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Some thoughts on designing a genomic query language

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Two perspectives on a query language

Surface syntax Easy to read, understand, & write queries correctly Sufficient power to express needed **queries** Prevent expensive queries

Abstract syntax

Easy to analyze, manipulate, and optimize

- Easy to cater for extensions
- Sufficient power to express needed algorithms

{ {x, z} | $(x,y) \in A, (y',z) \in B, y = y'$ }

select (a.x, b.z) from a in A, b in B where a.y = b.y'

U{ U{ if a.y = b.y'then { (a.x, bz) } else {} | b \in B} | a \in A}

Compositionality & orthogonality are key principles for query language design

Compositionality & orthogonality in NRC

Types

 $s,t ::= \mid bool \mid b \mid s \times t \mid \{s\}$

Expressions, constructs are provided for each type orthogonally

Translating into comprehension syntax

 $\bigcup \{! e_1 \mid x \in e_2\} = \{! y \mid x \in e_2, y \in e_1\}$

Translating from comprehension syntax

 $\{! e_1 \mid x \in e_2, \ \Delta\} = \bigcup \{! e_1 \mid \Delta\} \mid x \in e_2\}$ $\{! e_1 \mid C, \ \Delta\} = if \ C \ then \ \{! e_1 \mid \Delta\} \ else \ \{\}$ $\{! e_1 \mid \} = \{! e_1 \}$

 \Rightarrow Treat comprehension as a nice syntactic sugar

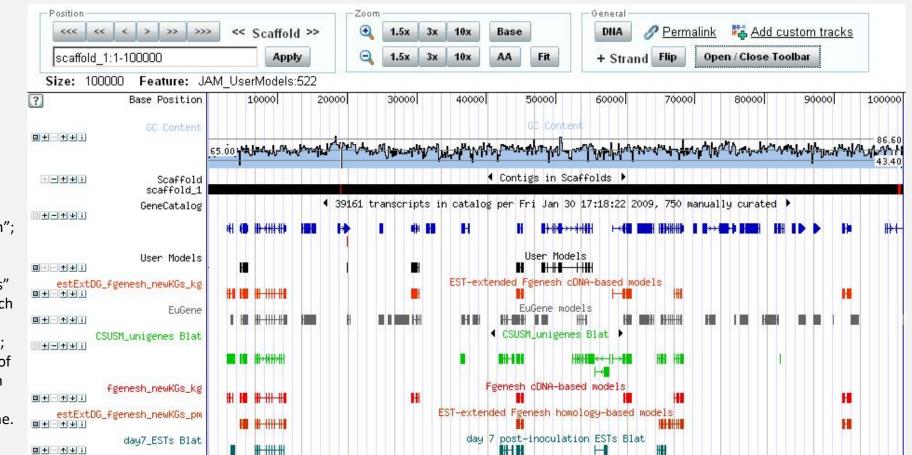
 $U\{e_1 \mid x \in e_2\} \text{ means}$ $f(o_1) \cup \dots \cup f(o_n),$ where $f(x) = e_1$ and $\{o_1, \dots, o_n\} = e_2$

Genomic data

Tracks Annotations

Loci

E.g. you see a row denoted "Base position"; this is the coordinates on a reference genome. The rest of the rows (e.g. "Gene catalog" and "day7_ESTs blat") are "tracks" bearing different kinds of annotations. Each track corresponds to one kind of experiments, one kind of predictions, etc.; e.g. "day7_ESTS blat" are short stretches of RNAs from a day-7 sample that have been mapped (using a tool called "blat") to specific positions on the reference genome.



Genomic data types

An annotation datatype !t and its subtype landmark !!t

of type t = (#name: string, #pval: real, ...)

are represented as (#loc: Loc, #anno: (name: string, #pval: real, ...))

