Formal Biochemical Space with Semantics in Kappa and BNGL

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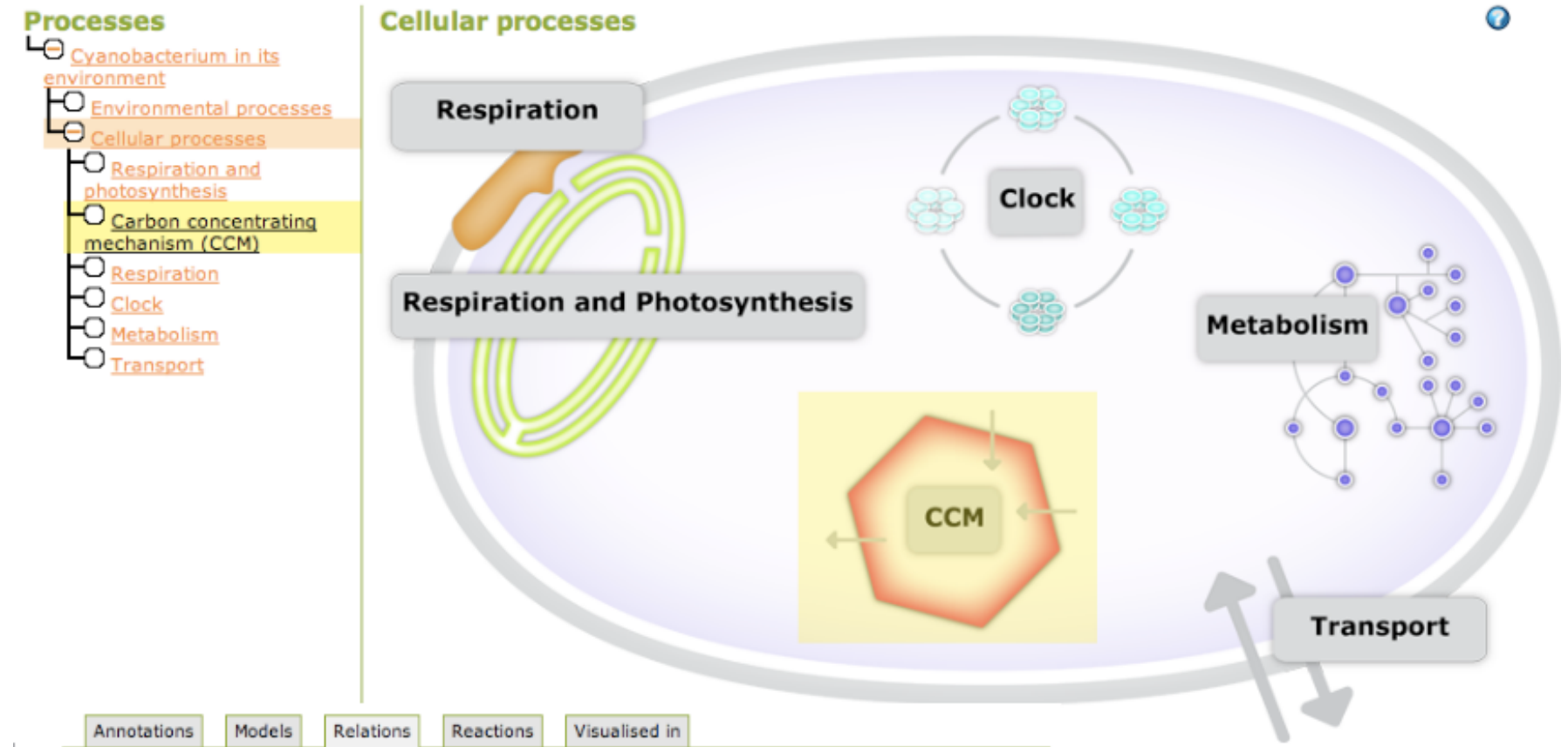
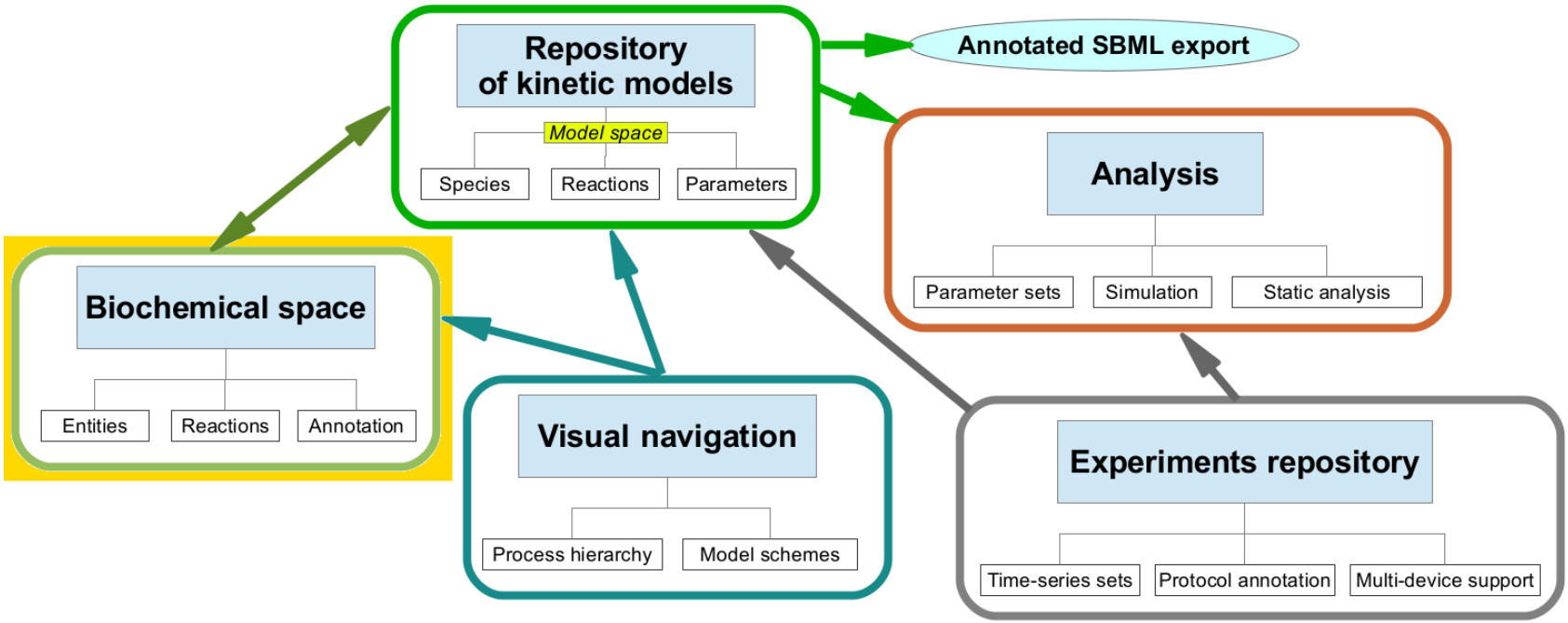
Background and Motivation

