```
(define tgfb-context
 (list
  (cons "title" "TGF-Beta signaling from cell membrane to nucleus through SMAD proteins.")
  (cons "author" "Heldin, C., Miayazono, K., and Dijke, P.")
  (cons "year" "1997")
  (cons "university" "Ludwig Institute for Cancer Research")
  (cons "topic" "Cell biology")
  (cons "journal" "Nature")
  (cons "pubmed" "9393997")
  (cons "locations" (list "loc_a1" "loc_b1"))))
```

```
(define tgfb-context
 (list
  (cons "title" "TGF-Beta signaling from cell membrane to nucleus through SMAD proteins.")
  (cons "author" "Heldin, C., Miayazono, K., and Dijke, P.")
  (cons "year" "1997")
  (cons "university" "Ludwig Institute for Cancer Research")
  (cons "topic" "Cell biology")
  (cons "journal" "Nature")
  (cons "pubmed" "9393997")
  (cons "locations" (list "loc_a1" "loc_b1"))))
```

```
'(CAUSE (SMADs p15) tgfb-context)
```

```
(define tgfb-context
 (list
  (cons "title" "TGF-Beta signaling from cell membrane to nucleus through SMAD proteins.")
  (cons "author" "Heldin, C., Miayazono, K., and Dijke, P.")
  (cons "year" "1997")
  (cons "university" "Ludwig Institute for Cancer Research")
  (cons "topic" "Cell biology")
  (cons "journal" "Nature")
  (cons "pubmed" "9393997")
  (cons "locations" (list "loc_a1" "loc_b1"))))
```

```
'(CAUSE (SMADs p15) tgfb-context)
'(BLOCK (p15 Cyclin-D:CDK4) tgfb-context)
```

```
(define tgfb-context
 (list
  (cons "title" "TGF-Beta signaling from cell membrane to nucleus through SMAD proteins.")
  (cons "author" "Heldin, C., Miayazono, K., and Dijke, P.")
  (cons "year" "1997")
  (cons "university" "Ludwig Institute for Cancer Research")
  (cons "topic" "Cell biology")
  (cons "journal" "Nature")
  (cons "pubmed" "9393997")
  (cons "locations" (list "loc_a1" "loc_b1"))))
```

```
'(CAUSE (SMADs p15) tgfb-context)
'(BLOCK (p15 Cyclin-D:CDK4) tgfb-context)
```

```
(is-true? BLOCK (SMADs Cyclin-D:CDK4))
```

```
(define tgfb-context
 (list
  (cons "title" "TGF-Beta signaling from cell membrane to nucleus through SMAD proteins.")
  (cons "author" "Heldin, C., Miayazono, K., and Dijke, P.")
  (cons "year" "1997")
  (cons "university" "Ludwig Institute for Cancer Research")
  (cons "topic" "Cell biology")
  (cons "journal" "Nature")
  (cons "pubmed" "9393997")
  (cons "locations" (list "loc_a1" "loc_b1"))))
```

```
'(CAUSE (SMADs p15) tgfb-context)
'(BLOCK (p15 Cyclin-D:CDK4) tgfb-context)
```

```
(is-true? BLOCK (SMADs Cyclin-D:CDK4))
```

TRUE!

Heldin, Carl-Henrik, Kohei Miyazono, and Peter Ten Dijke. "TGF-β signalling from cell membrane to nucleus through SMAD proteins." Nature 390.6659 (1997): 465-471.

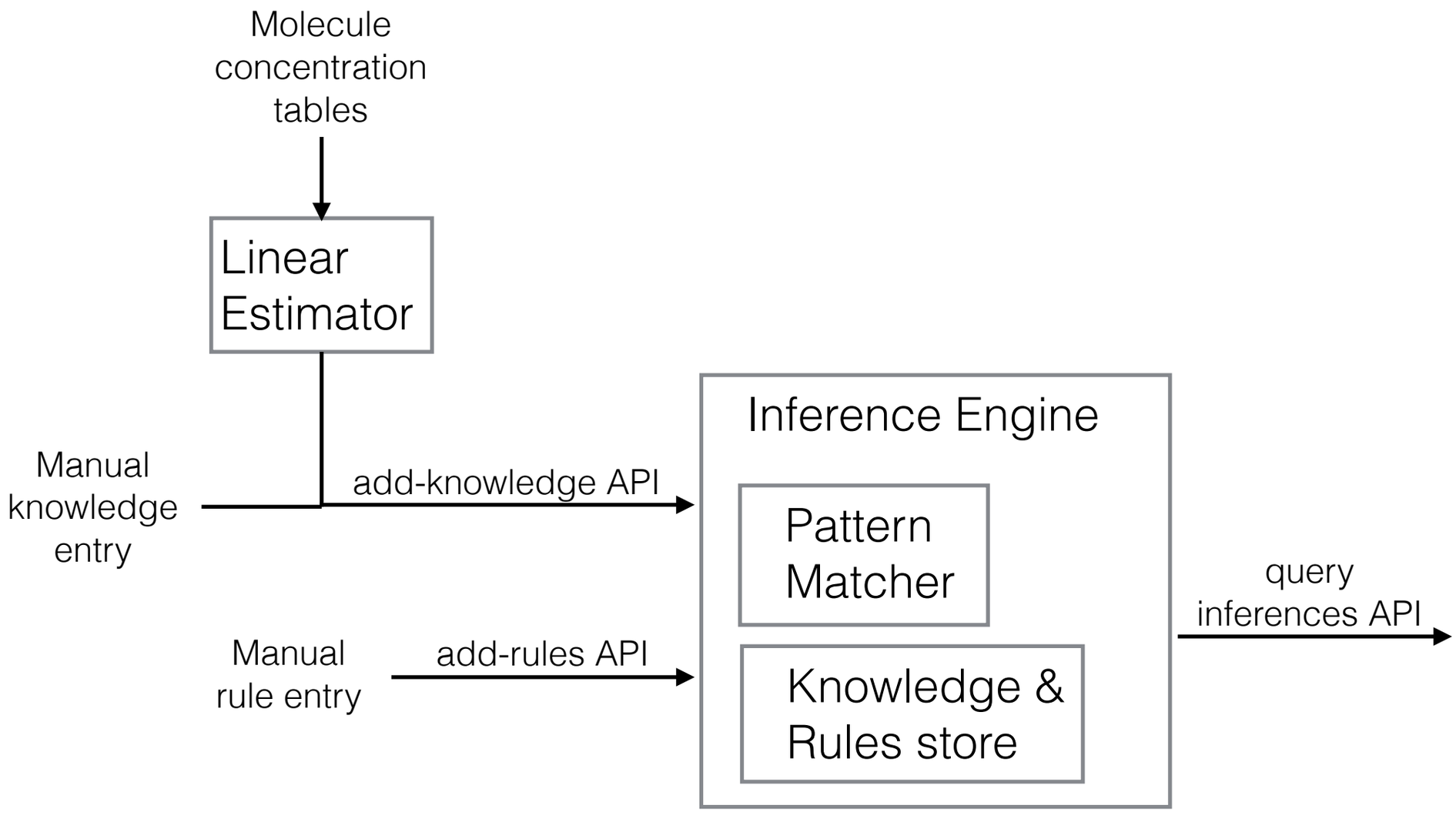
Inferred From:

