Action Language for Representing & Reasoning about Protein Interactions

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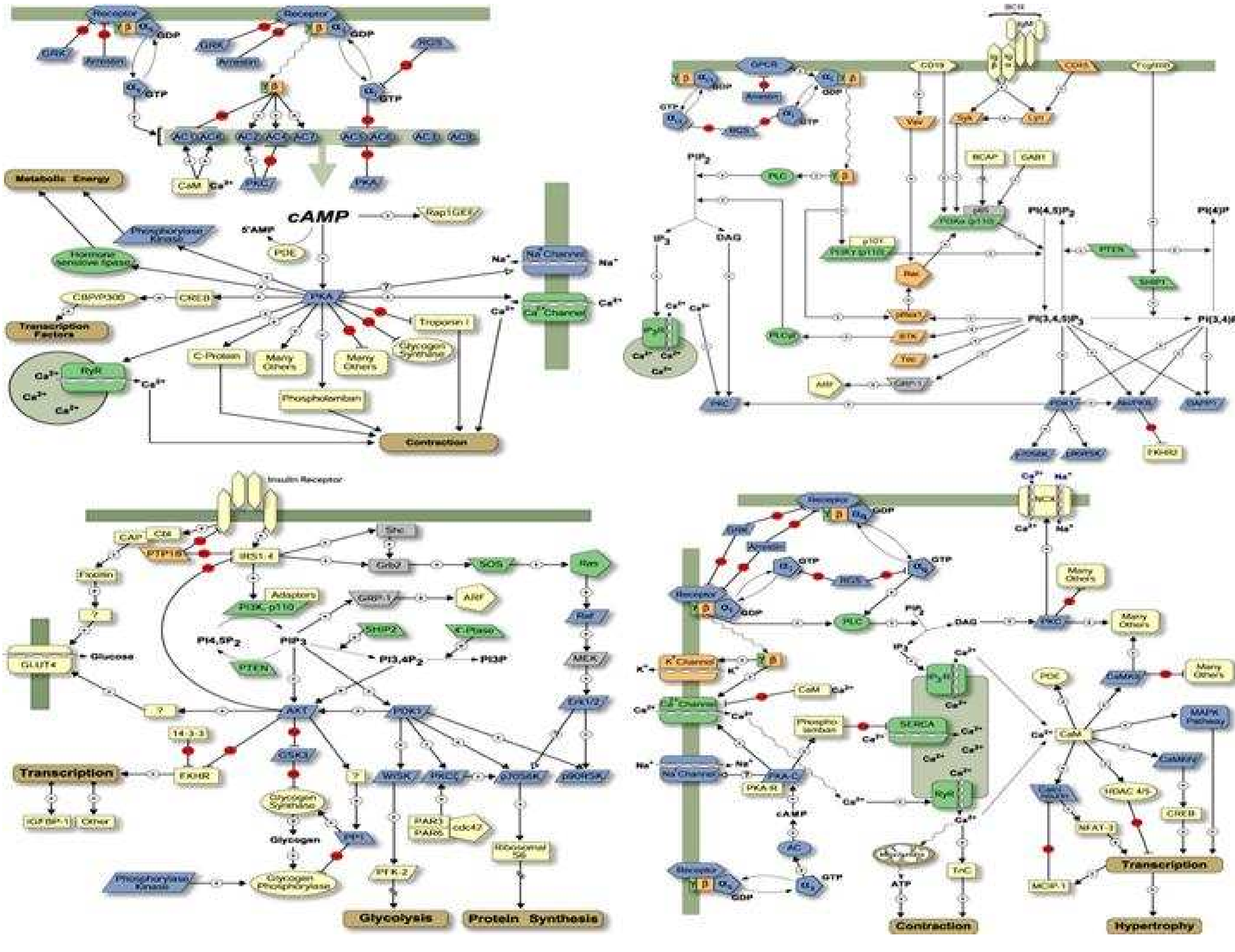
Motivation

- The cell's behavior is determined by protein interactions.
- Protein interactions are usually triggered in series by some conditions or other interactions.
- Biological knowledge of protein interactions are inherently imprecise.
- New knowledge of protein interactions quickly become outdated.
- Complexity of protein networks have outgrown human reasoning capability.



Receptor
GDP
GTP
GRK
Arrestin
RGS
CaM
PKC
PKA
Metabolic Energy
cAMP
5'AMP
PDE
Rap1GEF
Phosphorylase Kinase
Hormone Sensitive lipase
CBP/P300
CREB
Transcription Factors
Troponin I
Glycogen Synthase
C-Protein
Many Others
Phospholamban
RyR
Contraction
Na⁺ Channel
Ca²⁺ Channel
BCR
CD19
CD45
GPCR
PLC
PIP2
IP3
DAG
BCAP
GAB1
PI3K p110
PI(4,5)P2
PI(4)P
PI(3,4,5)P3
PI(3,4)P2
PTEN
SHIP1
BTK
Tec
ARF
PKC
PDK1
FKHR
Insulin Receptor
CAP
Cbl
PTP1B
IRS1-4
Shc
Grb2
SOS
Ras
Flotilin
Adaptors
PI3K-p110
GRP-1
SHIP2
Raf
MEK
ERK1/2
GLUT4
Glucose
PI4,5P2
PIP3
PI3,4P2
PI3P
AKT
14-3-3
GSK3
Transcription
Glycogen Synthase
Glycogen
Glycogen Phosphorylase
Phosphorylase Kinase
WNK
PKCζ
p70S6K
p90RSK
IGF BP-1
Other
PP1
PFK-2
PAR3
PAR6
cdc42
Ribosomal S6
Glycolysis
Protein Synthesis
NCX
Many Others
K⁺ Channel
Ca²⁺ Channel
Na⁺ Channel
PKA-C
PKA-R
cAMP
AC
Phospho-lamban
SERCA
CaM
CaMKII
MAPK Pathway
CaMKIV
HDAC 4/5
CREB
NFAT-3
MCIP-1
TnC
ATP
Transcription
Contraction
Hypertrophy

Problem Description

We want to build a knowledge base of protein interaction networks that encodes:

- a ontology of biological concepts;
- causal relationship between cellular properties;
- direct and indirect effects of protein interactions.