Comprehensive Modelling Platform (CMP)



Background and Motivation

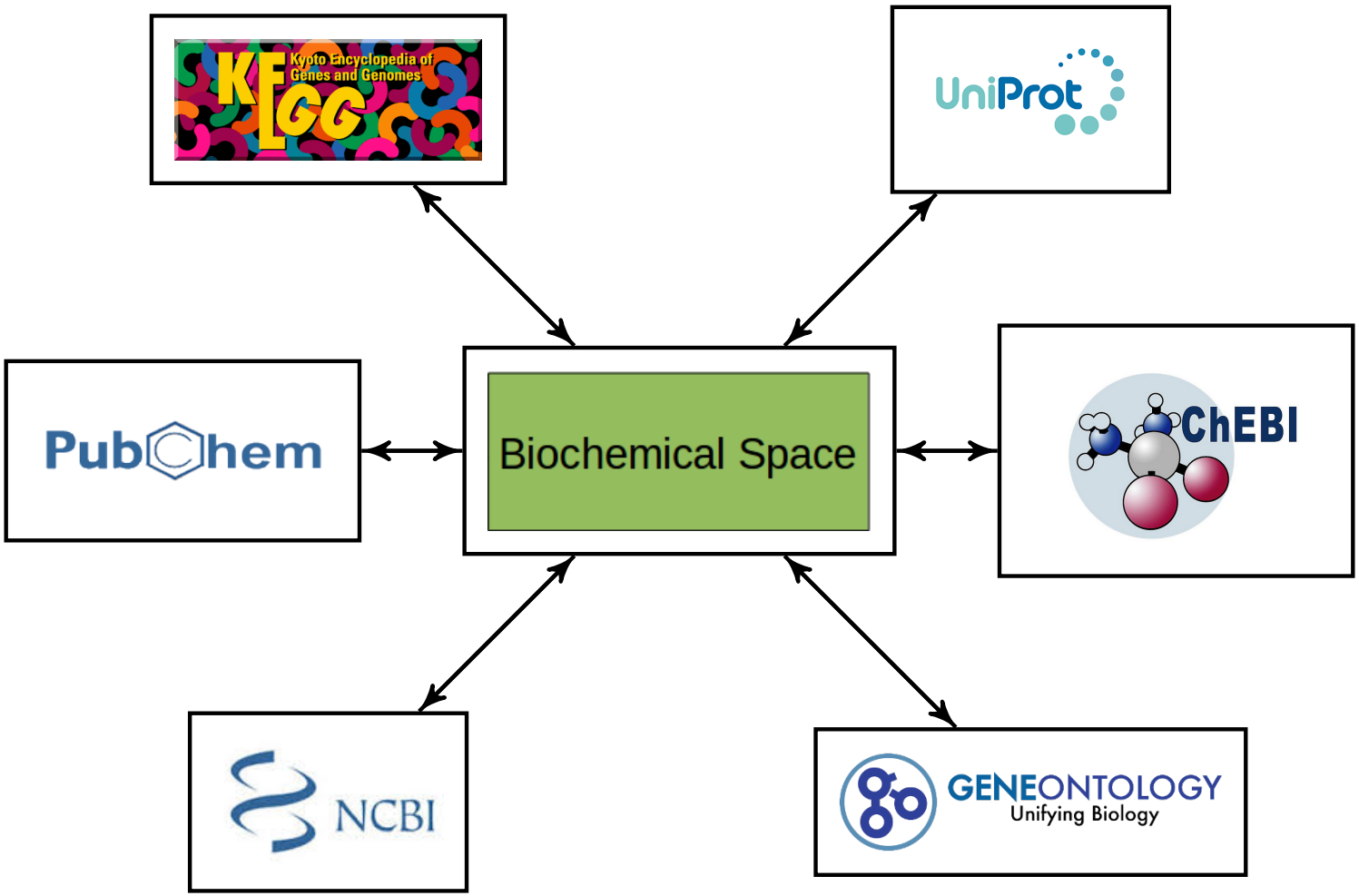
Biochemical Space in the context of CMP



- need for easy-to-understand but yet formal description of biological processes
- tackle the complexity - combinatorial explosion

Annotation Standards

Connection to Bioinformatics



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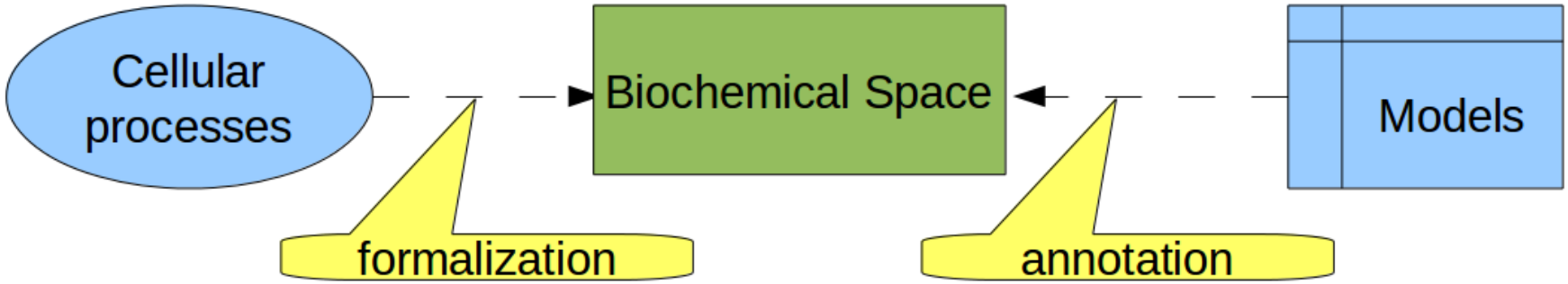
Biochemical Space