A **track** datatype {!t} and its subtype **landmark track** {!!t} are represented as { !t } and { !!t }

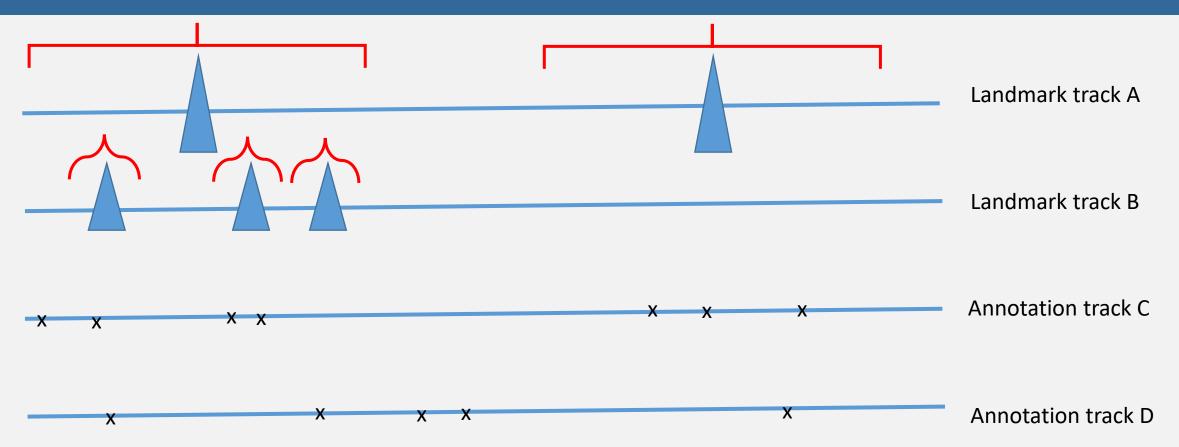
Meta info can be added to tracks. But let's not worry about these here

Equipped with some implicit / automatic normalizations / constraints, e.g. sorted by #loc, idempotency and non-overlapping loci on the same track

Landmarks on the same landmark track are non-overlapping, and all annotations can "see" no more than one landmark on the same landmark track

Landmarks can be used for organizing storage & distribution of annotations

Conceptual organization of annotation & landmark tracks



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Some operations for the loci type



satisfying "p can-see r whenever (p overlap or near q) & q = r.loc", plus maybe other convexity constraints to be thought up

Precise set of operations on loci (e.g. p is-nearer q_1 than q_2) is not important here

But a well-designed set of operations should constraint users from "bad" "expensive" queries, while providing sufficient expressive power for commonly needed queries

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Operations on annotations and tracks

 $\begin{array}{c} e_{1}: \{! \ t_{1} \ \}, \ e_{2}: \{! \ t_{2} \} \\ \cup \{! \ e_{1} \ | \ x \in e_{2} \ \}: \{! \ t_{1} \ \} \end{array}$ $\begin{array}{c} e: !t \\ \{! \ \}: \{! \ t \ \} \end{array} \quad \begin{array}{c} e: !t \\ \{! \ e\}: \{! \ t\} \end{array} \quad \begin{array}{c} e_{1}, \ e_{2}: \{! \ t \ \} \\ e_{1} \cup e_{2}: \{! \ t \ \} \end{array}$ Plus some set-track conversion ops & syntactic sugars

Semantics: Same as those for sets, except keep things sorted on #loc & maintains other constraints that we may come up with

Ditto for !!t, but maybe ban !!(#loc, #anno)

 p : Loc, e : t
 e : !t

 !(#loc: p, #anno: e) : !t
 e.loc : Loc, e.anno : t

Let's call this language NRC_{genome} in this talk

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"Extract from a track R, the annotations in a given region (e.g. 21q22.3) of the genome"

{! x | $x \in R$, x.loc overlap 21q22.3 }

"Extract from the HMMPFAM prediction track, those RBP predictions with pval < 1E-6"

{! $x \mid x \in HMMPFAM$, x.anno.name = "RBP", x.anno.pval < 1E-6 }

These queries operate on a single track They can be executed efficiently, viz. O(n), in NRC_{genome}

"Extract from the TP53 chip-seq track, those TP53 binding sites with pval < 1E-6 and are in promoters of genes"

{! x | y∈ GENES, x ∈ TP53, x.loc before y.loc, x.loc near y.loc, x.anno.pval < 1E-6 } This query operates on two tracks Its "natural" complexity is O(|GENES| * [TP53]) in NRC_{genome}

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are closest to each other in the promoters of the same genes"

{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: u, #hdac1: v)) | $g \in GENES$, (u, v) \in closest { (x, y) | $x \in TP53$, x.loc near g.loc, x.loc before g.loc, $y \in HDAC1$, y.loc near g.loc, y.loc before g.loc } }

This query has complexity O(|GENES| * |TP53| * |HDAC1|) in NRC_{genome}

Does this need to be cubic?

