Executable Knowledge for rule-based modelling

of cellular signalling networks

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Context

Cellular signalling

- Decentralized coordination of tissue formation and maintenance
 - *extra*-cellular ligands trigger *intra*-cellular signalling pathways to control cell growth, death, division, ...
- Perturbed in disease states, *e.g.* cancer, diabetes, ...
 - kinetic perturbations: over-expression, knock-outs, ...
 - causal perturbations: mutations, truncations, ...

Why model signalling?

- Signalling networks, *and their literature*, are mind-bogglingly complicated
 - 1000s of proteins and 10s (or even 100s) of thousands of PPIs [protein-protein interactions]
 - empirical knowledge is fragmented and scattered across a vast literature
 - impossible to 'work out' in your head

Traditional modelling

- Modelling as a primarily 'mental' activity
 - identify the key variables *and* their inter-dependencies under *standard* perturbations
 - amounts to making model-level assumptions *during* model construction and 'debugging'
 - model as 'synthesis of understanding'

Traditional modelling

- To put it differently:
 - the modelling is done 'in your head'
 - the model is an artifact that emerges fully-formed and is just 'written down'
 - the model is then debugged if it fails to meet your mental 'specification'

Modelling signalling

- Signalling needs models as 'tools for discovery'
 - a formal reification of the modelling process [rather than just the resulting artefact] as an 'audit trail'
 - precisely *in order to* achieve an understanding
 - reverse-engineer a specification by combining empirical knowledge with (biological) inference

Modelling signalling

- Models must therefore
 - be *easily* extensible and modifiable [since empirical knowledge is always changing]
 - be *arbitrarily* perturbable [since we wish to discover, not hard-wire, their effects]
 - incorporate empirical and inferred knowledge [at various levels of detail]

Rule-based modelling

- Formal representation for the (10s? of 1000s of) protein-protein interactions (PPIs) in signalling
 - graph rewriting formalism
 - scalable stochastic simulation
 - pathways as causal traces
- Handles kinetic, but not causal, perturbations

Serendipity

The cognitive barrier

- Have to read many papers to find various fragments of knowledge about a single PPI
 - many different 'puzzle pieces', at varying levels of detail, that must [somehow] be assembled into rules
 - the effects of causal perturbations must be hard-wired by enumerating all cases [rather than emerging]
 - not scalable for a human curator [believe me, I've done it]

Big Mechanism

- Seeks causal explanations of complex system behaviour [not 'just' correlations]
- Machine reading of papers, automatic assembly into models that yield causal explanations ...
- The chosen use case: signalling pathways in cancer!

Breaching the cognitive barrier

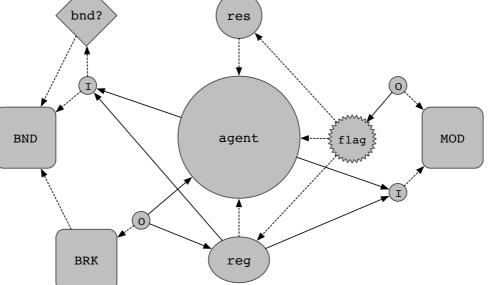
Assembly

- Big Mechanism aims to make reading scalable and RBM provides causal explanations — once your PPIs have been formalized as rules
- The hard problem is assembly
 - combining fragments of knowledge into rules ...
 - ... in such a way that (apparently) conflicting information can be accommodated ...
 - ... and the effects of causal perturbations emerge

KAMI

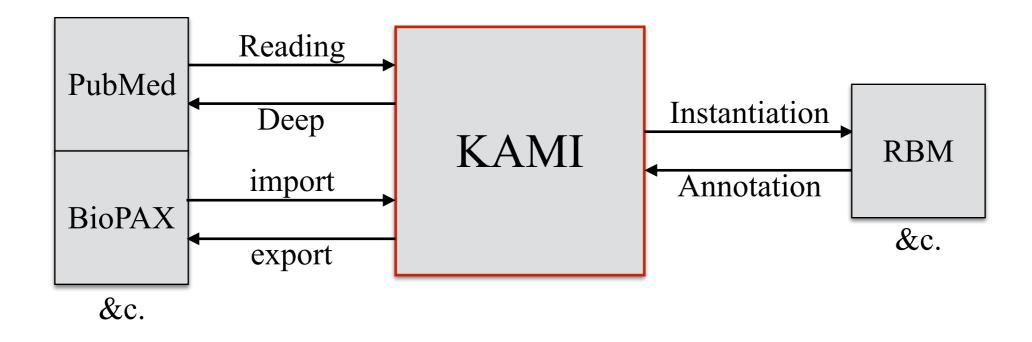
knowledge aggregator & model instantiator

- Uses a graph-based representation of PPIs
 - a graph with two directed edge structures, respecting a meta-model:

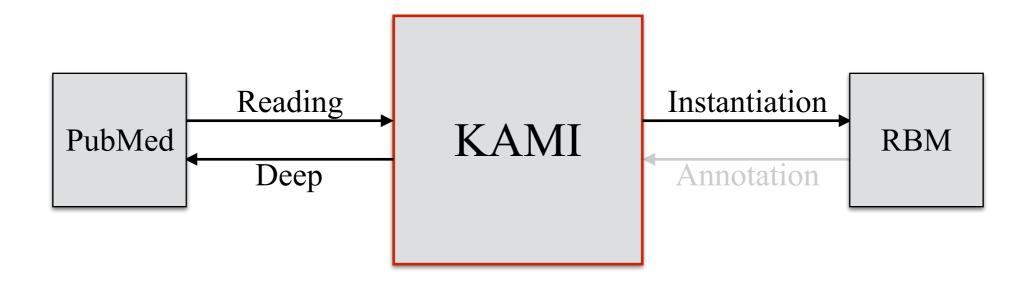


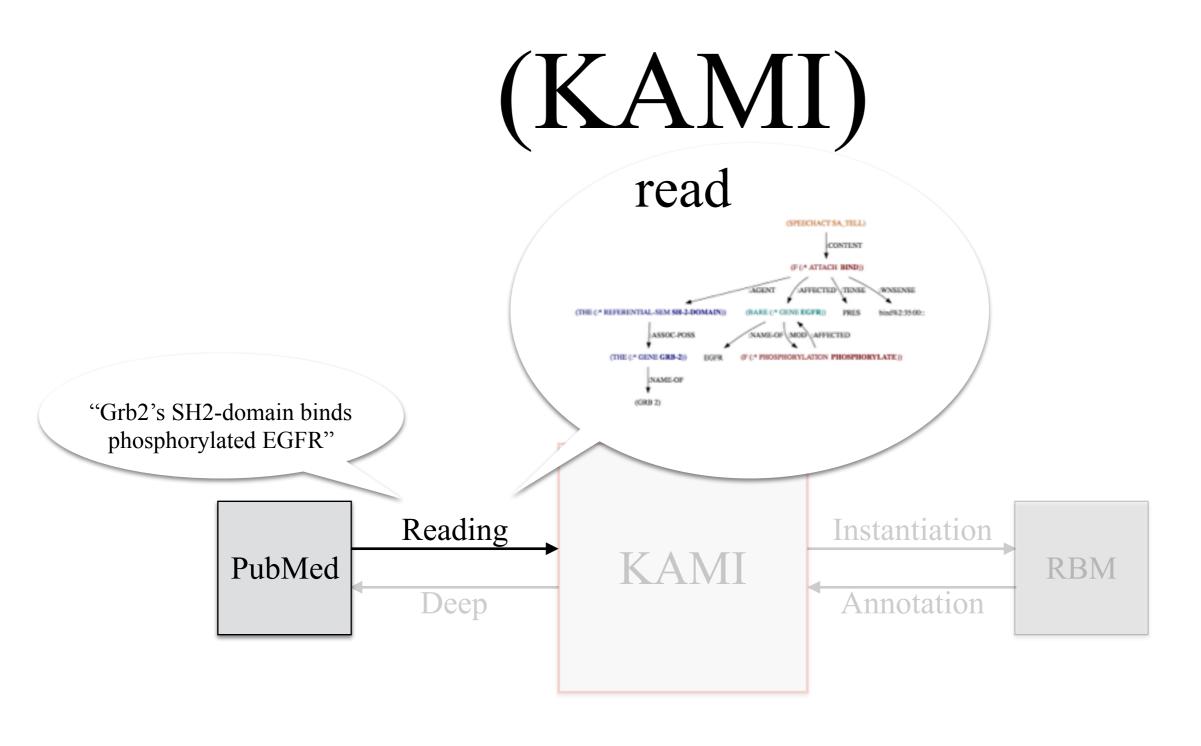
• uses graph rewriting to update and aggregate PPIs