Eliminating the Gap Between Biology and Math



- biophysics employs a lot of indirect approximation in models
- combining rule-based approach with reaction-based approach allows compact mechanistic description
- mapping the models to such a description allows better and faster understanding

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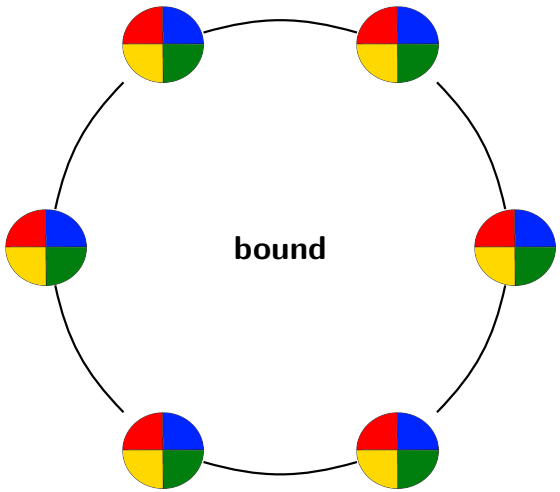
Abstraction from structural details

Biology

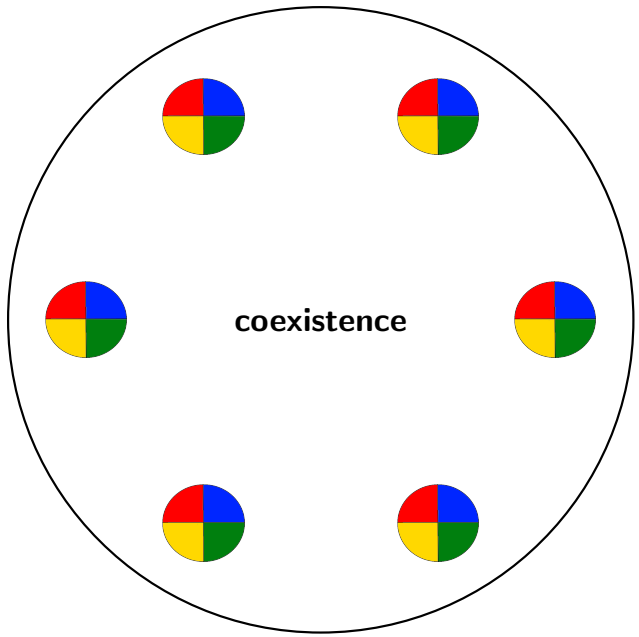
- graph "isomorphism"
- 700 different deviations



- Unphosphorylated protein
- Serine residue phosphorylated protein
- Threonine residue phosphorylated protein
- Both residues phosphorylated protein

BCS abstraction

- mixture $\rightarrow$ order not important
- 84 different deviations



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Biochemical Space Language

Key Features

- **stoichiometry** $\rightarrow$ enumerated shortened forms
- **states** $\rightarrow$ encoding different forms of an entity
- **composition**
  - **full** $\rightarrow$ complexation, coexistence in a solution
  - **partial** $\rightarrow$ inner structure of interest
- **locations** $\rightarrow$ spatial organisation
- **variables** $\rightarrow$ wildcards in definitions

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Differences from Other Formalisms

BioChemical **S**pace **L**anguage is a rule-based language which has:

