Biocuration and rule-based modelling of protein interaction networks in KAMI

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What does KAMI stand for?

Knowledge Aggregator and Model Instantiator

What is special about KAMI?

- Rule-based strategy
- Incremental aggregation of large models
- Allows a posteriori understanding of models
Outline

KAMI
1) KAMI Studio (KAMI GUI)
2) Knowledge representation (Nugget / ActionGraph)
3) Building a model

Kappa
4) Rule-based executable model
5) Pathway discovery (Causality analysis)

6) The pYnet model
Knowledge representation

Split in two layers, the nuggets and action graph
- Unambiguously specify interactions
- Limited set of symbols

Can read a model using KAMIStudio

Every nugget is independent
- Facilitates incremental aggregation
Building a KAMI model

**KAMI interaction (programmatic)**

```python
Binding(
    RegionActor(
        gene=Gene(uniprot_ac="P00519", hgcnc_symbol="ABL1"),
        region=Region(name="SH2", interproid="IPR000980"))
),
SiteActor(
    gene=Gene(uniprot_ac="P11274", hgcnc_symbol="BCR"),
    site=Site(name="pY246", residues=[[Residue(aa="Y", loc=246, state=State("phosphorylation", True))]])
),
rate=0.001,
desc="ABL1 binds BCR-Y246"
)
```

**KAMI nugget (graph representation)**
How does it work?

\[ \tilde{N} : \text{Nugget} \]

\[ A : \text{Action Graph} \]

\[ \text{Arrow} : \text{Typing} \]

KAMI graph hierarchy
Typing
Typing

Diagram with nodes and edges illustrating the typing process involving EGFR, SHC1, and other related proteins.
Typing

Diagram of biological pathways involving EGFR, SHC1, SH2, and GRB2, with annotations for each node and edge.
Semantic nuggets
Knowledge aggregation
Knowledge aggregation
Knowledge aggregation (continued)
Knowledge aggregation (continued)
Biocuration with KAMI

Allows users to easily add new data

- Detects elements already present in action graph
- Semantic checks
- Completes interaction if more detailed
- Ignores new data if it already exists
Kappa rule-based model

**KAMI nugget**

- ABL1
- SH2
- bnd
- pY246
- Y246
- BCR

**Kappa rule**

`ABL1(SH2[./1]), BCR(pY246[./1] Y246_phos{True})`
1 nugget ≈ 1 rule (info from AG)

IFGR1(pY1281[./1] Y1281_phos{True}), ABL1(SH2[./1])

IFGR1(pY1280[./1] Y1280_phos{True}), ITK(SH2[./1])
1 nugget ≈ 1 rule  
(info from AG)

**Nuggets**

\[
\text{IFGR1}(\text{pY1281}[./1], \text{Y1281\_phos}\{\text{True}\}), \text{ABL1}(\text{SH2}[./1])
\]

\[
\text{IFGR1}(\text{pY1280}[./1], \text{Y1280\_phos}\{\text{True}\}), \text{ITK}(\text{SH2}[./1])
\]
1 nugget ≈ 1 rule (info from AG)

IFGR1(\(\text{pY1280-1[./1]}\) Y1281_phos\{True\}), ABL1(\(\text{SH2[./1]}\))
||
IFGR1(\(\text{pY1280-1[./1]}\) Y1280_phos\{True\}), ITK(\(\text{SH2[./1]}\))
Simulations with KaSim

- Rule-based
- Deals with combinatorial complexity
- Quantitative
- Stochastic
- No spatial dimension
- Analysis system dynamics
Causality Analysis (KaStor)

EGF binds EGFR ➔ EGFR-EGFR dimer ➔ EGFR phosphorylates EGFR-Y1092 ➔ GRB2 binds EGFR-Y1092 ➔ GRB2 recruitment through EGFR ➔ Recruited GRB2
Causality Analysis (KaStor)

Discovered pathway
ZAP70 involved in GRB2 recruitment
The pYnet model

Cell signaling
  - Tyrosine phosphorylation
  - SH2 domain bindings

900 interactions extracted from
  - PhosphoSite
  - Phospho.ELM
  - NCI Pathway Interaction Database

Well suited to showcase rule-based modelling
  - Combinatorial complexity
  - Large
  - Scaffolding
Important combinatorial compl.

Processive phosphorylation
Summary

KAMI allows

- Representation of individual interactions
- Aggregation into an interaction network

KAMI works with Kappa to

- Produce dynamic simulations
- Discover pathway using causality analysis
Summary

Fundamentally different approach to modelling

- No need to know exactly where new data fits
- Can just “smash” interactions together
- No need to explicitly build the pathways (bias)
- Can discover the pathways through analysis
Using KAMI and Kappa

In development
KAMI: github.com/Kappa-Dev/KAMI
KAMISTudio: github.com/Kappa-Dev/KAMISTudio

Graph rewriting
ReGraph: github.com/Kappa-Dev/ReGraph

Kappa
KaSim: github.com/Kappa-Dev/KaSim.git
Web Site: kappalanguage.org
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