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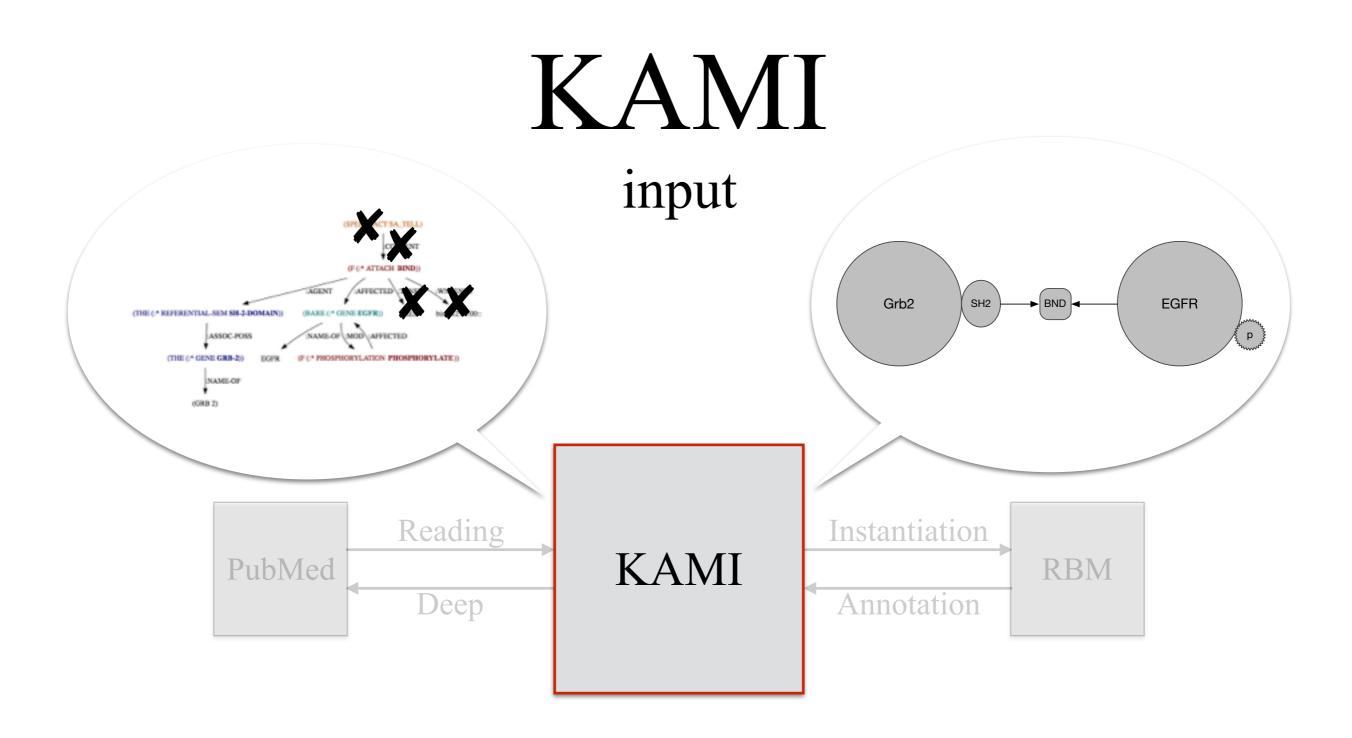