- **no binding sites** $\rightarrow$ details of complexes formation abstracted out
  - abstract from bonds
- **annotation purpose** $\rightarrow$ specify what interacts with what without details of the interaction
- **no quantitative data** $\rightarrow$ only qualitative dynamics

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Entity Declaration by Example

ENTITY ID: KaiC
ENTITY NAME: circadian clock protein kinase KaiC
STATES:
LOCATIONS: cyt
CLASSIFICATION: enzyme
DESCRIPTION: Monomer component representing a core component of the circadian clock system
LINKS: uniprot::Q79PF4, kegg::K08482, ncbi::AAM82686
ORGANISM: SYNPCC7942{Synpcc7942_1216}
NOTES:
COMPOSITION: S | T

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Abstract Entity Specification

Class

KaiC.KaiC::cyt

Specialized class

KaiC(S{u}|T{u}).KaiC::cyt
KaiC(S{u}).KaiC::cyt

Object

KaiC(S{u}|T{u}).KaiC(S{u}|T{p}))::cyt

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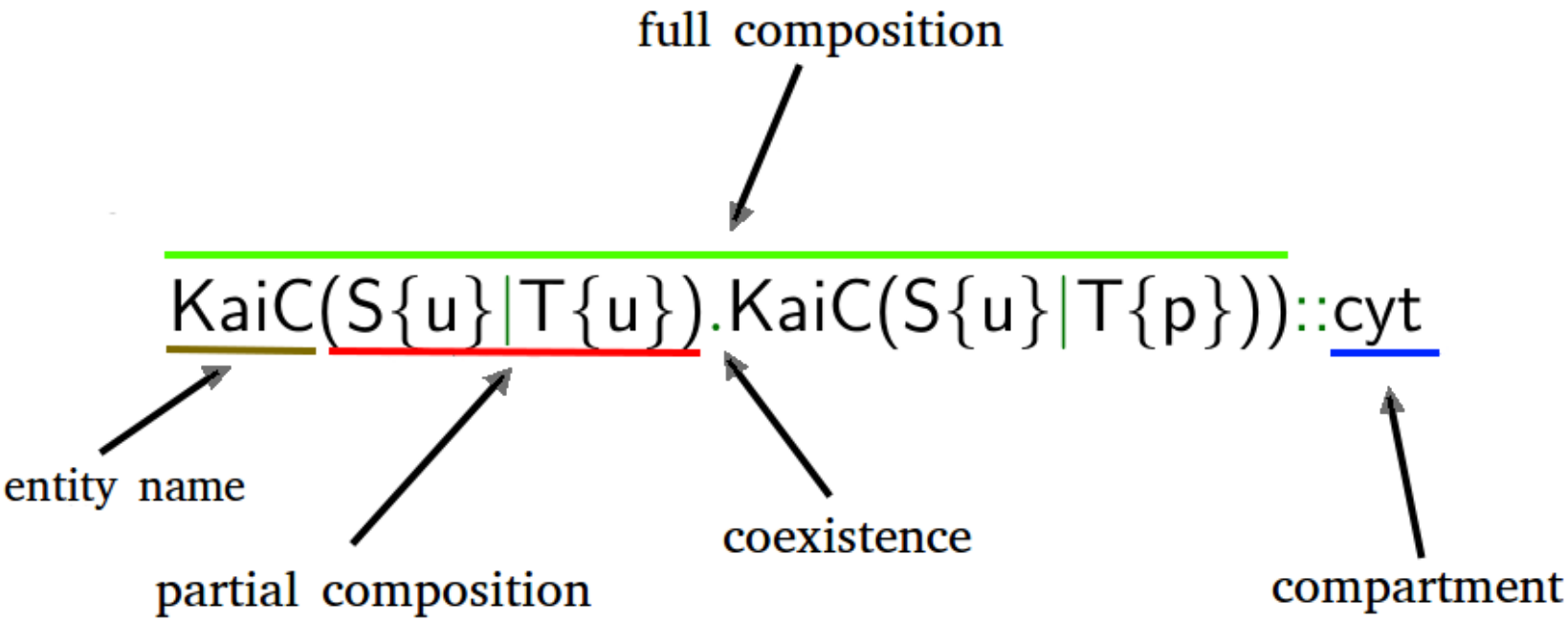
Entity Identifier