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are in the promoters of the same genes"

{! u | u \in {! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: { x | x \in TP53, x.loc near g.loc, x.loc before g.loc}, #hdac1: { y | y \in HDAC1, y.loc near g.loc, y.loc before g.loc})) | g \in GENES }, u.anno.tp53 \neq {! }, u.anno.hdac1 \neq {! }}

This query has complexity O(|GENES| * (|TP53| + |HDAC1|)) in NRC_{genome}

Does this need to be quadratic?

What is needed? An idea

$$\begin{array}{c} e: \{! \ t \ \}, \ e_1: \{!! \ t_1 \ \}, \ e_2: \{! \ t_2 \ \}, \ \dots, \ e_k: \{! \ t_k \ \} \\ \hline \cup \{! \ e \ \mid (x_1 \ , \ X_2, \ \dots, \ X_k) \in \in (e_1, \ e_2, \ \dots, \ e_k) \ \}: \{! \ t \ \} \end{array}$$

Semantics

$$\cup \{! \ e \ | \ (x_1, \ X_2, \ \dots, \ X_k) \in \{ \ (x_1, \ \{ \ x_2 \ | \ x_2 \in e_2, \ x_2.loc \ can-see \ x_1 \}, \ \dots, \\ \{ \ x_k \ | \ x_k \in e_k, \ x_k.loc \ can-see \ x_1 \}) \\ [\ x_1 \in e_1 \ \} \ \}$$

The part in bold is executed for each landmark, considering only annotations which can see that landmark (assuming these are stored with that landmark)

Common genomic queries revisited

"Extract from the TP53 chip-seq track those TP53 binding sites with pval < 1E-6 and are in promoters of genes"

 $\{ \begin{array}{ll} x \mid y \in \text{GENES}, \ x \in \text{TP53}, \\ x.\text{loc before y.loc}, \\ x.\text{loc near y.loc}, \\ x.\text{anno.pval} < 1\text{E-6} \, \} \end{array}$

GENES is a landmark track

 $\{ ! x \mid (y, X) \in \in (GENES, TP53), x \in X, \\ x.loc before y.loc, \\ x.loc near y.loc, \\ x.anno.pval < 1E-6 \}$

Complexity is maybe O(|GENES| * 1% of |TP53|)

Common genomic queries revisited

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are closest to each other in the promoters of the same genes"

> {! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: u, #hdac1: v)) | (g, U, V) $\in \in$ (GENES, TP53, HDAC1), (u, v) \in closest {(x,y) | x \in U, x.loc near g.loc, x.loc before g.loc, y \in V, y.loc near g.loc, y.loc before g.loc} }

Complexity is maybe O(|GENES| * (1% of |TP53| * 1% of |HDAC1|))

Common genomic queries revisited

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are in the promoters of the same genes"

{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: { x | x ∈ TP53, x.loc near g.loc, x.loc before g.loc}, #hdac1: { y | y ∈ HDAC1, y.loc near g.loc, y.loc before g.loc})) | g ∈ GENES}

Is it necessary to process U and V twice? Complexity is maybe O(|GENES| * (1% of |TP53| + 1% of |HDAC1|)

A better idea?

 $e: \{! t\}, e_1: \{!! t_1\}, e_2: \{! t_2\}, \dots, e_k: \{! t_k\}, \gamma_1: bool, \dots, \gamma_k: bool \\ \cup\{! e \mid x_1 \in \in e_1 \text{ st } \gamma_1, X_2 \subseteq e_2 \ni x_2 \text{ st } \gamma_2, \dots, X_k \subseteq e_k \ni x_k \text{ st } \gamma_k\}: \{! t\} \\ FV(\gamma_j) \setminus \{x_1, x_j\} \subseteq FV(\cup\{! e \mid x_1 \in \in e_1, X_2 \subseteq e_2 \ni x_2 \text{ st } \gamma_2, \dots, X_k \subseteq e_k \ni x_2 \text{ st } \gamma_k\}), \text{ and } FV(e) \cap \{x_2, \dots, x_k\} = \{\}$

Semantics

The part in bold is executed for each landmark, considering only annotations which can see that landmark (assuming these are stored with that landmark) Copyright © 2019 by National University of Singapore. All Rights Reserved.