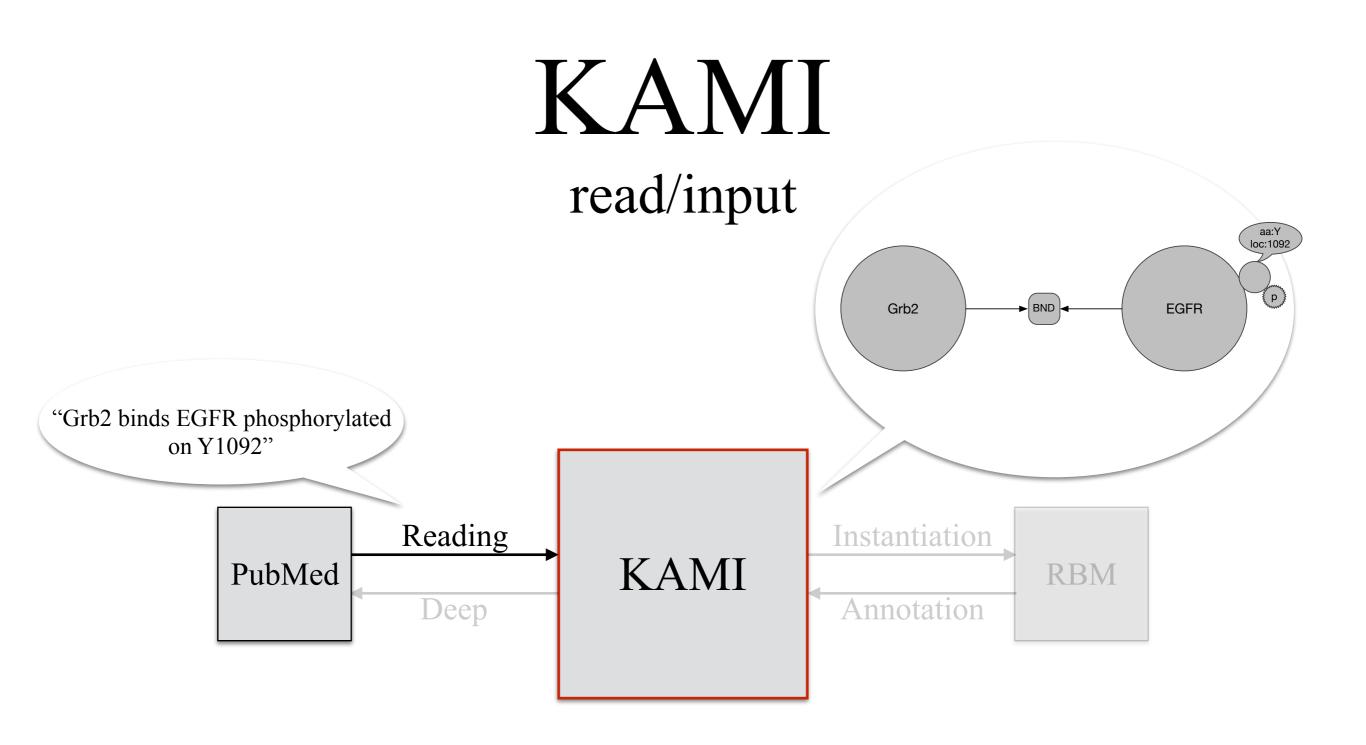


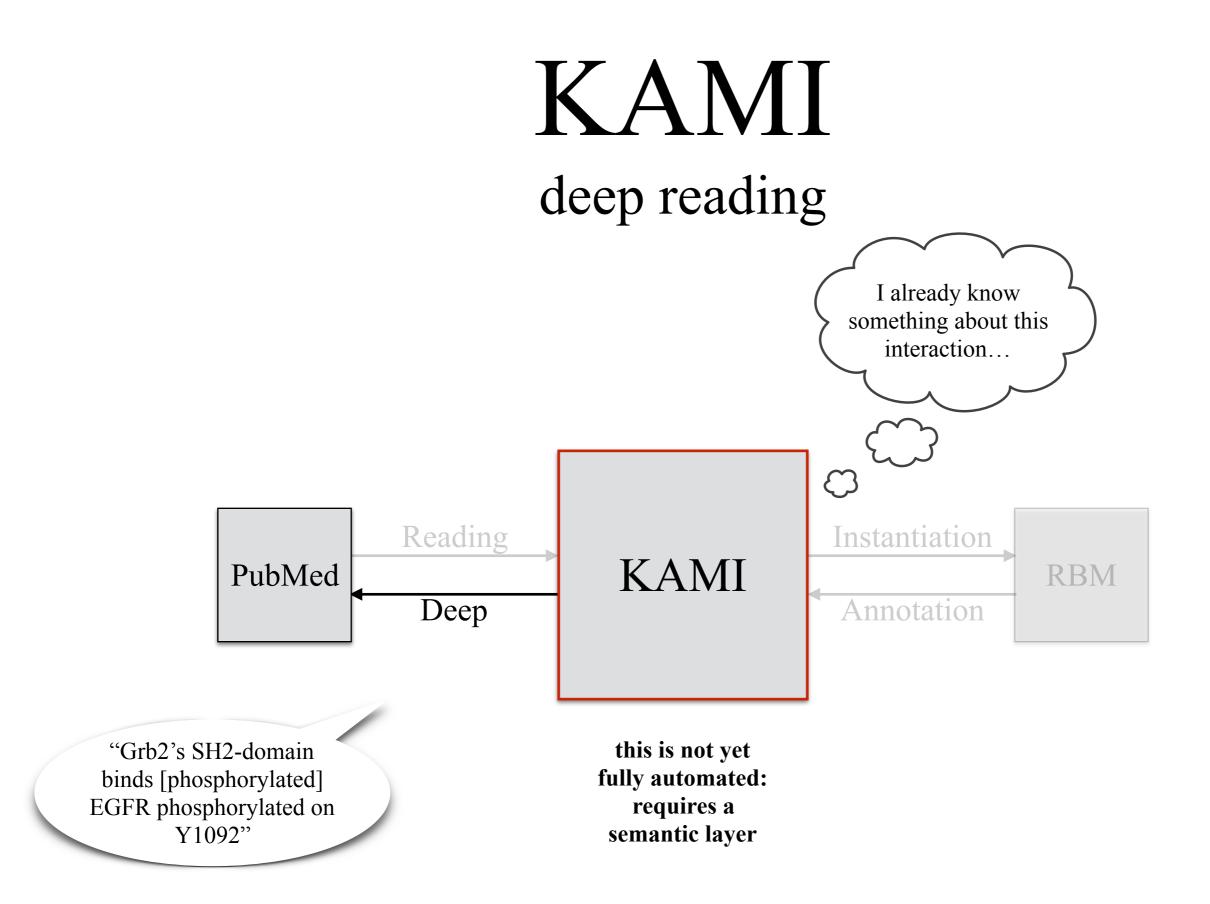


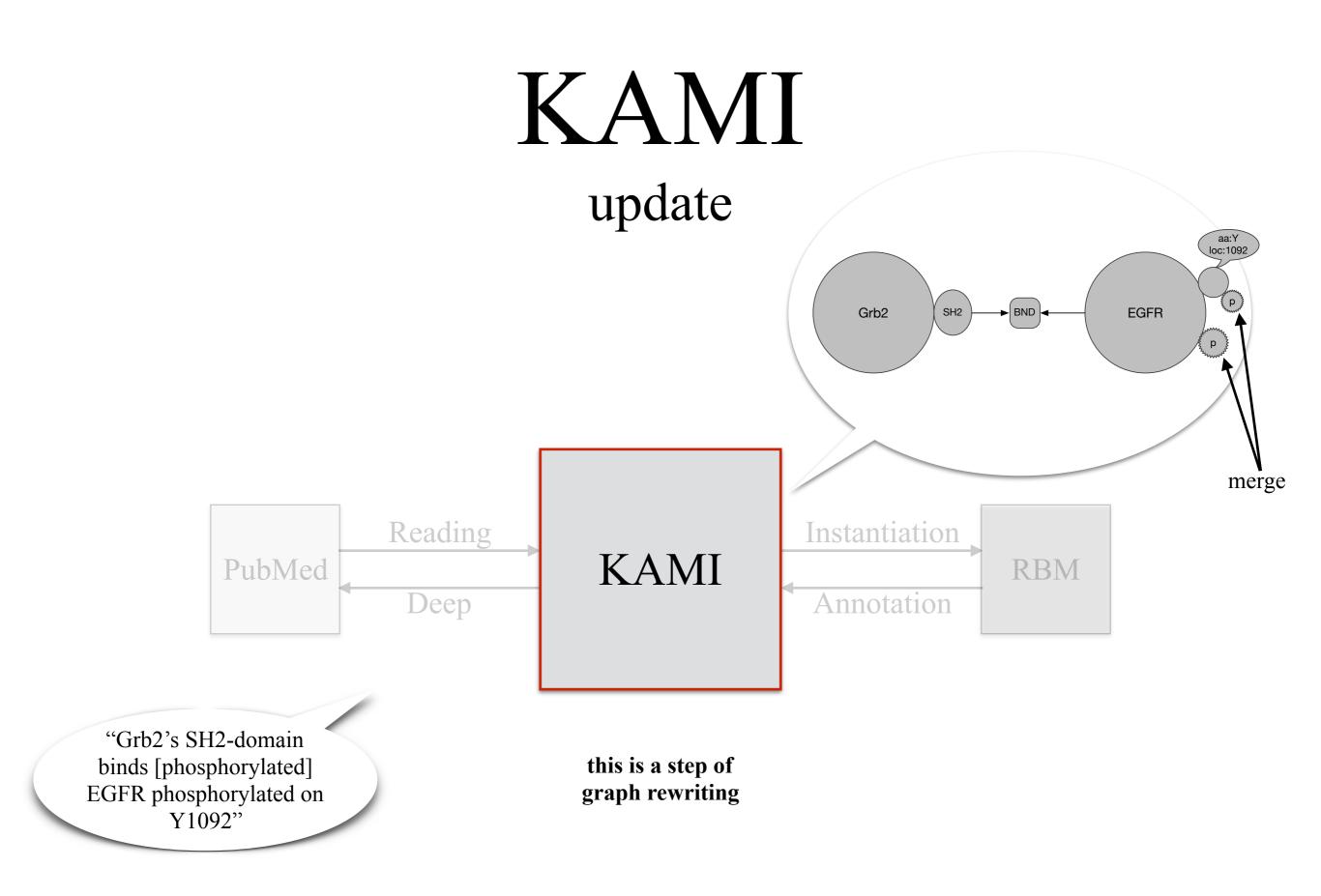
thanks to Lucian Galescu *et alia*!