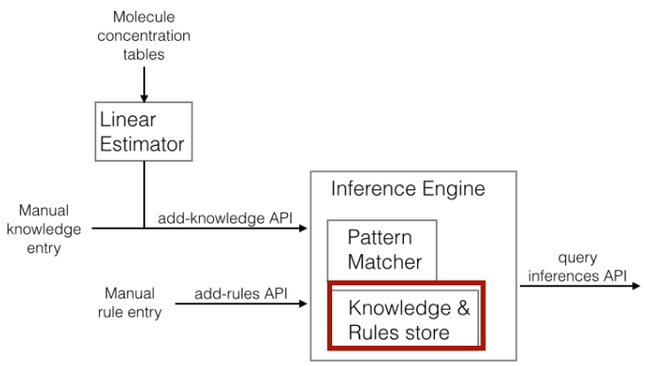
(CAUSE (SMADs p15))
(BLOCK (p15 Cyclin-D:CDK4))

Symbolic Representation and Inferences from Scientific Publications

James Woodward Weis
Yasemin Gokce
Leo Liu

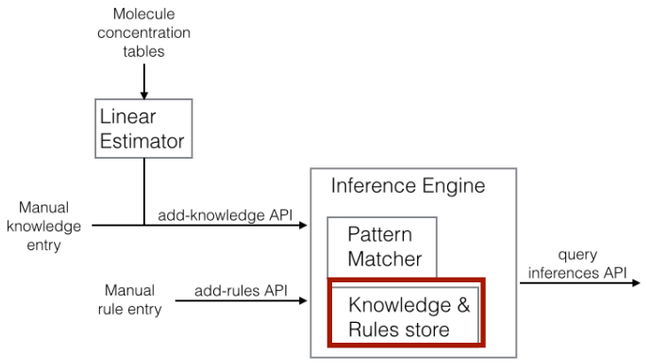
System Diagram





Knowledge

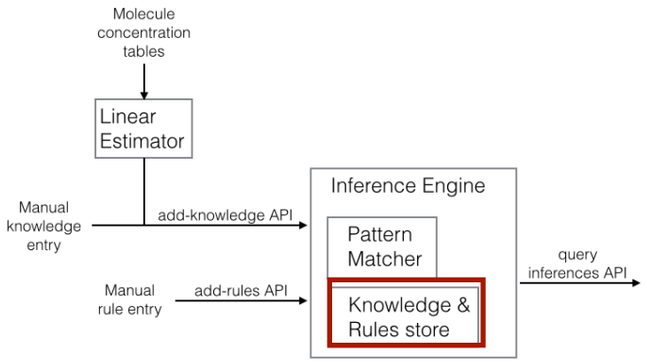
```
;; TGF-Beta Pathway
    '(CAUSE (TGF-Beta TGF-Beta-R TGF-Beta:TGF-Beta-R) tgfb-
context)
    '(BLOCK (Cyclin-D:CDK4 Rb) tgfb-context)
    '(BLOCK (HPV-E7 Rb) tgfb-context)
```



Knowledge

```
;; TGF-Beta Pathway
    '(CAUSE (TGF-Beta TGF-Beta-R TGF-Beta:TGF-Beta-R) tgfb-
context)
    '(BLOCK (Cyclin-D:CDK4 Rb) tgfb-context)
    '(BLOCK (HPV-E7 Rb) tgfb-context)
```

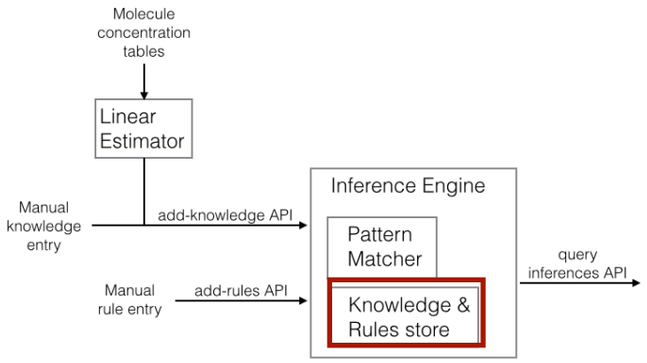
```
;; Cytokine Pathway
    '(CAUSE (Cytokines Cytokine-R Jaks) cytokine-context)
    '(CAUSE (Jaks Stat3) cytokine-context)
    '(CAUSE (Jaks Stat5) cytokine-context)
```



Knowledge

```
;; TGF-Beta Pathway
    '(CAUSE (TGF-Beta TGF-Beta-R TGF-Beta:TGF-Beta-R) tgfb-
context)
    '(BLOCK (Cyclin-D:CDK4 Rb) tgfb-context)
    '(BLOCK (HPV-E7 Rb) tgfb-context)
```

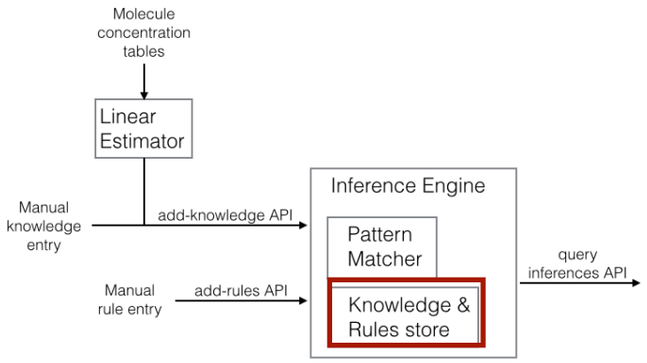
```
;; Cytokine Pathway
    '(CAUSE (Cytokines Cytokine-R Jaks) cytokine-context)
    '(CAUSE (Jaks Stat3) cytokine-context)
    '(CAUSE (Jaks Stat5) cytokine-context)
```



Knowledge

```
;; TGF-Beta Pathway
    '(CAUSE (TGF-Beta TGF-Beta-R TGF-Beta:TGF-Beta-R) tgfb-
context)
    '(BLOCK (Cyclin-D:CDK4 Rb) tgfb-context)
    '(BLOCK (HPV-E7 Rb) tgfb-context)
```

```
;; Cytokine Pathway
    '(CAUSE (Cytokines Cytokine-R Jaks) cytokine-context)
    '(CAUSE (Jaks Stat3) cytokine-context)
    '(CAUSE (Jaks Stat5) cytokine-context)
```

