sybila

Executable Biochemical Space for Specification and Analysis of Biochemical Systems

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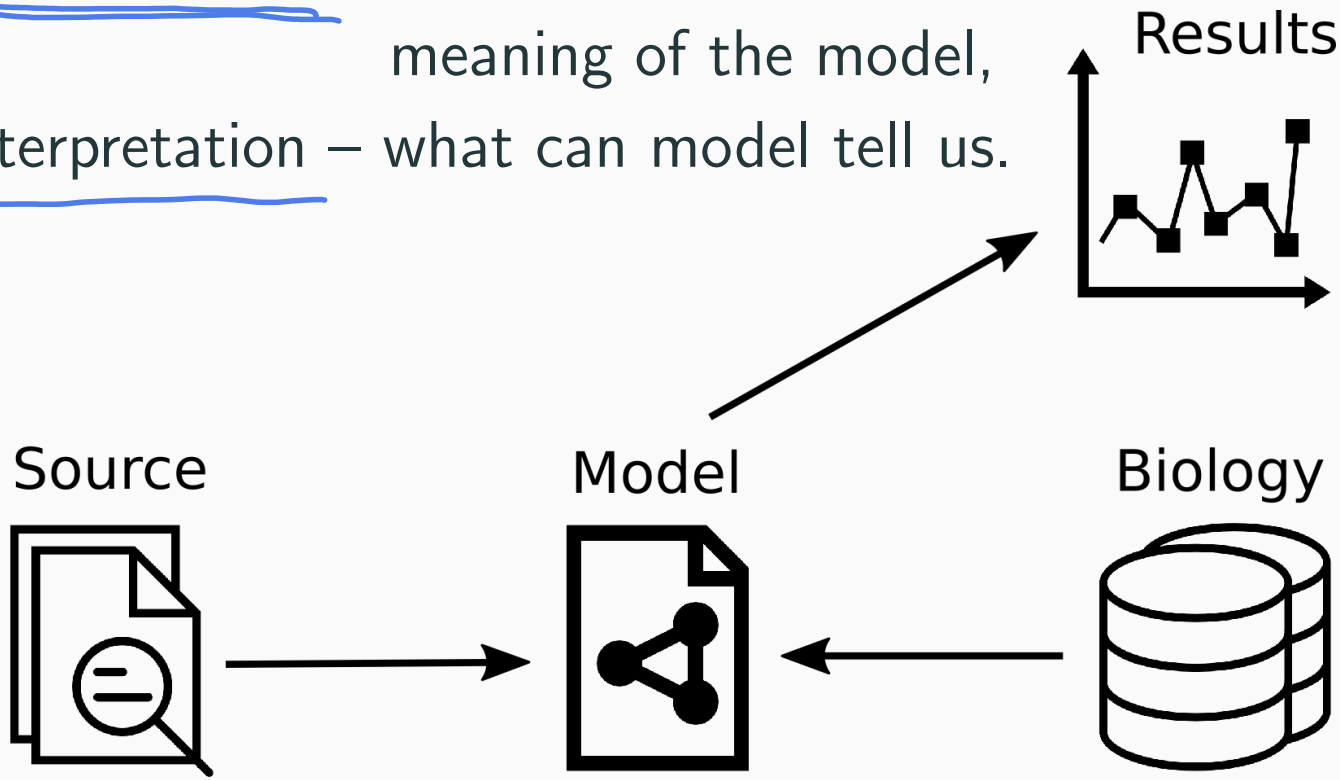
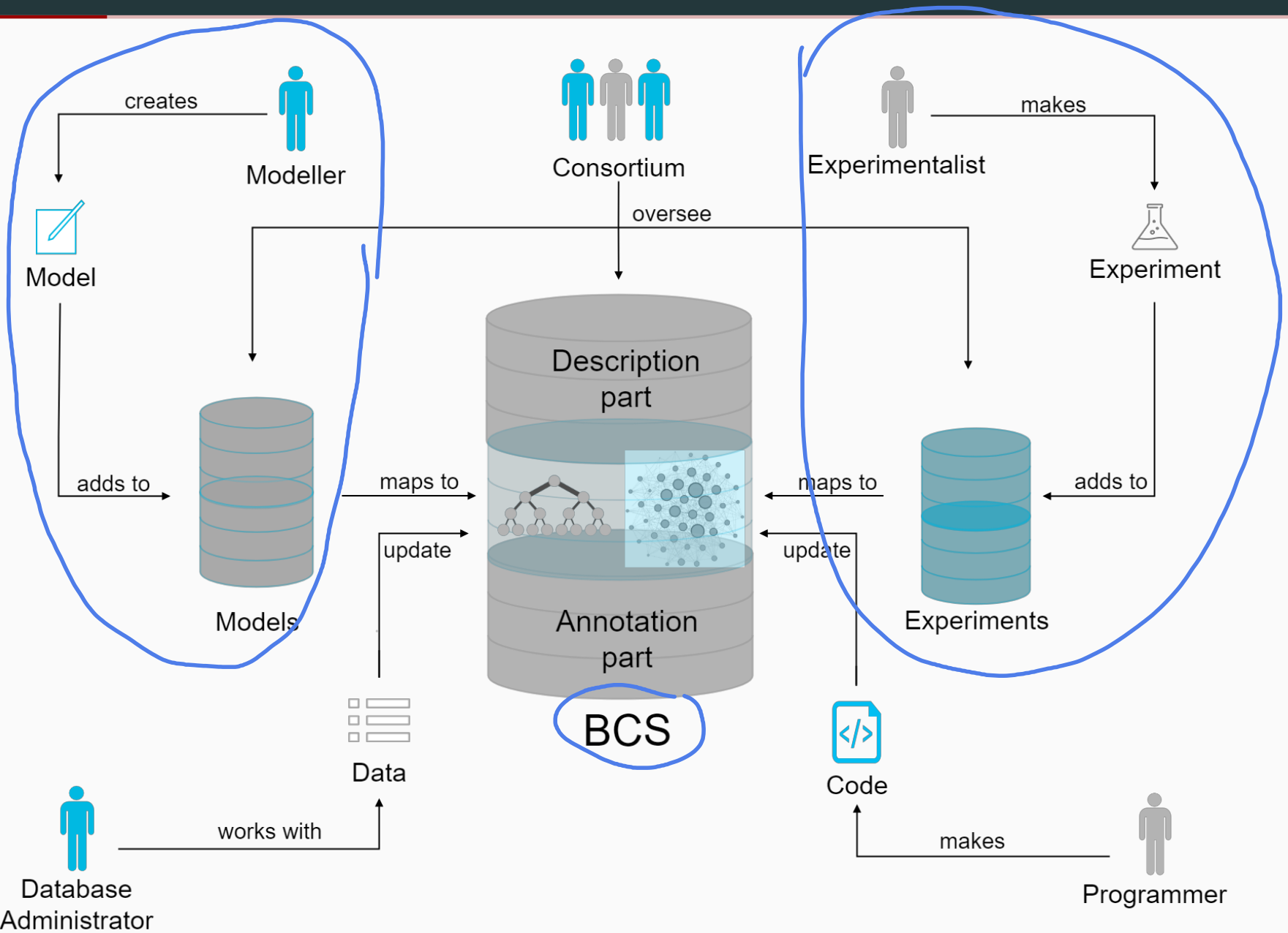
Motivation