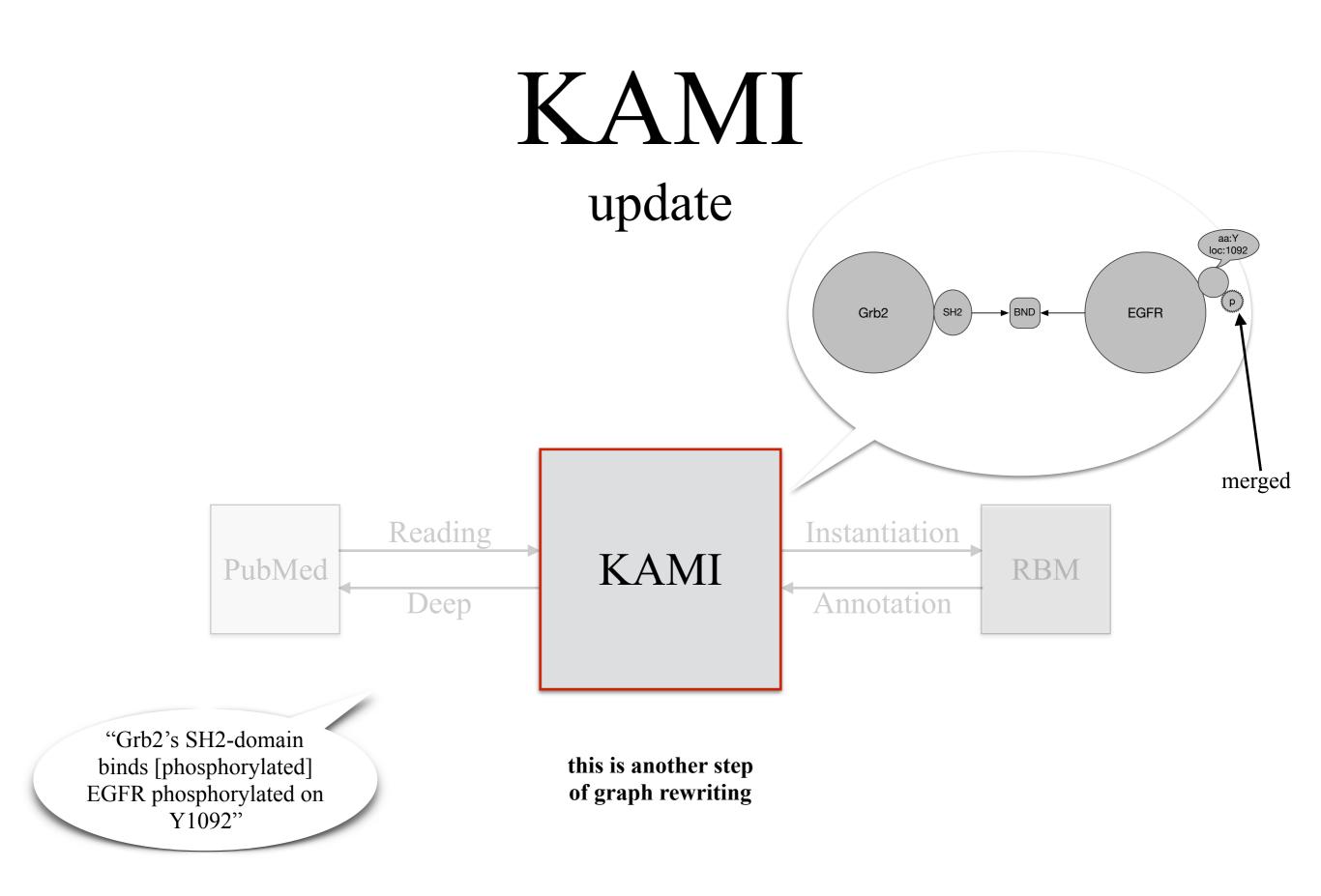


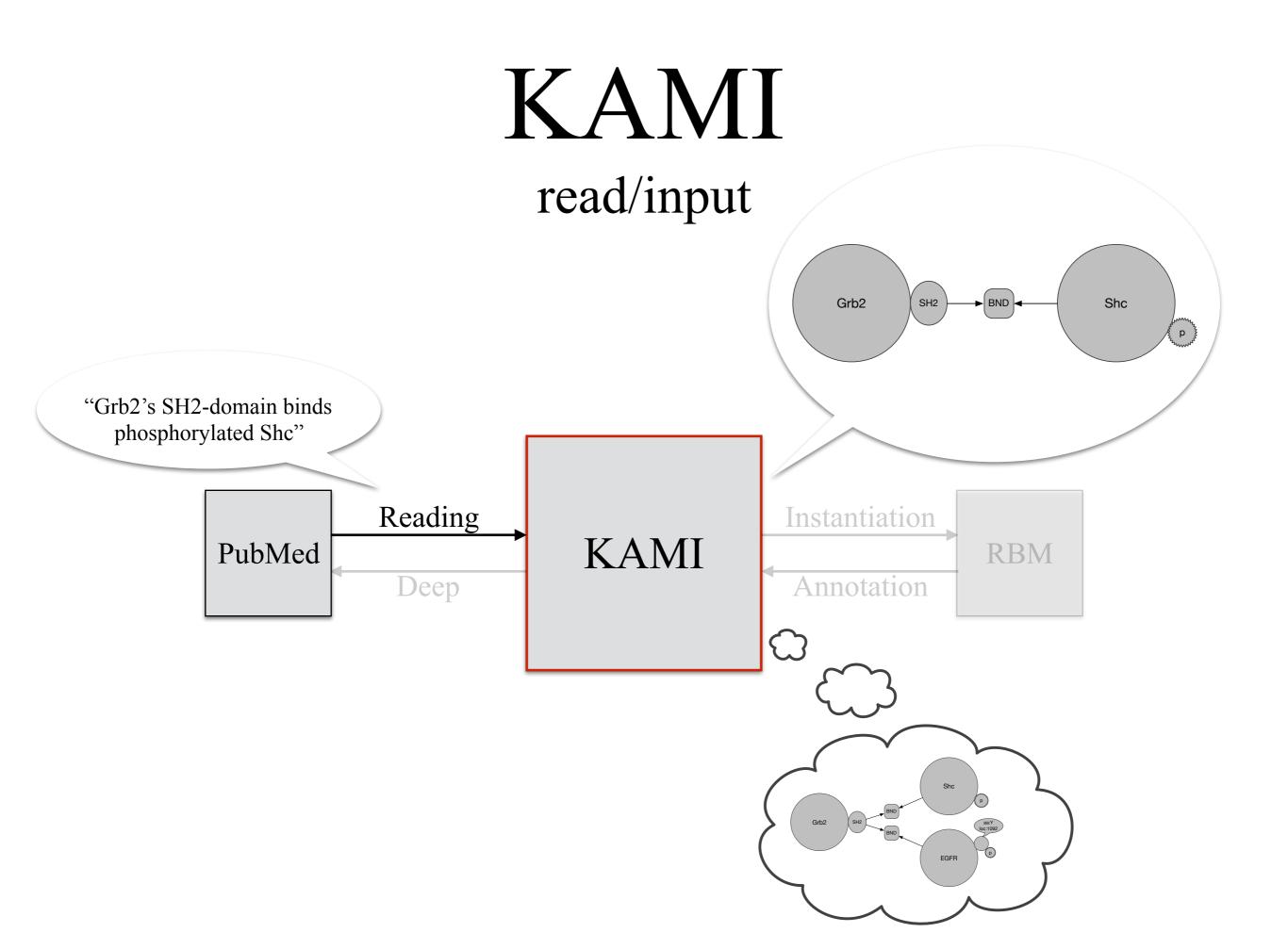
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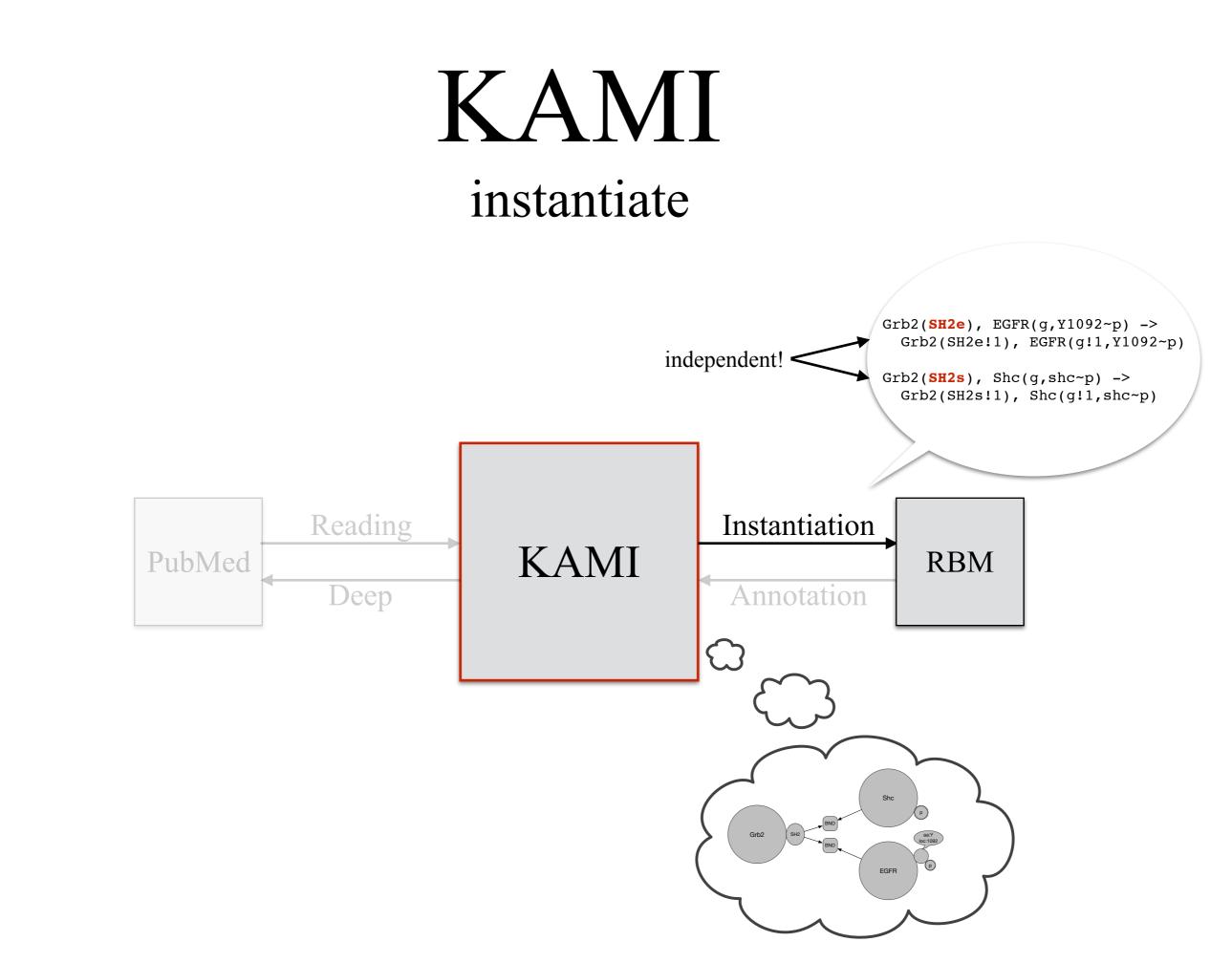