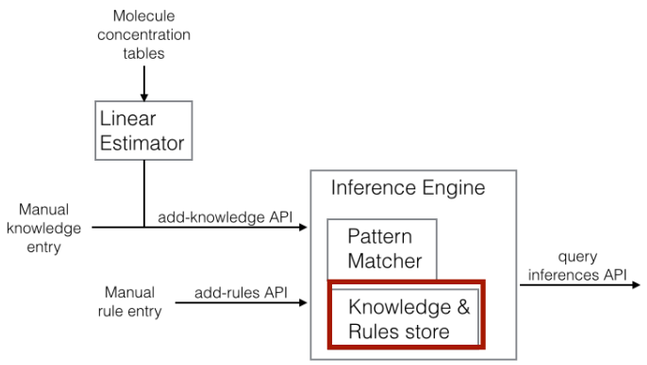


Knowledge

```
;; TGF-Beta Pathway
    '(CAUSE (TGF-Beta TGF-Beta-R TGF-Beta:TGF-Beta-R) tgfb-
context)
    '(BLOCK (Cyclin-D:CDK4 Rb) tgfb-context)
    '(BLOCK (HPV-E7 Rb) tgfb-context)
```

```
;; Cytokine Pathway
    '(CAUSE (Cytokines Cytokine-R Jaks) cytokine-context)
    '(CAUSE (Jaks Stat3) cytokine-context)
    '(CAUSE (Jaks Stat5) cytokine-context)
```

```
(define cytokine-context
  (list
   (cons "title" "The Hallmarks of Cancer")
   (cons "author" "Hanahan, D., and Weinberg, R.A.")
   (cons "year" "2000")
   (cons "university" "University of California at San Francisco")
   (cons "topic" "Cancer")
   (cons "journal" "Cell")
   (cons "pubmed" "10647931")
   (cons "locations" (list "loc_a1" "loc_b1"))))
```



Rules

A → B & B → C ⇒ A → C

```
(cons
    (list '(CAUSE (? a) (? b))
          '(CAUSE (? b) (? c)))
    '(CAUSE (? a) (? c)))
```

A ⊣ B & B → C ⇒ A ⊣ C

```
(cons
    (list '(BLOCK (? a) (? b))
          '(CAUSE (? b) (? c)))
    '(BLOCK (? a) (? c)))
```

Make inferences by pattern matching
(similar to term rewriting)

Each pattern on LHS of rule matches one statement

RHS gives new statement

Usage

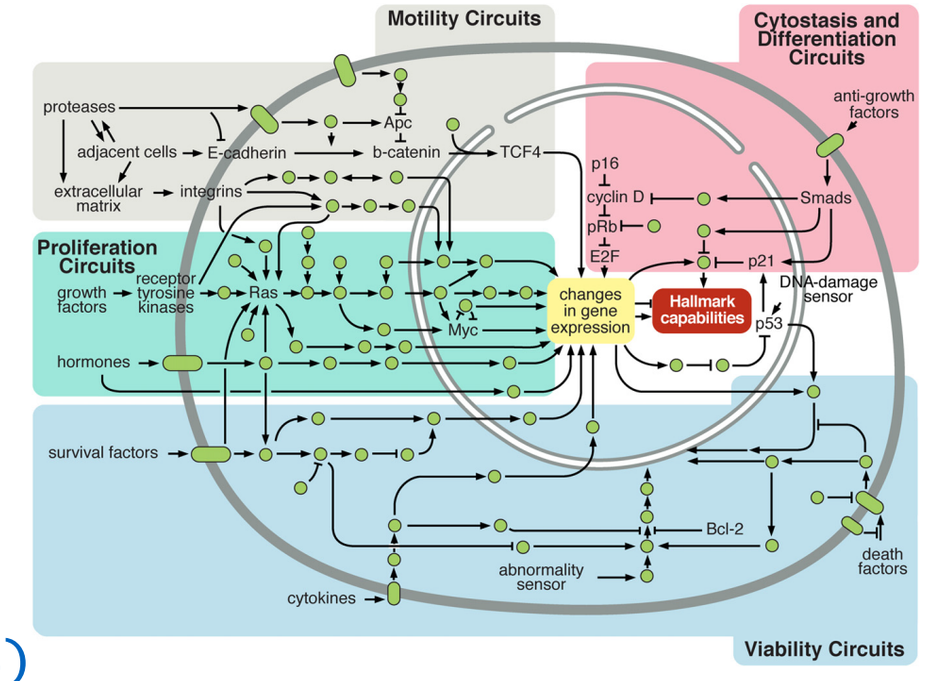
```
; load knowledge and rules from scientific
publications
(load "data/cancer_biology/knowledge.scm")
(load "data/cancer_biology/rules.scm")

; add them to the engine
(ie:add-knowledge knowledge)
(ie:add-aliases compound_obj_aliases)
(ie:add-rules rules)

; ask the system whether a statement is true
(ie:is-true '(CAUSE (p15 cell-
proliferation)) '())
```

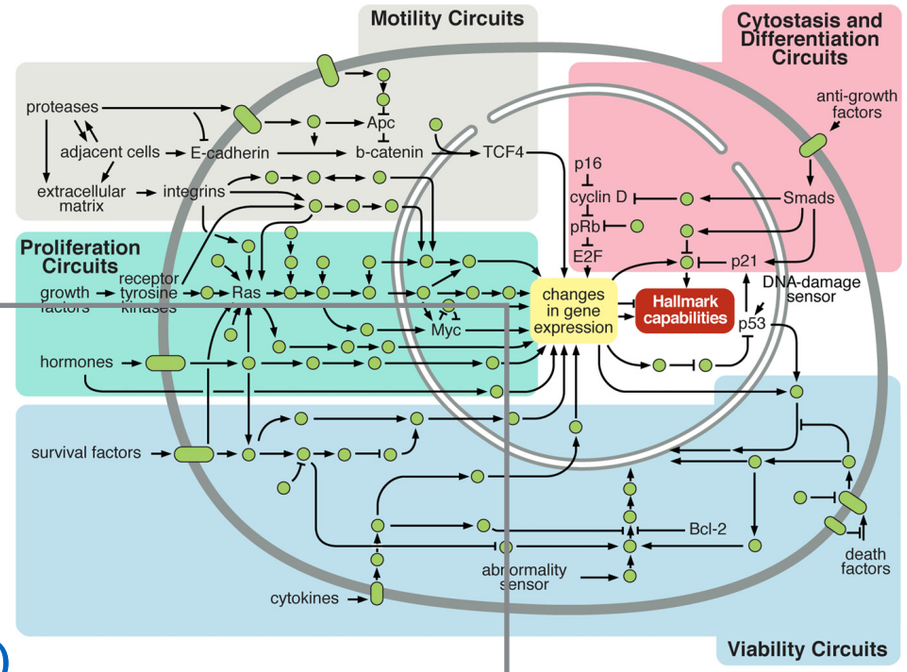
TRUE. Your statement is correct:

```
(cause
  (p15 cell-proliferation)
  (("inferred_from"
    cause
    (p15 changes-in-gene-expression)
    (("inferred_from"
      cause
      (p15 rb)
      (("inferred_from" block
                        (p15 cyclin-d:cdk4)
                        tgfb-context
                        block
                        (cyclin-d:cdk4 rb)
                        tgfb-context))
      cause
      (rb changes-in-gene-expression)
      (("inferred_from" block
                        (rb e2fs)
                        tgfb-context
                        block
                        (e2fs changes-in-gene-expression)
                        tgfb-context))))
   cause
   (changes-in-gene-expression cell-proliferation)
   (("inferred_from" cause
                     (changes-in-gene-expression cyclin-e:cdk2)
                     tgfb-context
                     cause
                     (cyclin-e:cdk2 cell-proliferation)
                     tgfb-context)))))
```