Composition

Full composition $\rightarrow$ structure of a complex

- KaiBC == KaiC.KaiB
- KaiC6 == KaiC.KaiC.KaiC.KaiC.KaiC.KaiC

Partial composition $\rightarrow$ inner structure of an entity

- KaiC(S{u}|T{p})
- cytb6f(f{-}|bl{n}|bhc{2-})
- ps2(qb{2-}|qa{n}|chl{*}|p680{+}|pheo{-}|oec{4+}|yz{n})

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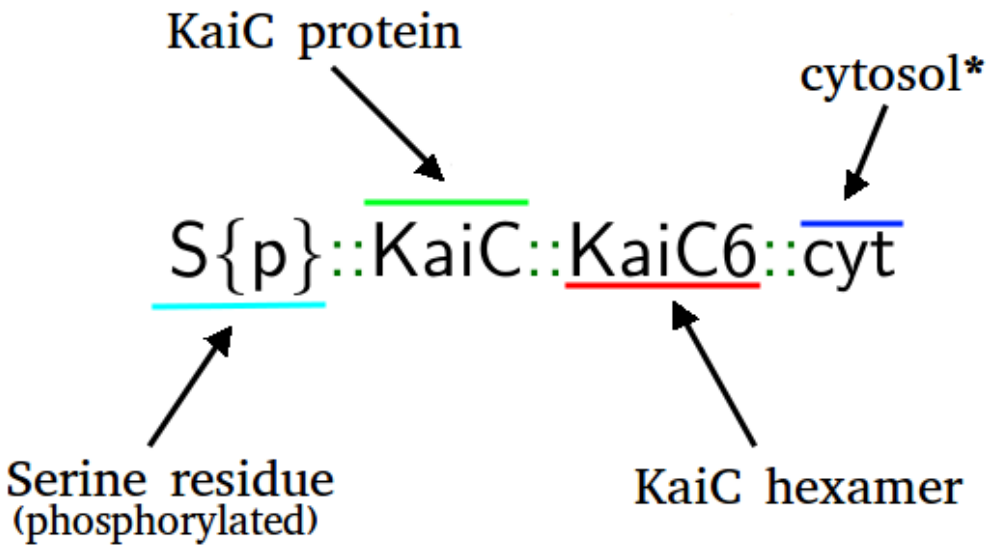
Nested Entity Identifier

- another way to specify a class entity



- *compartment specification is obligatory

Examples of Entity Identifiers

- KaiC6::cyt
- KaiA.KaiA::cyt
- ATP::cyt
- CO3{2-}::liq
- KaiC(S{u}|T{p})::cyt
- CO_2::**?X** ; **X** = {lum, cell, liq, bub, pps, cyt}

Rules vs. Reactions

Reaction

$$\text{KaiC(S\{u\}|T\{u\})::cyt} + \text{KaiC(S\{p\}|T\{p\})::cyt} \Rightarrow \text{KaiC(S\{u\}|T\{u\}).KaiC(S\{p\}|T\{p\})::cyt}$$

$$\text{object} \quad + \quad \text{object} \quad \Rightarrow \quad \text{object}$$

Rule

$$\text{KaiC::cyt} + \text{KaiC::cyt} \Rightarrow \text{KaiC.KaiC::cyt}$$

$$\text{class} \quad + \quad \text{class} \quad \Rightarrow \quad \text{class}$$

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Stringency of Entity Identifiers

- consider the rule:

$$S\{p\}::KaiC::KaiC6::cyt \Rightarrow S\{u\}::KaiC::KaiC6::cyt$$

- both sides identify the same object in location **cyt**
- it is a complex **KaiC6** (assume it has a given well-defined full composition)
- which contains at least one **KaiC** protein
- whose partial composition contains **S{p}**

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Translation of Entities to Kappa

Assume every entity composition is lexicographically ordered.