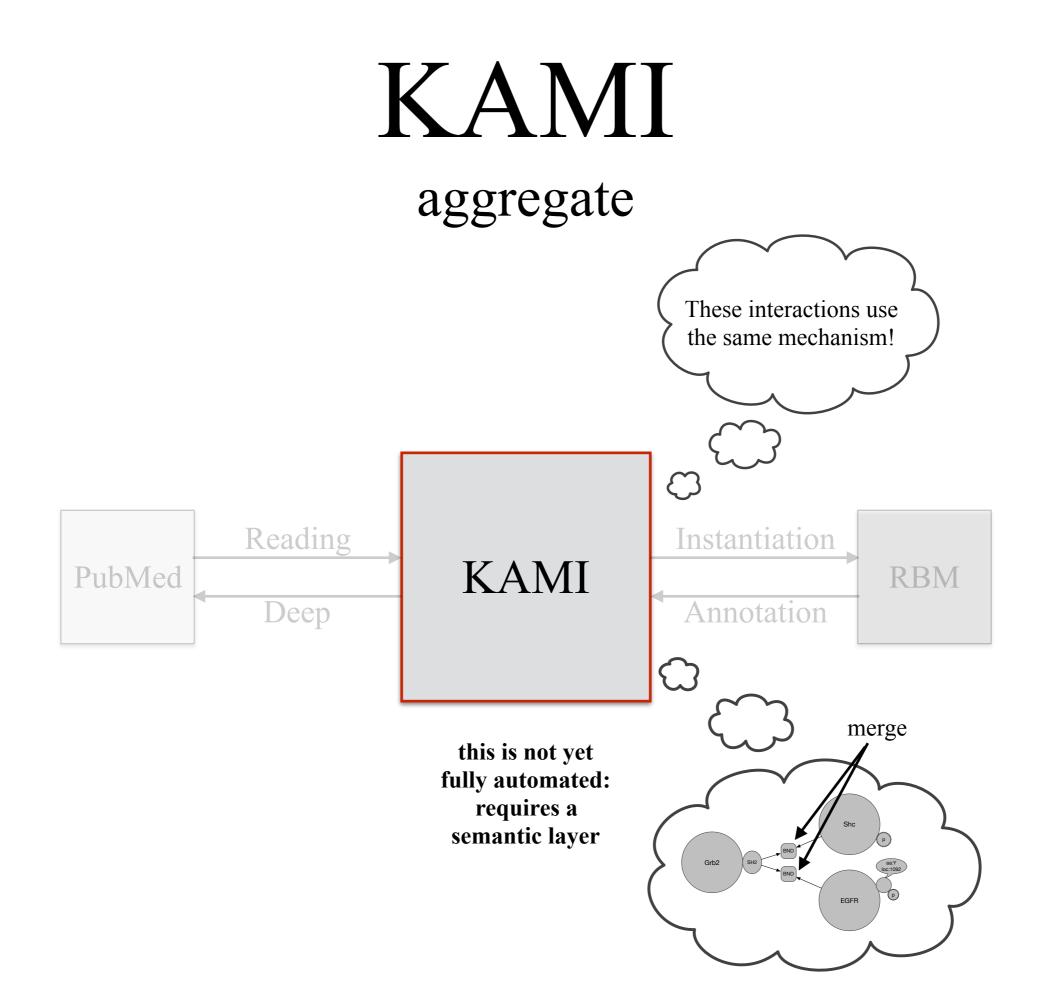






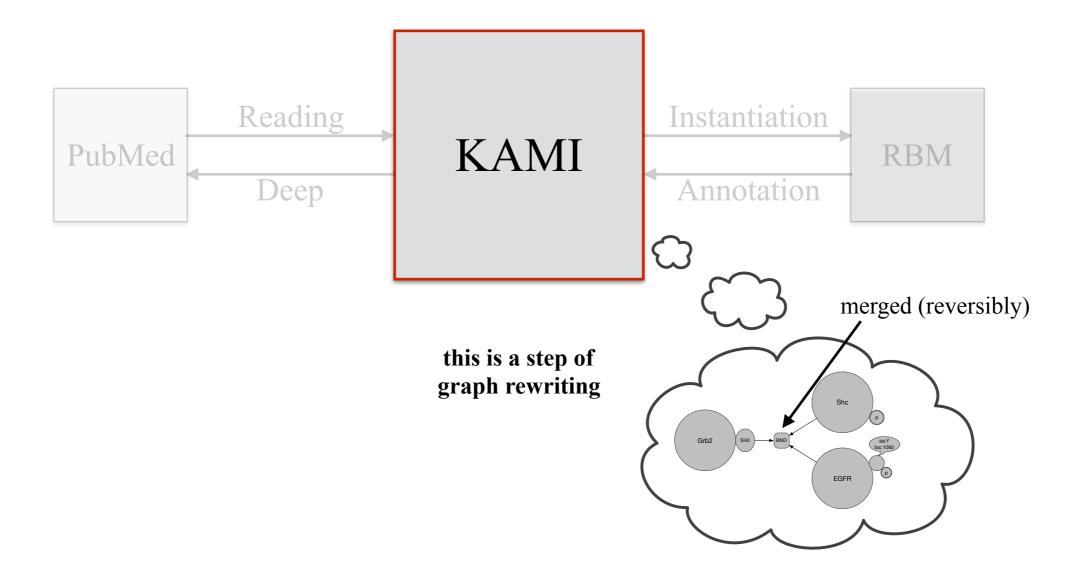