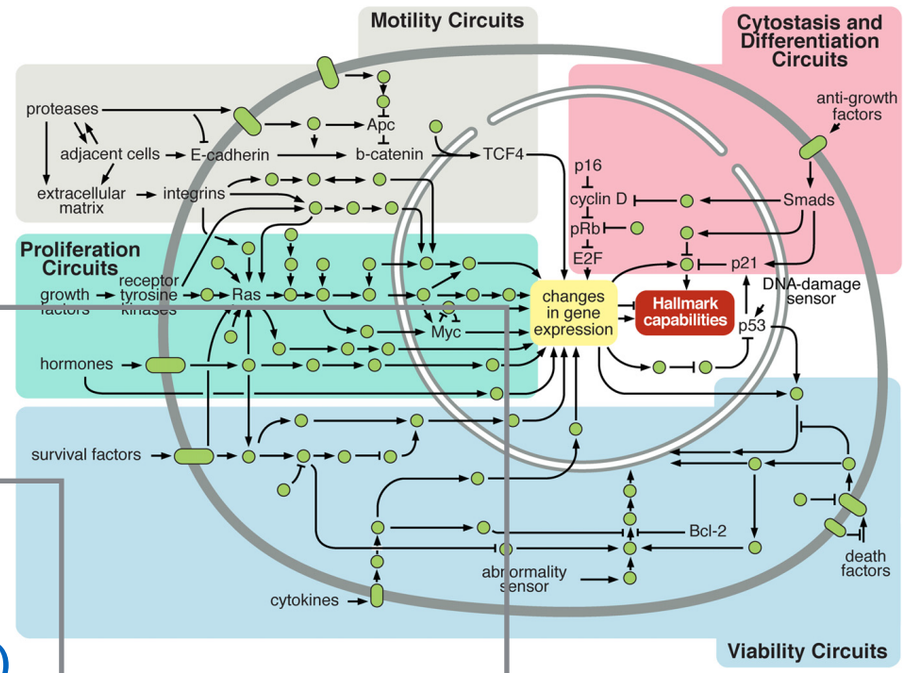
TRUE. Your statement is correct:

```
(cause
  (p15 cell-proliferation)
  (("inferred_from"
    cause
    (p15 changes-in-gene-expression)
    (("inferred_from"
      cause
      (p15 rb)
      (("inferred_from" block
                        (p15 cyclin-d:cdk4)
                        tgfb-context
                        block
                        (cyclin-d:cdk4 rb)
                        tgfb-context))
       cause
       (rb changes-in-gene-expression)
       (("inferred_from" block
                         (rb e2fs)
                         tgfb-context
                         block
                         (e2fs changes-in-gene-expression)
                         tgfb-context))))
     cause
     (changes-in-gene-expression cell-proliferation)
     (("inferred_from" cause
                       (changes-in-gene-expression cyclin-e:cdk2)
                       tgfb-context
                       cause
                       (cyclin-e:cdk2 cell-proliferation)
                       tgfb-context)))))
```



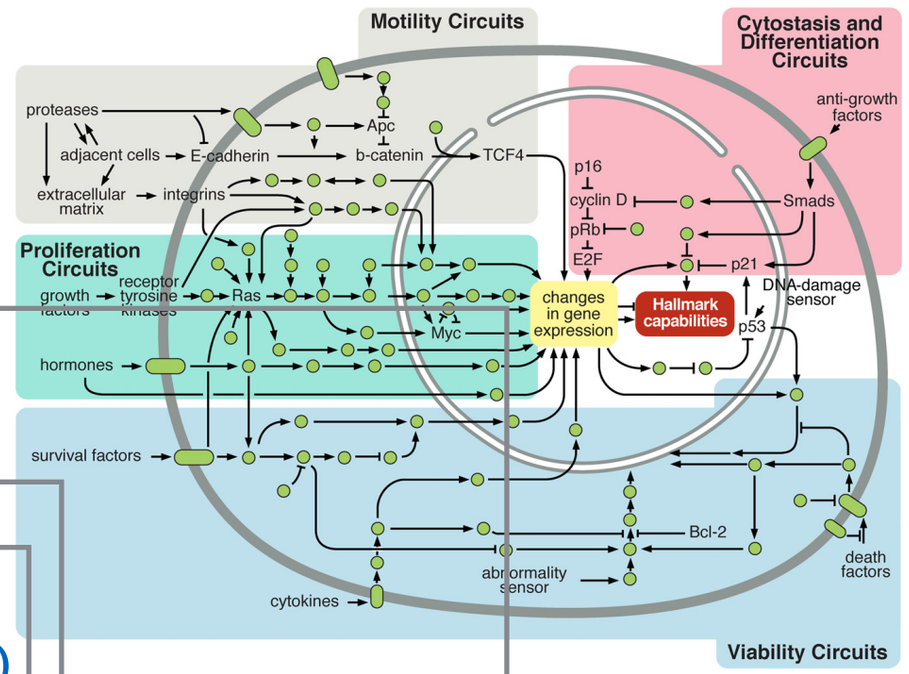
TRUE. Your statement is correct:

```
(cause
  (p15 cell-proliferation)
  (("inferred_from"
    cause
    (p15 changes-in-gene-expression)
    (("inferred_from"
      cause
      (p15 rb)
      (("inferred_from" block
                        (p15 cyclin-d:cdk4)
                        tgfb-context
                        block
                        (cyclin-d:cdk4 rb)
                        tgfb-context))
       cause
       (rb changes-in-gene-expression)
       (("inferred_from" block
                         (rb e2fs)
                         tgfb-context
                         block
                         (e2fs changes-in-gene-expression)
                         tgfb-context))))
     cause
     (changes-in-gene-expression cell-proliferation)
     (("inferred_from" cause
                       (changes-in-gene-expression cyclin-e:cdk2)
                       tgfb-context
                       cause
                       (cyclin-e:cdk2 cell-proliferation)
                       tgfb-context)))))
```