Frequent issues with **mathematical models** in systems/synthetic biology:

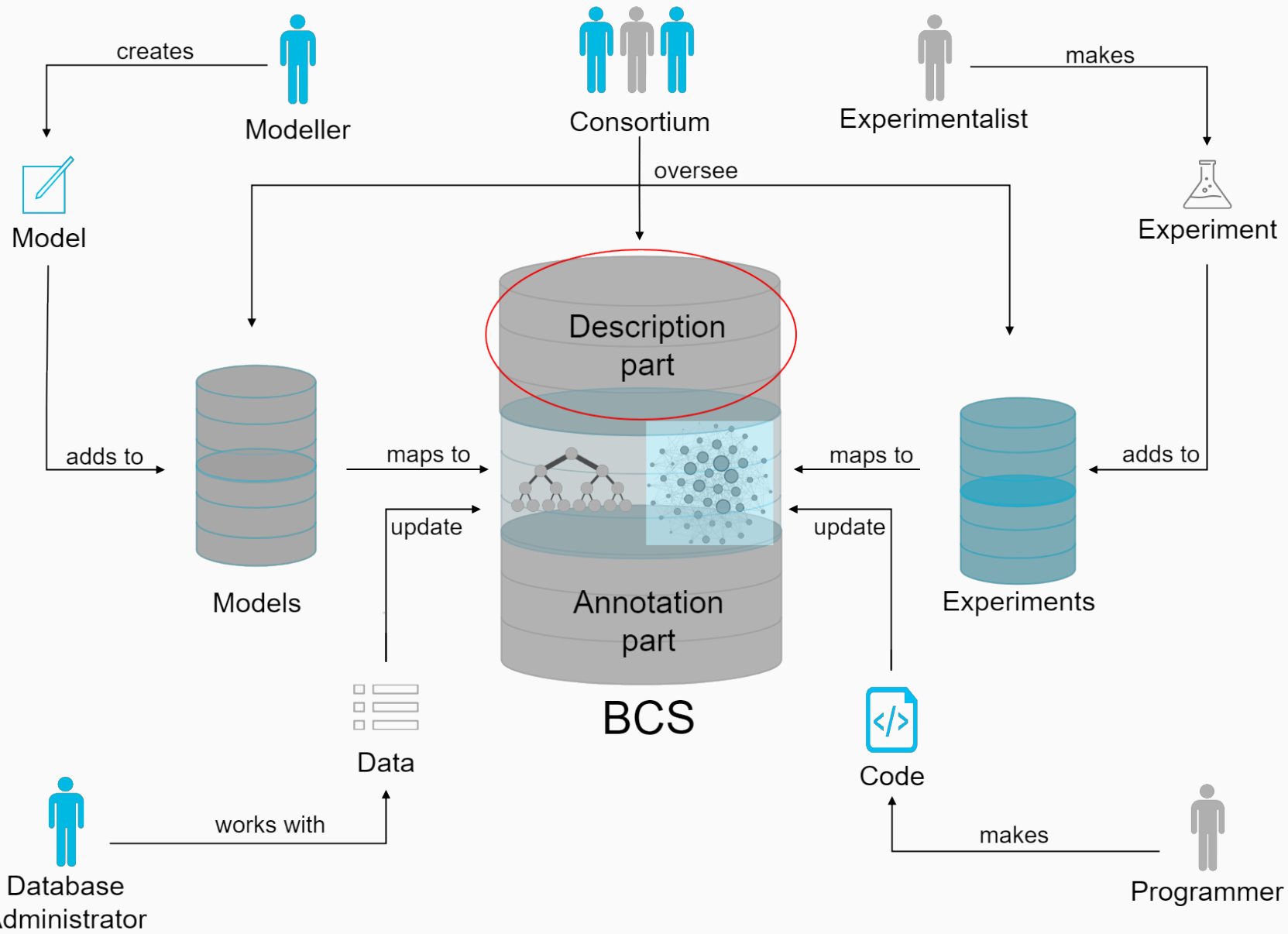
- reconstruction – from data and previous models,
- understanding – what is the biological meaning of the model,
- interpretation – what can model tell us.