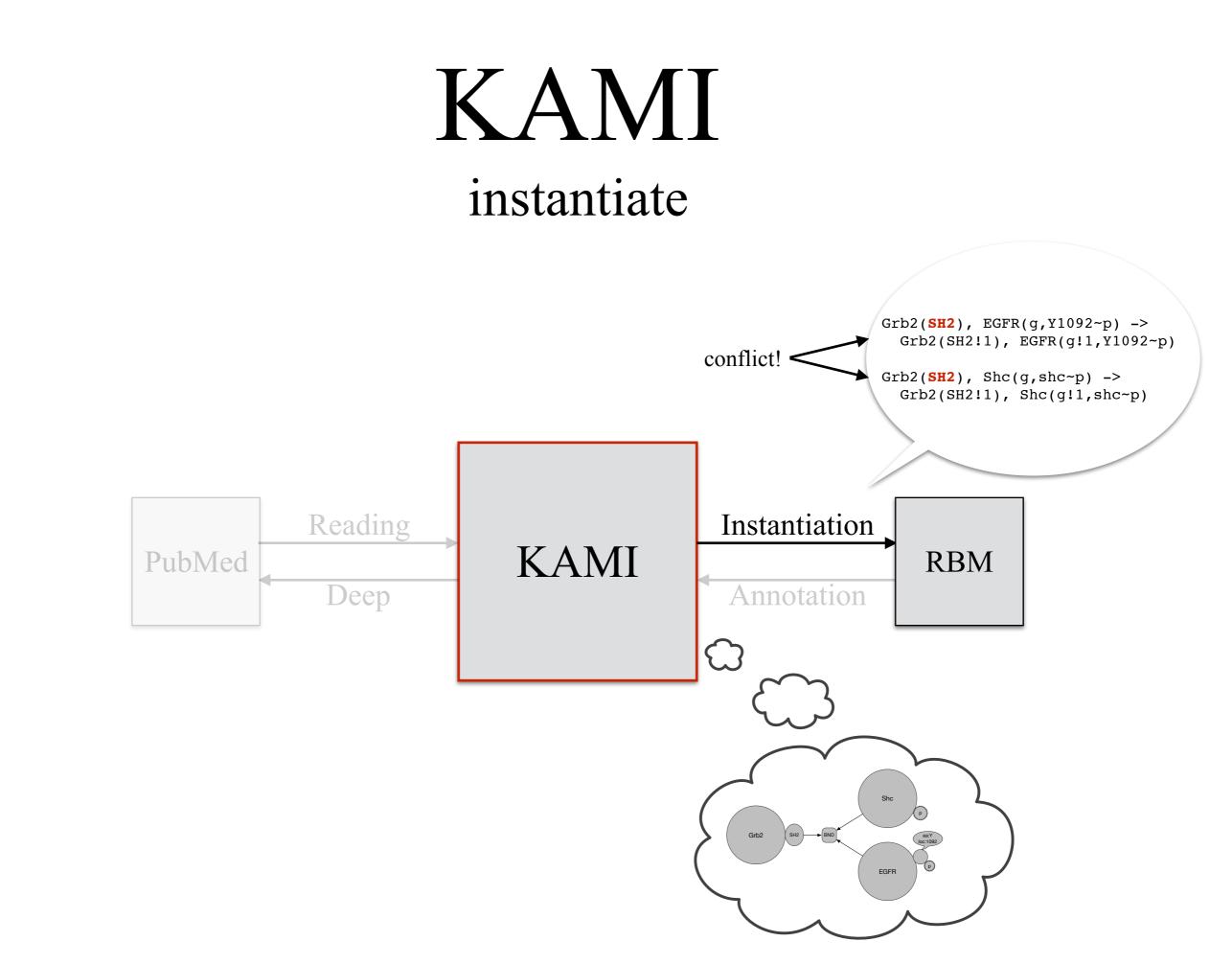


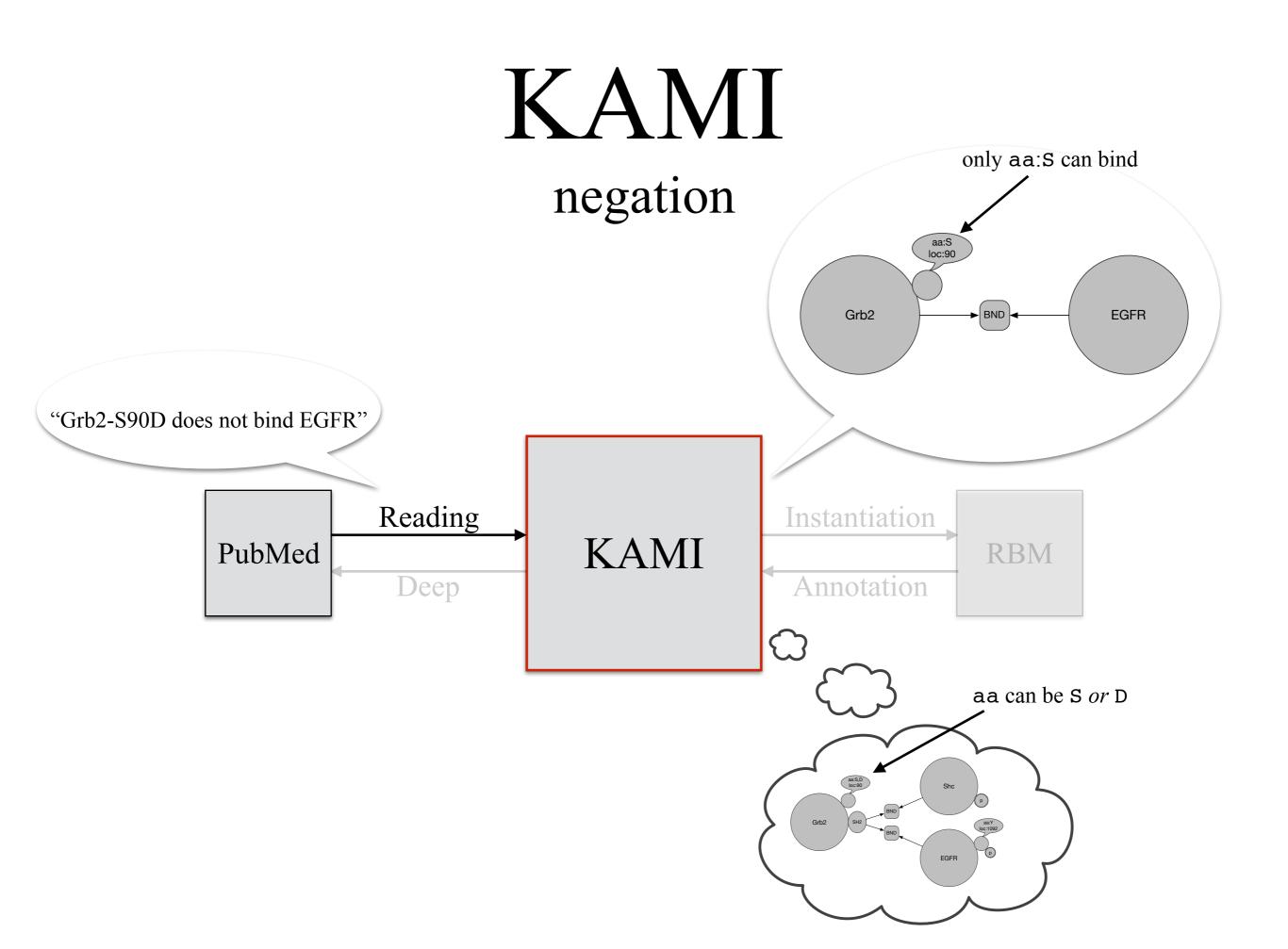


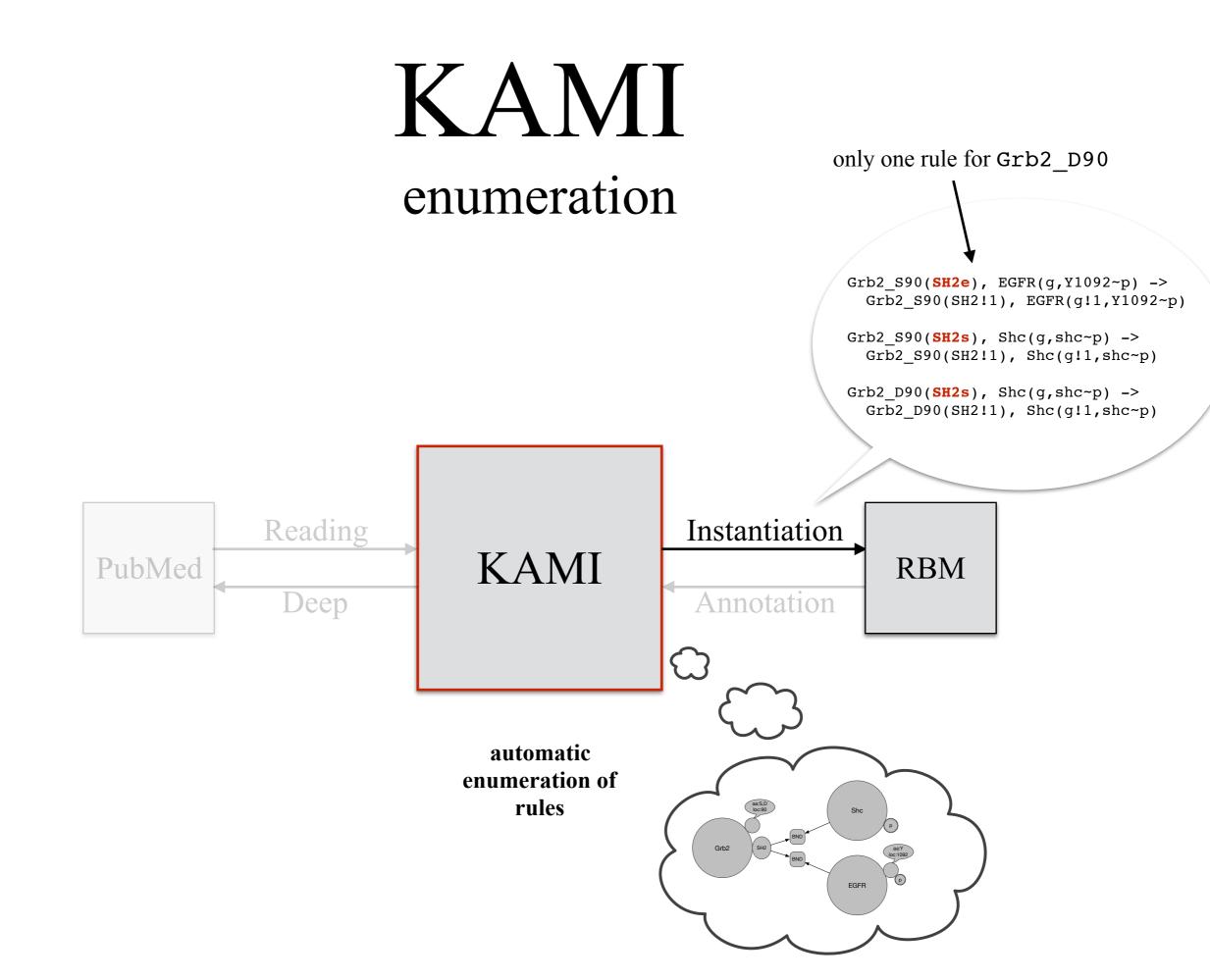