TRUE. Your statement is correct:

```
(cause
  (p15 cell-proliferation)
  (("inferred_from"
    cause
    (p15 changes-in-gene-expression)
    (("inferred_from"
      cause
      (p15 rb)
      (("inferred_from" block
                        (p15 cyclin-d:cdk4)
                        tgfb-context
                        block
                        (cyclin-d:cdk4 rb)
                        tgfb-context))
       cause
       (rb changes-in-gene-expression)
       (("inferred_from" block
                         (rb e2fs)
                         tgfb-context
                         block
                         (e2fs changes-in-gene-expression)
                         tgfb-context))))
     cause
     (changes-in-gene-expression cell-proliferation)
     (("inferred_from" cause
                       (changes-in-gene-expression cyclin-e:cdk2)
                       tgfb-context
                       cause
                       (cyclin-e:cdk2 cell-proliferation)
                       tgfb-context)))))
```



Experiment with cancer biology knowledge

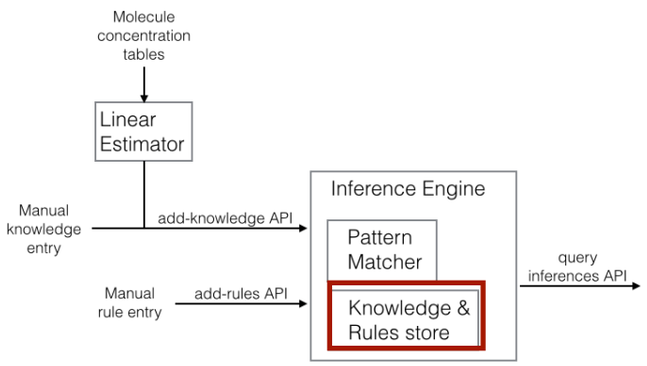
Added 40 statements from cancer papers

```
; TGF-Beta pathway
'(CAUSE (Cyclin-D CDK4 Cyclin-D:CDK4)
tgfb-context)
'(BLOCK (p16 Cyclin-D:CDK4) tgfb-
context)
```

Ran inference engine

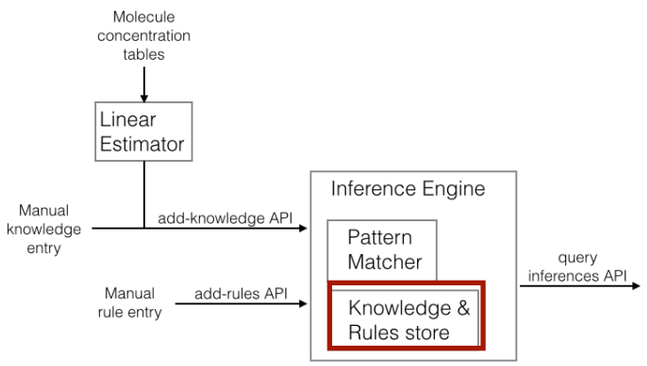
6 minutes -> 2000 lines of new statements and context data

Additional Features



Aliases

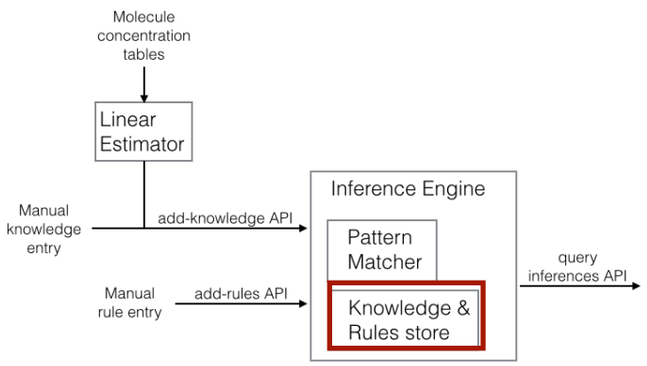
```
(define compound_obj_aliases '(list
    (cons "Cyclins" (list 'Cyclin-D 'Cyclin-E))))
```



Aliases

```
(define compound_obj_aliases '(list
    (cons "Cyclins" (list 'Cyclin-D 'Cyclin-E))))
```

(is-true? ‘CAUSE **‘Cyclin-D** ‘someEffect)

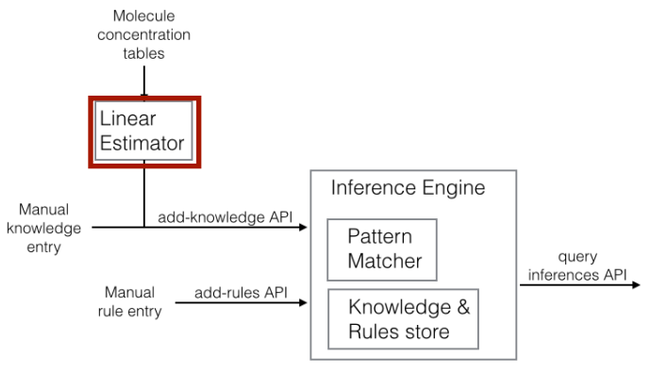


Aliases

```
(define compound_obj_aliases '(list
    (cons "Cyclins" (list 'Cyclin-D 'Cyclin-E))))
```

(is-true? ‘CAUSE **‘Cyclin-D** ‘someEffect)

(is-true? ‘CAUSE **“Cyclins”** ‘someEffect)



Linear Estimator

Molecule X (nM)	Molecule Y (nM)
59	350
34	459
26	684
12	798

covariance of X & Y

variance of Y

correlation of X & Y

corr > t

corr < -t

‘(CAUSE X Y)

‘(BLOCK X Y)

Recap

https://github.com/yasho/6.945-FinalProj

1. Hanahan, D., and Weinberg, R.A. (2000). The Hallmarks of Cancer. Cell 100, 57-70.
2. Hanahan, D., and Weinberg, R.A. (2011). The Hallmarks of Cancer: The Next Generation. Cell 144, 646-674.
3. Heldin, C., Miayazono, K., and Dijke, P. (1997). TGF-Beta signalling from cell membreane to nucleus through SMAD proteins.
4. Huelsken, J., and Juergen, B. (2000). The Wnt signalling pathway. J. Cell Sci. 113, 3545.
5. Muller, H., et al. (2001). E2Fs regulate the expression of genes involved in differentiation, development, proliferation, and apoptosis. Genes Dev., 15(3): 257-285.
6. Wertheimer, Jeremy. Reasoning from experiments to causal models in molecular cell biology. (Doctoral dissertation). MIT, 1996.