- **agent** ← entity name
- **agent name** ← entity name suffixed with a location
- **interface** ← partial composition (at least two internal states are required)
- **site** ← each member entity of partial composition
- **site name** ← name of a member entity
- **internal state** ← state of the entity
- **binding state** ← assign a generic structure, i.e., linear

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BCSL Rules Expressed in Kappa

- left/right side **S** of a BCS rule is set of entities
  $\Rightarrow$ expressed as a set **E** of agents in Kappa
- since each entity in **S** is lexicographically ordered, rules are ensured to be unique (up-to structural equivalence of reaction complexes),
- for full compositions ('.' operator) a labeling by bound sites is created (concretisation)
  $\Rightarrow$ abstract meaning of coexistence is lost

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Examples

BCS: $2\ \mathrm{KaiC(S\{p\})} \Rightarrow \mathrm{KaiC(S\{p\}).KaiC(S\{p\})}$

Kappa : $\mathrm{KaiC}(S_p),\ \mathrm{KaiC}(S_p) \rightarrow \mathrm{KaiC}(S^1_p),\ \mathrm{KaiC}(S^1_p)$

BCS: $\mathrm{S\{p\}::KaiC::KaiC6::cyt} \Rightarrow \mathrm{S\{u\}::KaiC::KaiC6::cyt}$

Kappa :

$\mathrm{KaiC}(S^1_p),\ \mathrm{KaiC}(S^1,T^2),\ \mathrm{KaiC}(S^2,T^3),\ \mathrm{KaiC}(S^3,T^4),\ \mathrm{KaiC}(S^4,T^5),\ \mathrm{KaiC}(S^5) \rightarrow$

$\rightarrow \mathrm{KaiC}(S^1_u),\ \mathrm{KaiC}(S^1,T^2),\ \mathrm{KaiC}(S^2,T^3),\ \mathrm{KaiC}(S^3,T^4),\ \mathrm{KaiC}(S^4,T^5),\ \mathrm{KaiC}(S^5)$

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Case Study: Synechocystis

Metabolism

- over 1000 entities (objects) and over 500 rules
- entities concrete since there is no combinatorial explosion (rules are reactions)
- two mathematical models are mapped

Photosynthesis and Respiration

- over 100 entity classes and over 50 rules
- compaction is significant mainly for reactions
- one (lumped) mathematical model is mapped

Cyanobacterial circadian clock

- 18 class entities interacting in 18 rules
- creates over 500 object entities
- two (lumped) mathematical models are mapped