Common genomic queries revisited again

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are in the promoters of the same genes"

```
{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0,
#tp53: { x \mid x \in TP53, x.loc near g.loc, x.loc before g.loc},
#hdac1: { y \mid y \in HDAC1, y.loc near g.loc, y.loc before g.loc} ) )
| g \in GENES}
```

{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: U, #hdac1: V))
| g ∈ ∈ GENES,
U ⊆ TP53 ∋ u st u.loc near g.loc & u.loc before g.loc ,
V ⊆ HDAC1 ∋ v st v.loc near g.loc, v.loc before g.loc }

Complexity is maybe O(|GENES| * (1% of |TP53| + 1% of |HDAC1|)

Common genomic queries revisited again

"Extract from the TP53 and the HDAC1 chip-seq tracks, those TP53 and HDAC1 binding sites that are closest to each other in the promoters of the same genes"

{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: u, #hdac1: v)) $| g \in GENES$,

 $(u, v) \in closest \{ (x, y) | x \in TP53, x.loc near g.loc, x.loc before g.loc, x.loc be$

 $y \in HDAC1$, y.loc near g.loc, y.loc before g.loc } }

{! (#loc: g.loc, #anno: (#name: g.anno.name, #pval: 0, #tp53: x, #hdac1: y)) | $g \in GENES$, $U \subseteq TP53 \ni u$ st u.loc near g.loc & u.loc before g.loc, $V \subseteq HDAC1 \ni v$ st v.loc near g.loc & v.loc before g.loc, (x, y) \in closest {(u,v) | $u \in U, v \in V$ }

Complexity is maybe O(|GENES| * (1% of |TP53| * 1% of |HDAC1|))

And this idea? It is really a syntactic sugar

e : {! t }, e₁ : {!! t₁ } , e₂ : {! t₂ } , ... , e_k : {! t_k }, γ_1 : bool, ..., γ_k : bool

 $\cup \{! e \mid x_1 \in \in e_1 \text{ st } \gamma_1, x_2 \in e_2 \text{ st } \gamma_2, \dots, x_k \in e_k \text{ st } \gamma_k \} : \{! t \}$

 $\mathsf{FV}(\gamma_j) \setminus \{x_1, x_j\} \subseteq \mathsf{FV}(\cup \{! e \mid x_1 \in \in e_1, x_2 \in e_2 \text{ st } \gamma_2, \dots, x_k \in e_k \text{ st } \gamma_k\})$

Semantics

The part in bold is executed for each landmark, considering only annotations which can see that landmark (assuming these are stored with that landmark) Copyright © 2019 by National University of Singapore. All Rights Reserved.

Common genomic queries revisited again

"Extract from the TP53 chip-seq track those TP53 binding sites with pval < 1E-6 and are in promoters of genes"

{! x | $y \in GENES$, $x \in TP53$, x.loc before y.loc, x.loc near y.loc, x.anno.pval < 1E-6 }

$\{ \begin{array}{ll} x \mid & y \in \in \mathsf{GENES}, \\ & x \in \mathsf{TP53} \text{ st x.loc before y.loc } \& \\ & x.loc near y.loc \& x.anno.pval < 1E-6 \end{array} \}$

Complexity is maybe O(|GENES| * 1% of |TP53|)