Recap

Add knowledge and rules to the system

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Recap

Add knowledge and rules to the system

User queries (is-true? statement)

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Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences

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4. Huelsken, J., and Juergen, B. (2000). The Wnt signalling pathway. J. Cell Sci. 113, 3545.
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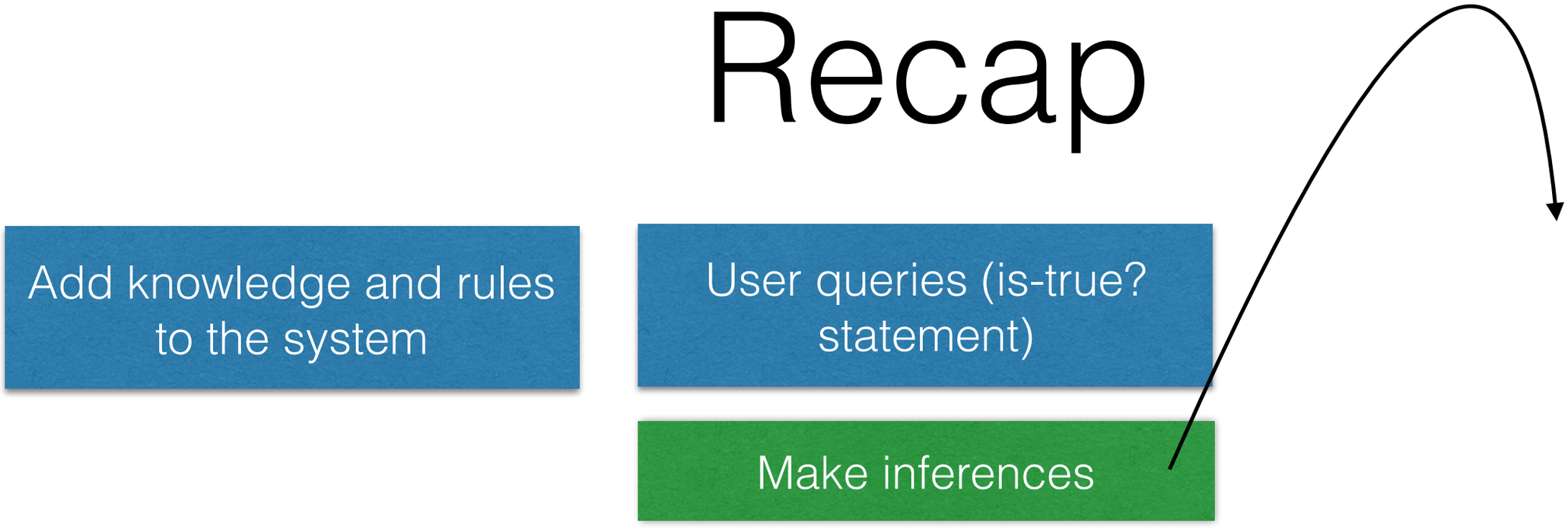
Recap



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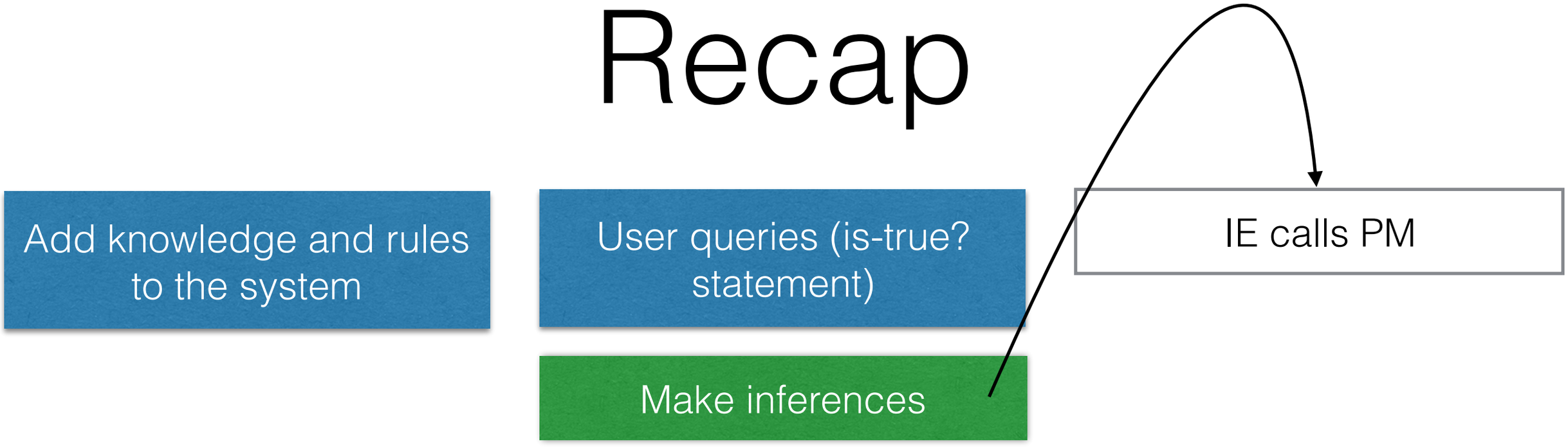
Recap



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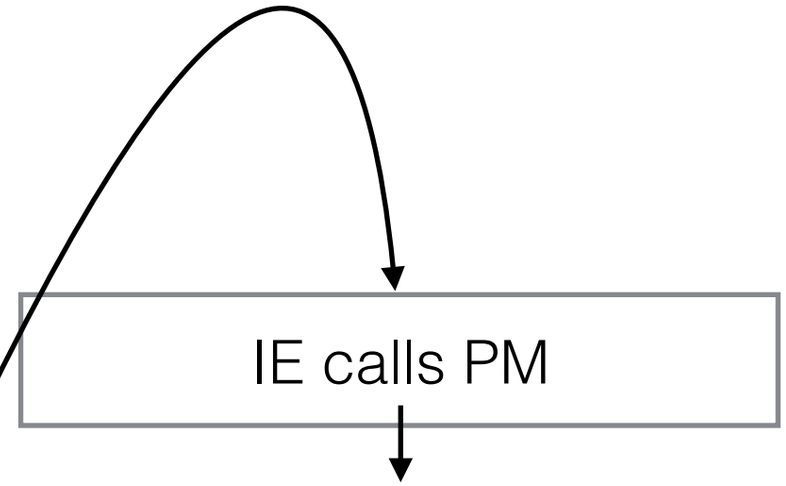
Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences