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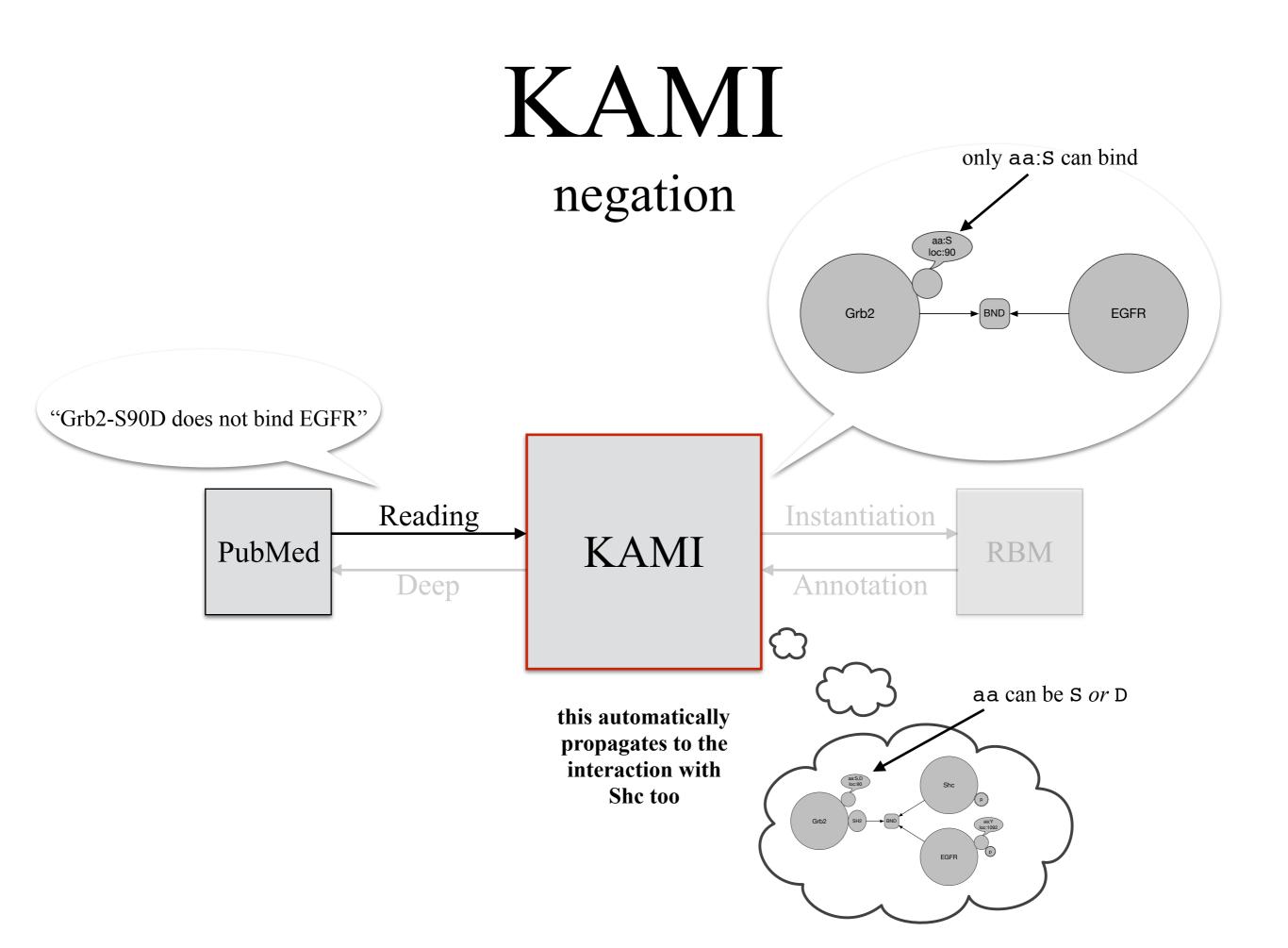
aggregate