GENES is a landmark track

Implementing "synchronized" processing of multiple lists / tracks

```
\begin{aligned} \text{lzip:} & (t_1 \rightarrow \text{bool}) * (t_1 * t_2 \rightarrow \text{bool}) * (t_1 * t_2 \rightarrow \text{bool}) * (t_2 * t' \rightarrow t') * (t_1 * t' \rightarrow t') * (t' \rightarrow \{t\}) * t' * t' \\ & \rightarrow \{t_1\} * \{t_2\} \rightarrow \{t\} \end{aligned}
```

```
Izip (sx, sy, ay, h, g, f, a, e) ({}, Y) = f a
Izip (sx, sy, ay, h, g, f, a, e) (X, {}) = f a
Izip (sx, sy, ay, h, g, f, a, e) (x::X, y::Y) =
         if sx(x)
         then if sy(x, y)
               then if ay(x,y)
                     then Izip (sx, sy, ay, h, g, f, h(y, g(x, a)), e) (x::X, Y)
                     else lzip (sx, sy, ay, h, g, f, g(x, a), e) (x::X, Y)
               else f (g(x, a)) \cup lzip (sx, sy, ay, h, g, f, e, e) (X, y::Y)
         else f a \cup lzip (sx, sy, ay, h, g, f, e, e) (X, y::Y)
```

At every step, either x or y gets shifted. So complexity is $O(|X| + |Y| * \alpha)$, where α is complexdity of sx, sy, etc.

Implementing $\cup \{! e \mid x_1 \in \in e_1 \text{ st } \gamma_{1,} X_2 \subseteq e_2 \text{ st } \chi_2 \text{ st } \gamma_2, \dots, X_k \subseteq e_k \text{ st } \chi_k \text{ st } \gamma_k \}$

 $\cup \{! e \mid X_1 \in \in e_1 \text{ st } \gamma_1, X_2 \subseteq e_2 \ni X_2 \text{ st } \gamma_2 \} :=$ $Izip(sx, sy, ay, h, g, f, (\{!!, \}, \{!, \}), (\{!!, \}, \{!, \})) (e_1, e_2)$ where $SX(X_1) := \gamma_1,$ $ay(x_1, x_2) := x_2$.loc can-see $x_1 \& \gamma_2$, $sy(x_1, x_2) := x_2$.loc before x_1 .loc or $ay(x_1, x_2)$, $|zip: (t_1 \rightarrow bool) * (t_1 * t_2 \rightarrow bool) * (t_1 * t_2 \rightarrow bool) * (t_2 * t' \rightarrow t') * (t_1 * t' \rightarrow t') * (t' \rightarrow \{t\}) * t' * t'$ \rightarrow {t₁} * {t₂} \rightarrow {t} $h(x_2, (X_1, X_2)) := (X_1, X_2 \cup \{!, X_2\}),$ $lzip(sx, sy, ay, h, g, f, a, e)({}, Y) = f a$ $g(x_1, (X_1, X_2)) := (X_1 \cup \{!! \ x_1 \}, X_2),$ lzip (sx, sy, ay, h, g, f, a, e) (X, {}) = f a lzip (sx, sy, ay, h, g, f, a, e) (x::X, y::Y) = if sx(x) $f(X_1, X_2) := \bigcup \{! e \mid X_1 \in X_1\};$ then if sy(x, y)then if ay(x,y) then lzip (sx, sy, ay, h, g, f, h(y, g(x, a)), e) (x::X, Y) else lzip (sx, sy, ay, h, g, f, g(x, a), e) (x::X, Y) Synchronized scan else f (g(x, a)) \cup lzip (sx, sy, ay, h, g, f, e, e) (X, y::Y) else f a \cup lzip (sx, sy, ay, h, g, f, e, e) (X, y::Y) Copyright © 2019 by National University of Singapore. All Rights Reserved.

A nice property of \bigcup {! $e \mid x_1 \in e e_1 \text{ st } \gamma_{1,}$ $X_2 \subseteq e_2 \ni x_2 \text{ st } \gamma_2, \dots, X_k \subseteq e_k \ni x_k \text{ st } \gamma_k$ }

```
 \cup \{! e \mid x_1 \in \in e_1 \text{ st } \gamma_{1,} \ X_2 \subseteq e_2 \ \ni x_2 \text{ st } \gamma_2 \} := 
Izip (...) (e<sub>1</sub>, e<sub>2</sub>) where ...
```