Comprehensive Modelling Platform



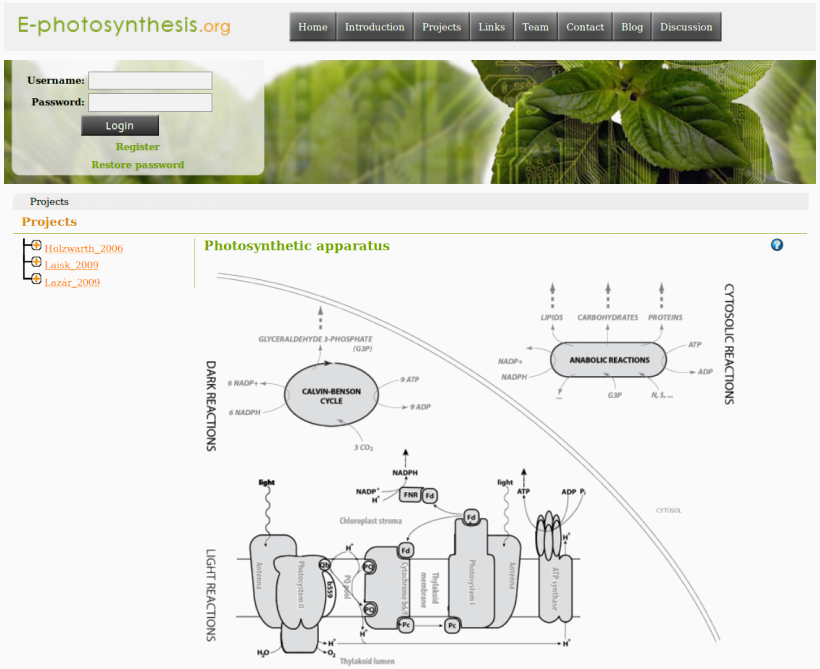
Comprehensive Modelling Platform

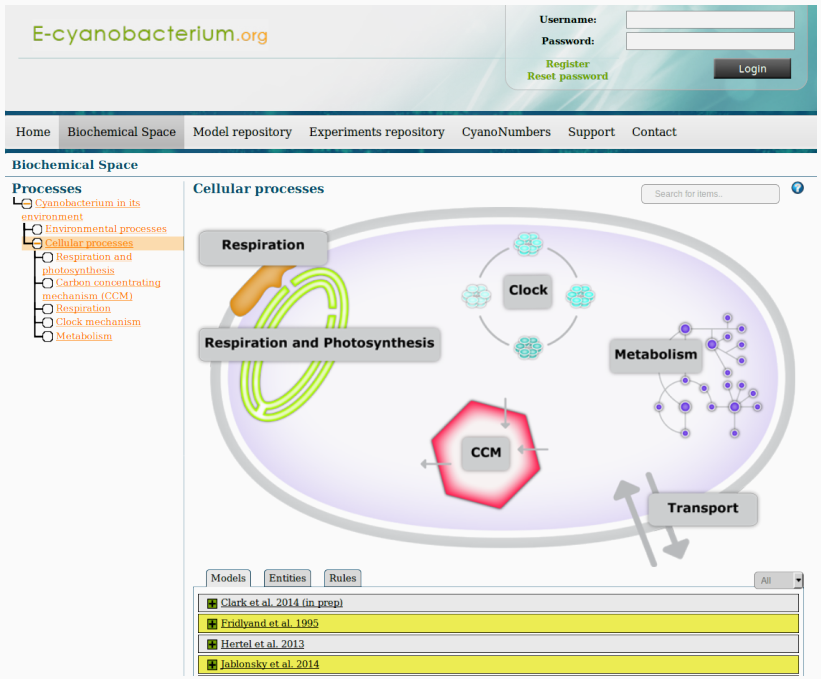


Comprehensive Modelling Platform

Web-based framework for integration of biological knowledge with computational models and wet-lab experiments.