https://github.com/yasho/6.945-FinalProj

1. Hanahan, D., and Weinberg, R.A. (2000). The Hallmarks of Cancer. Cell 100, 57-70.
2. Hanahan, D., and Weinberg, R.A. (2011). The Hallmarks of Cancer: The Next Generation. Cell 144, 646-674.
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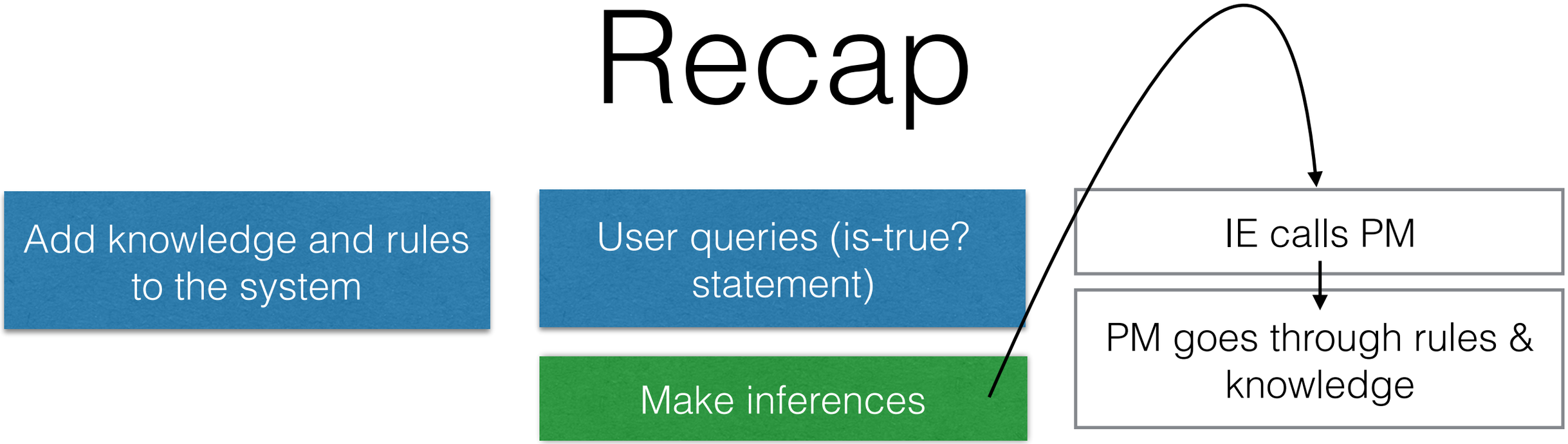
4. Huelsken, J., and Juergen, B. (2000). The Wnt signalling pathway. J. Cell Sci. 113, 3545.
5. Muller, H., et al. (2001). E2Fs regulate the expression of genes involved in differentiation, development, proliferation, and apoptosis. Genes Dev., 15(3): 257-285.
6. Wertheimer, Jeremy. Reasoning from experiments to causal models in molecular cell biology. (Doctoral dissertation). MIT, 1996.

Recap



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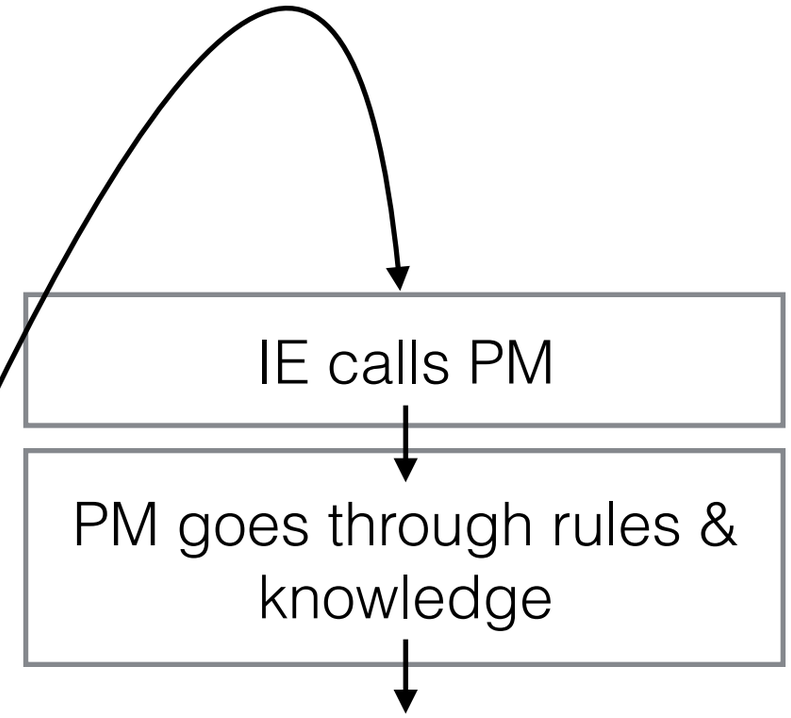
Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences



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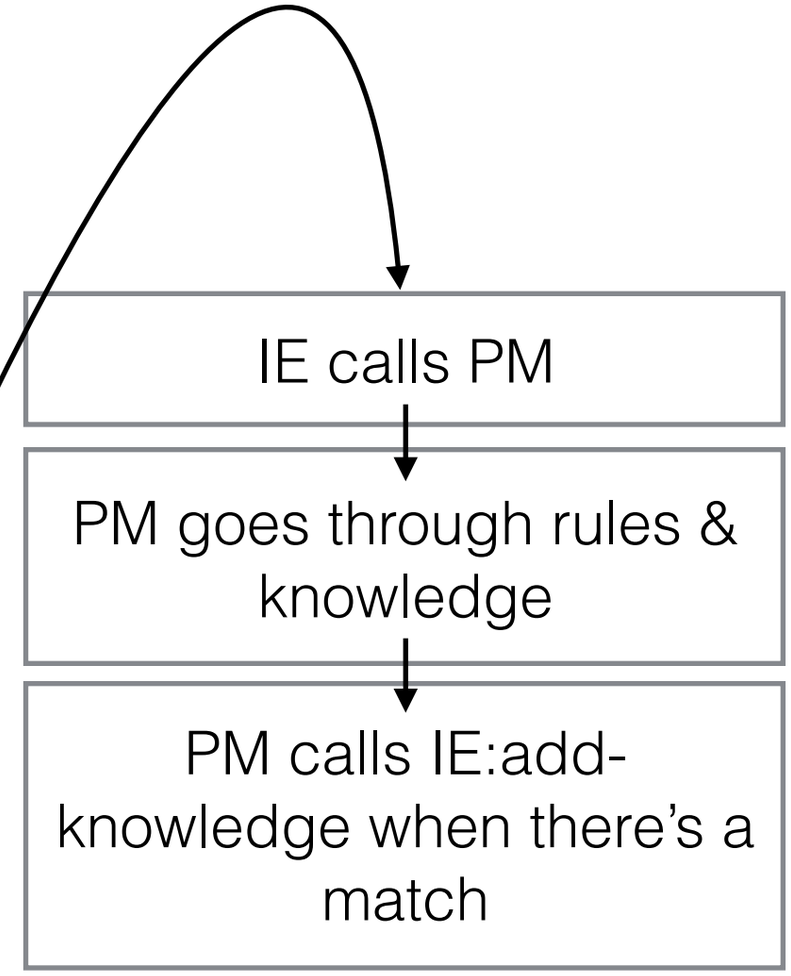
Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences



