsf{spec}^{ab}_{\tilde{x},\tilde{y}}(\mathsf{D}^a(x_1,\ldots,x_i,\ldots,x_k), \mathsf{D}^b(y_1,\ldots,y_j,\ldots,y_q))\backslash x_i\backslash y_j \rightarrow \mathsf{spec}^{ab}_{\tilde{x}',\tilde{y}'}(\mathsf{D}^a(x_1,\ldots,z,\ldots,x_k), \mathsf{D}^b(y_1,\ldots,z,\ldots,y_q))\backslash z$$

Mixtures

Definition 5 (Mixture). *Say that a term P is a* mixture *if:*
– $w(P) = 1,\ fn(P) = \emptyset$ *and P is parameter free*
– *Site edges have exactly two sites and do not cross compartments*
– *Backbone hyper edges cross at most one compartment*
– *Each species node contains a single connected component*

Property 1 (Preservation). Let $\mathcal{R}$ be a set of generated rules and let P be a mixture. If $P \rightarrow_r Q$ with $r \in \mathcal{R}$ then Q is a mixture.

Summary

- A language expressive enough to model a large swath of systems biology in an algebraic fashion
- Relies on a minimal set of generators (thanks to projectivity)
- Simulating generators is enough (the rest are refinements)!

«I took biology because I didn’t want to do math»

a biologist at HMS