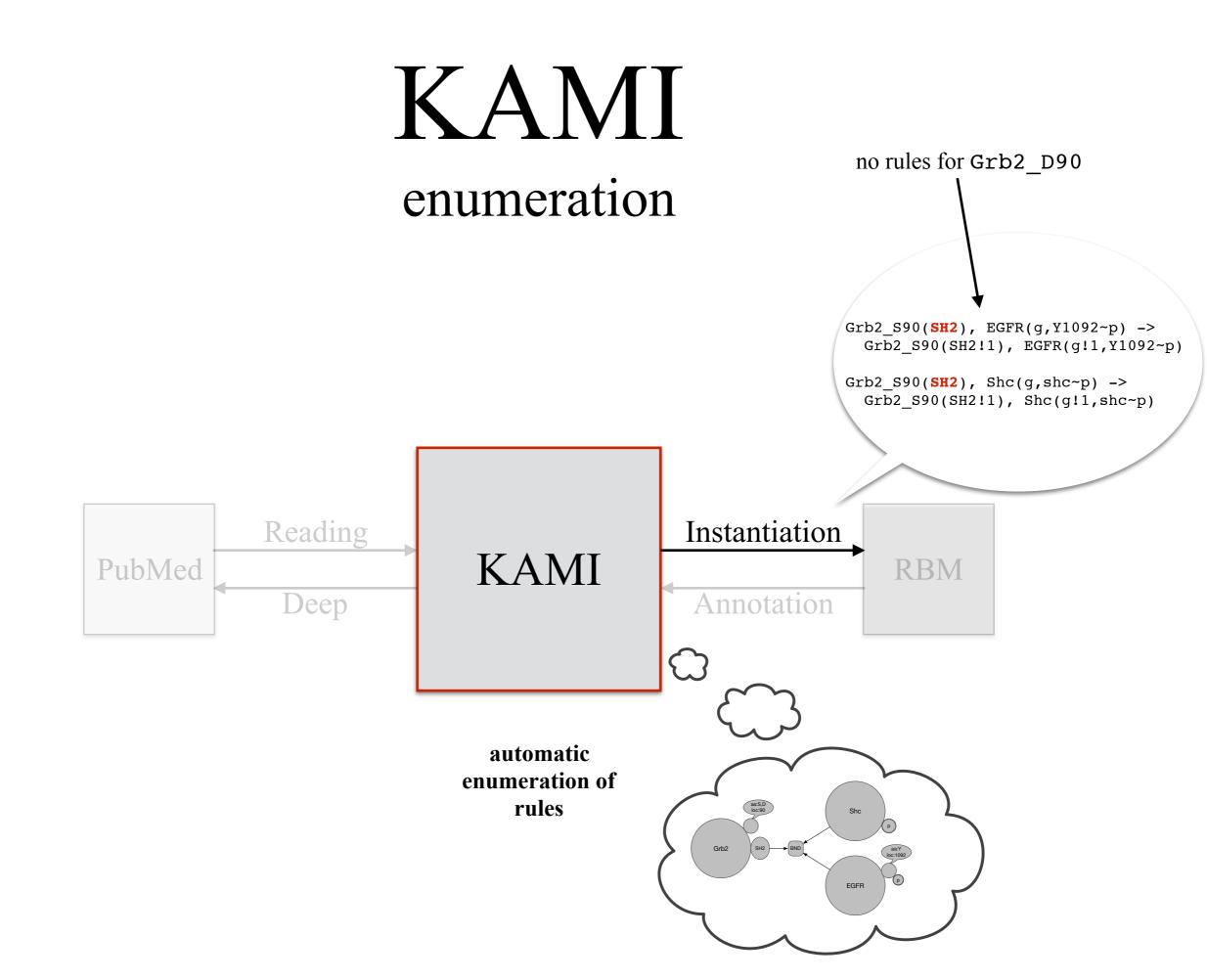












Wrapping up

Summary

- A purely formal graph rewriting foundation
 - represents knowledge and [revokable] hypotheses using formal operations of (update and) aggregation
- Model instantiation into RBM
 - automatically maintains desired [conflict] invariants and handles the effects of mutations because all enumeration is done by the machine

Automation?

- Other than an expert user, where could the steps of rewriting come from?
 - semantics: typically steric or functional properties of certain regions, e.g. SH2 or kinase domains
 - also allows for semantic checking and inference
 - more general inference ...

Work in progress

- Open re-implementation as a Python library
 - standard meta-models and meta-model transformations
 - can also be user-defined
- Based on a graph rewriting Python library
 - itself built on top of NetworkX
 - multi-level rewriting with upward propagation