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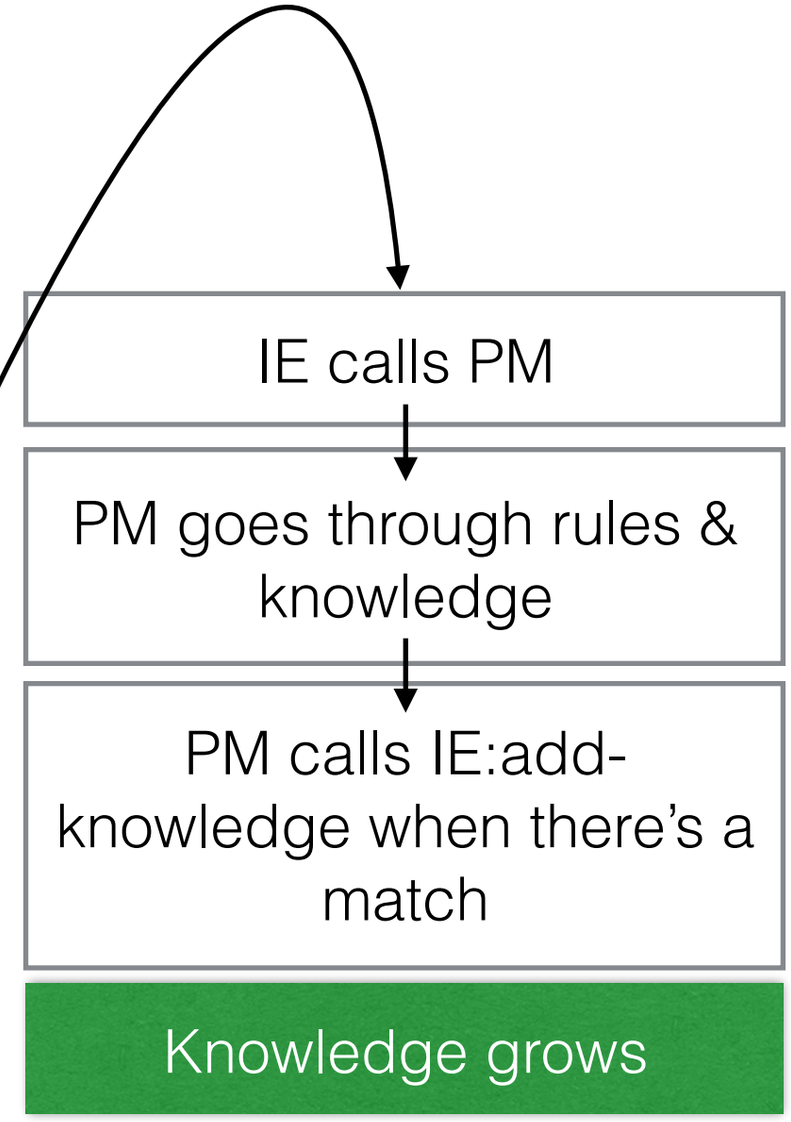
Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences



Knowledge grows

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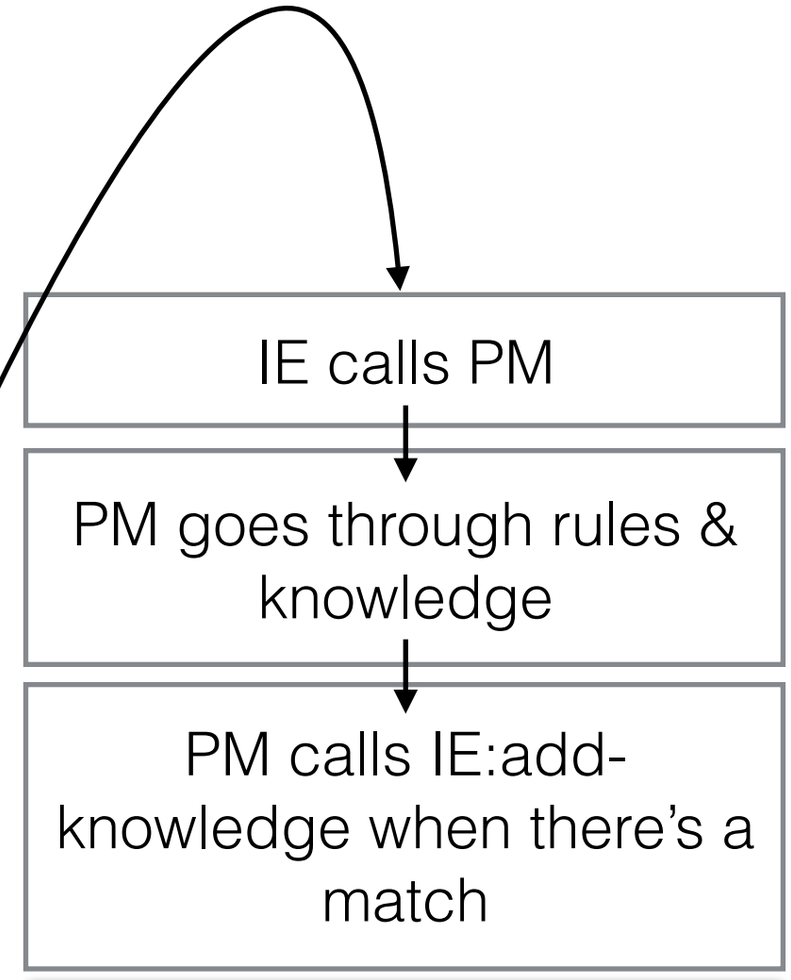
Recap

Add knowledge and rules to the system

User queries (is-true? statement)

Make inferences

Check if statement is in knowledge



Knowledge grows

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