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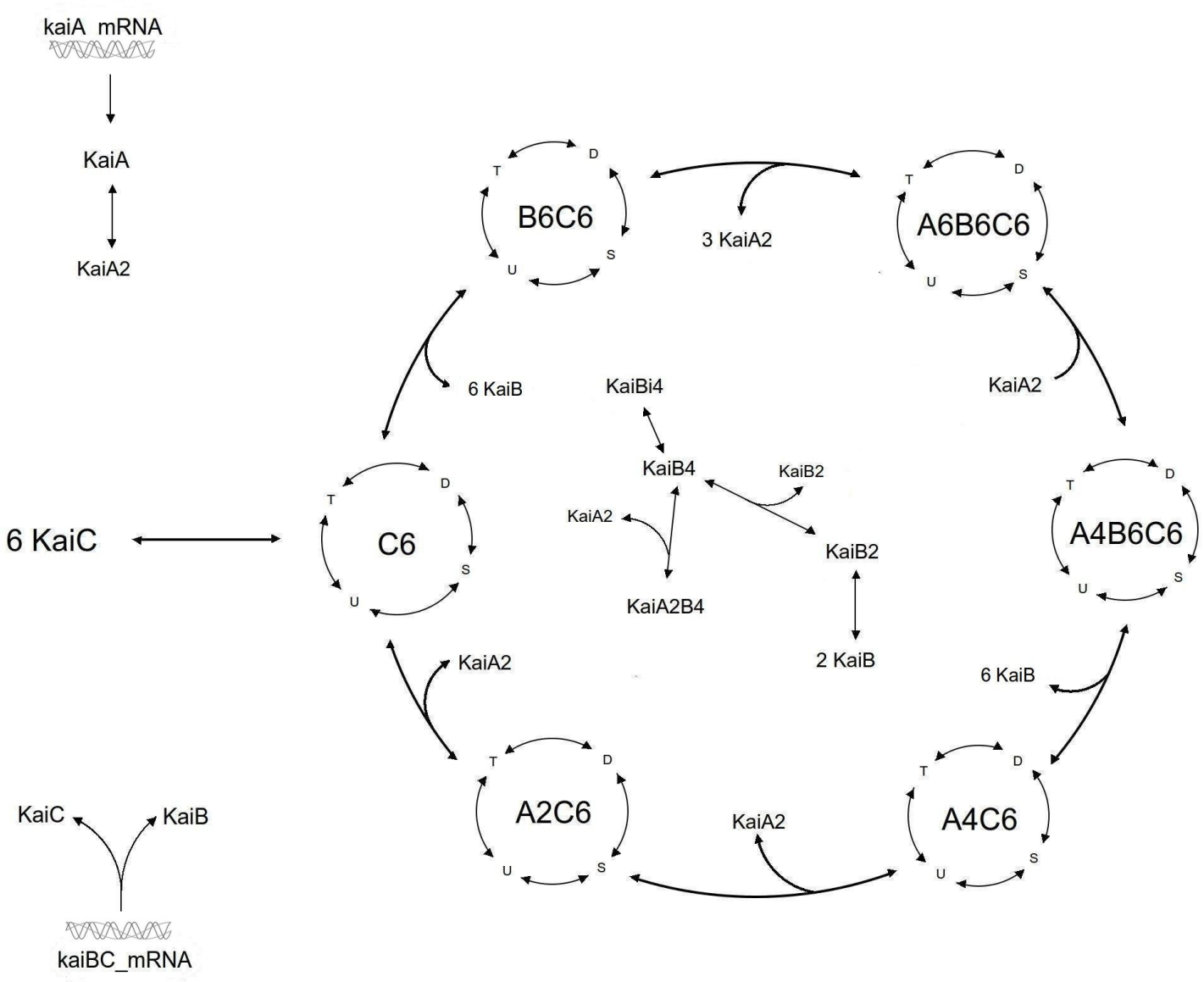
Cyanobacteria Circadian Clock BCS



Conclusions

- in the paper: formal syntax and semantics of BCS
- implementation: operational semantics in BNGL (then translated to DiVinE)
- currently we work on direct SOS to employ CTL model checking directly on BCS
- it will allow to study equivalences and reduction directly at the syntactic level of BCS

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The End

Thank You for your attention.

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The Project Team

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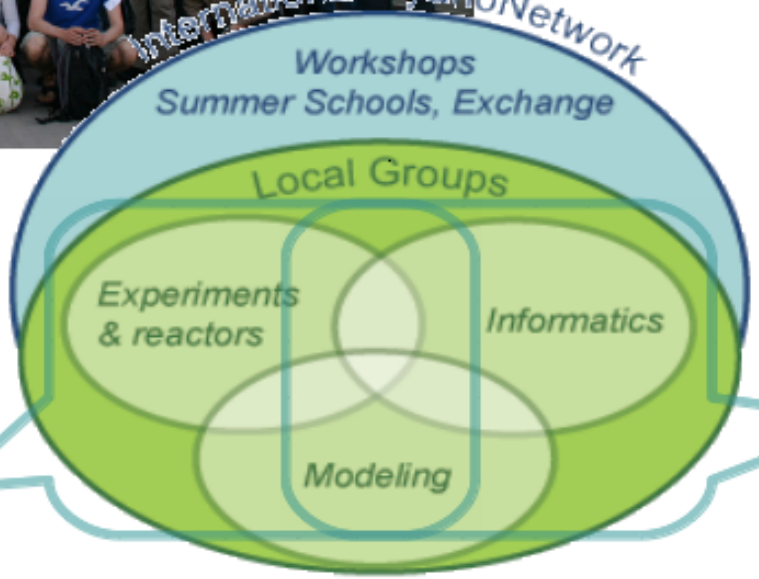

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