is a homomorphism on e_1 . Thus

 $\begin{array}{l} \left\{ \begin{array}{l} \text{lzip } (\text{sx, sy, ay, h, g, f, a, e) } (X, \{\} \right) = \text{f a} \\ \text{lzip } (\text{sx, sy, ay, h, g, f, a, e) } (X::X, y::Y) = \\ & \text{if sx}(x) \\ & \text{then if sy}(x, y) \\ & \text{then if ay}(x, y) \\ & \text{then if ay}(x, y) \\ & \text{then lzip } (\text{sx, sy, ay, h, g, f, h}(y, g(x, a)), e) (x::X, Y) \\ & \text{else lzip } (\text{sx, sy, ay, h, g, f, g}(x, a), e) (x::X, Y) \\ & \text{else f } (g(x, a)) \cup \text{lzip } (\text{sx, sy, ay, h, g, f, e, e) } (X, y::Y) \\ & \text{else f } a \cup \text{lzip } (\text{sx, sy, ay, h, g, f, e, e) } (X, y::Y) \end{array} \right\}$

 $lzip(sx, sy, ay, h, g, f, a, e)({}, Y) = f a$

 \rightarrow {t₁} * {t₂} \rightarrow {t}

 $\begin{array}{l} \cup \{ ! \ e \ | \ x_1 \in \in \{ ! ! \ o_1, \ \dots, \ o_k \} \ \text{st } \gamma_1, \ X_2 \subseteq e_2 \ \ni x_2 \ \text{st } \gamma_2 \} \\ = \\ \cup \{ ! \ e \ | \ x_1 \in \in \{ ! ! \ o_1 \} \ \text{st } \gamma_1, \ X_2 \subseteq e_2 \ \ni x_2 \ \text{st } \gamma_2 \} \cup \ldots \cup \\ \cup \{ ! \ e \ | \ x_1 \in \in \{ ! ! \ o_k \} \ \text{st } \gamma_1, \ X_2 \subseteq e_2 \ \ni x_2 \ \text{st } \gamma_2 \} \end{array}$

When annotations on track e2 are "clustered" (i.e. stored with) the specific landmarks on track e1 these annotations "can see", each \cup {! e | $x_1 \in \in \{!! \circ_j\}$ st $\gamma_1, X_2 \subseteq e_2 \ni x_2$ st γ_2 } can be run in parallel on each cluster

Some optimization rules

 $\cup \{! e \mid x_1 \in \in e_1 \text{ st } \gamma_l, x_2 \in e_2 \text{ st } \gamma_2, \dots, \textbf{x}_j \in \textbf{e}_j \text{ st } \gamma_j \text{ \& } \phi, \dots, x_k \in e_k \text{ st } \gamma_k \}$

And ϕ is a "positive" condition on loci in both rules

```
 \begin{array}{l} \cup \{! \cup \{! \text{ if } \phi \text{ then } e \text{ else } \{! \} \mid x \in X_j \} \\ \mid x_1 \in \in e_1 \text{ st } \gamma_1, X_2 \subseteq e_2 \ni x_2 \text{ st } \gamma_2, \dots, X_k \subseteq e_k \ni x_2 \text{ st } \gamma_k \} \\ \downarrow \\ \\ \cup \{! \cup \{! e \mid x \in X_j \} \\ \mid x_1 \in \in e_1 \text{ st } \gamma_1, \\ X_2 \subseteq e_2 \ni x_2 \text{ st } \gamma_2, \dots, X_j \subseteq e_j \ni x_j \text{ st } \gamma_j \& \phi[x_j/x], \dots, X_k \subseteq e_k \ni x_2 \text{ st } \gamma_k \} \end{array}
```

And

$$\begin{array}{c} \cup \{! \cup \{! \text{ if } \phi \text{ then } e \text{ else } \{! \} \mid x_2 \in e_2\} \mid x_1 \in e_1\} \\ \downarrow \\ \downarrow \\ \psi \\ \downarrow e_1 : !!t_1 \& e_2 : !t_2 \& \\ \downarrow \\ x_1 \notin FV(e_2) \& FV(\phi) \cap \{x_1, x_2\} = \{x_1, x_2\} \& \\ \downarrow \\ \psi \\ \psi \\ \downarrow \end{array}$$

 \cup {! \cup {! if ϕ then e else {! } | $x_1 \in e_1$ st true, $x_2 \in e_2$ st true }

So a user does not need to worry about when to use $\cup \{! e \mid x_1 \in \in e_1, ...\}$



It is not necessary for a user to use {!, {!!, etc.

These can be inferred by a simple type system

And transformed into synchronized/parallel scans by an optimizer