The knowledge based should be elaboration tolerant.

Problem Description

The knowledge base should be able to:

- reason about triggered interactions;
- reason with imprecise knowledge;
- predict the outcome of a series of interactions;
- find out interventions to alter the cellular behavior in a particular way;
- determine the cause behind some abnormal cellular behavior.

Related Works

Petri nets

- A language for modeling concurrent systems.
- Properties relevant to biological systems: liveness, boundedness, soundness and reachability.
- Extensions for time, hierarchies and stochasticness.

Pi-calculus

- A formal language for concurrent systems.
- Proteins = biological processes, binding sites = communication channels.
- Protein interaction and modification = communication and channel transmission.

Related Works

Pathway Logic

- An abstract algebraic formalism.
- Biological structures = algebraic expression.
- Biological processes = rewriting rules.

It is not clear how these approaches can handle several or all of important issues, namely elaboration tolerance, imprecise knowledge, and complex reasoning.

(More detailed discussion and references can be found in [ISMB04])

Proposed Solution

- We propose using action languages.
  There have been extensive research in action languages dealing with causality, actions, prediction, explanation, planning.
- We start with the most basic action language – the language **A** – and add new features as necessary.
- We experiment first with simple networks then with more complex ones.

Proposed Solution

- Major issues: triggered interactions and imprecise knowledge.
- We have extended action languages to deal with triggered actions (KR04; NRAC03), and actions with probabilistic effects (AAAI02;AAAI04).
- We have been testing our approach with real biological domains (ISMB04; KR04).

Proposed Solution

The language for triggered actions:

- It extends **A** with triggered actions.
- Domain description contains:

a ***causes*** f ***if*** $f_1, \ldots, f_n$

$g_1, \ldots, g_m$ ***triggers*** b

$h_1, \ldots, h_k$ ***inhibits*** c

where f_i, g_j, h_l are fluents; a, b, c are actions.

- Semantics is based on trajectory models.

Proposed Solution

The language for probabilistic actions:

- It extends **A** of unknown variables.
- E.g.: a coin is fair or fake with probability *p*. Fair coins land head with probability q_1. Fake coins land head with probability q_2.

  The domain description:

  toss ***causes*** head ***if*** u, v_1

  toss ***causes*** ¬head ***if*** u, ¬v_1

  toss ***causes*** head ***if*** ¬u, v_2

  toss ***causes*** ¬head ***if*** ¬u, ¬v_2

  $Pr(u) = p$; $Pr(v_1) = q_1$; $Pr(v_2) = q_2$

- u is **inertial** and v_1, v_2 are **non-inertial**.

Future Thesis Work

- *Delay of triggered action occurrence:*

  f ***triggers*** a means that when f is true, a will occur in current state or some state later.

- *Observations are recorded at situations instead of exact time steps.*
- *Not only inhibition can override triggering but also vice versa.*
- *Modifiers like 'always', 'normally', 'rarely', 'never' are used together with 'causes', 'triggers', 'inhibits' to deal with imprecise knowledge.*

Future Thesis Work

- *Rules with modifiers can override each other:*

  f ***normally triggers*** a
  g ***always inhibits*** **a**

  then in state {**f**, **g**} action **a** will not be triggered.

- *Various granularity of time:*

  New knowledge can decompose interactions into sub-interactions, which correspond to finer time scale.

- *The notion of inhibition as undoing:*

  Saying that interaction X inhibits Y means if X can undo the effect of Y.

Future Thesis Work

- *Missing or uncertain elements in domain descriptions .*
- *Application of probabilistic action language to protein interactions.*
- *Complexity and scalability in dealing with real-world domains.*
- *Integration of triggered actions and probabilistic actions into one language.*
- *Target protein network: the Kohn's interaction map [ISMB04].*

References

[AAAI02] Baral, C., and Tran, N. 2002. Reasoning about actions in a probabilistic setting. In *Proceedings of AAAI'02*, 507–512.

[NRAC03] Baral, C., and Tran, N. 2003. Representation and reasoning about evolution of the world in the context of reasoning about actions. In *Nonmonotonic Reasoning, Action, and Change (NRAC'03)*.

[KR04] Tran, N., and Baral, C. 2004. Reasoning about triggered actions in Ansprolog and its application to molecular interactions in cells. In *KR 2004*.

[ISMB04] Baral, C.; Chancellor, K.; Tran, N.; Tran, N.; and Berens, M. 2004. A knowledge based approach for representing and reasoning about signaling networks. In *Intelligent Systems for Molecular Biology/European Conference on Computational Biology 2004*.

[AAAI04] Tran, N., and Baral, C. 2004. Encoding probabilistic causal models in probabilistic action language. In *AAAI'04*.

(All the papers are available electronically at http://www.public.asu.edu/~nhtran)