- e-photosynthesis.org
- e-cyanobacterium.org





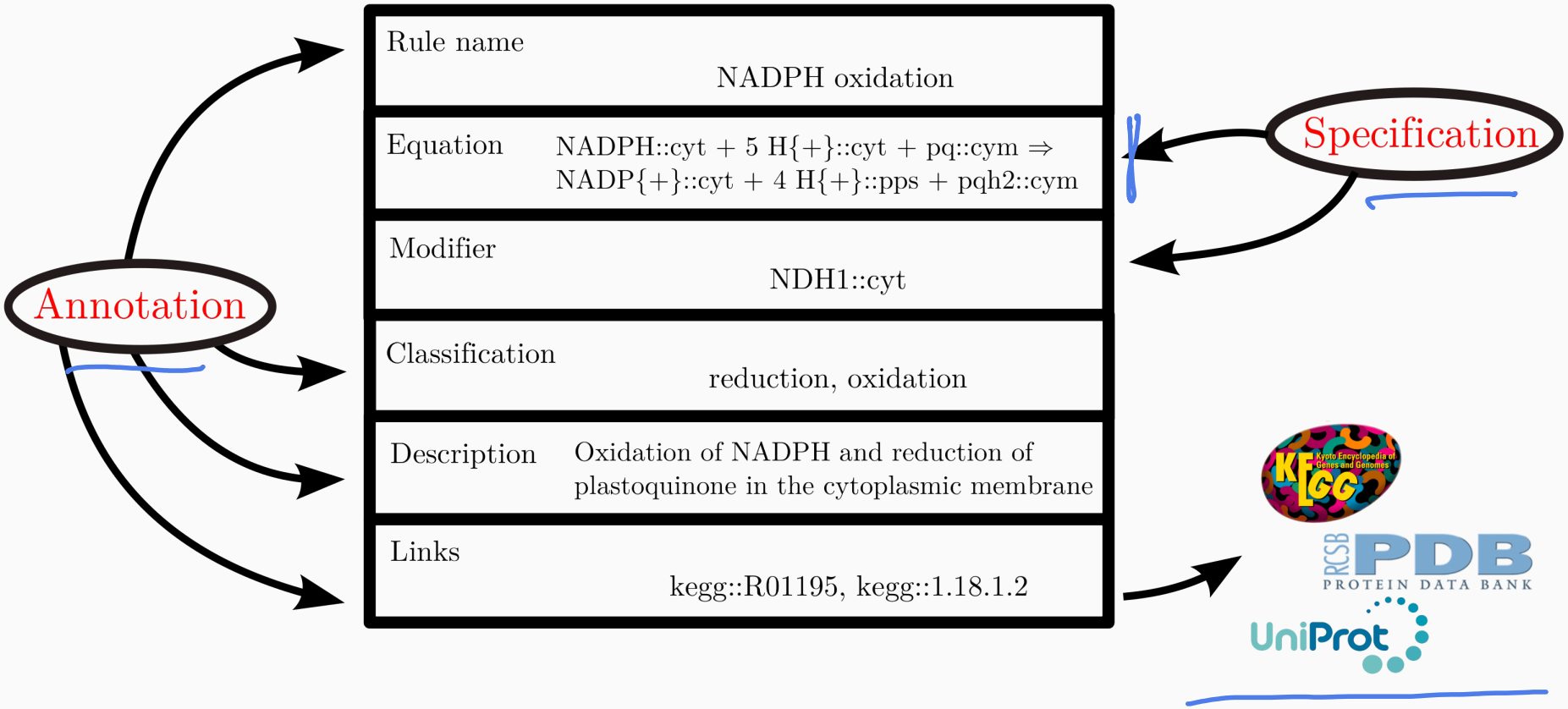
BioChemical Space

BioChemical Space (BCS) – a formal knowledge-base providing

- *specification* – we need to specify objects and relationships among them;
- *annotation* – determine meaning of the objects and relationships in a particular context

of domain-specific biological systems.

Example


Rule name
NADPH oxidation
Equation
NADPH::cyt + 5 H{+}::cyt + pq::cym ⇒
NADP{+}::cyt + 4 H{+}::pps + pqh2::cym
Modifier
NDH1::cyt
Classification
reduction, oxidation
Description
Oxidation of NADPH and reduction of
plastoquinone in the cytoplasmic membrane
Links
kegg::R01195, kegg::1.18.1.2
Annotation
Specification
KEGG
Kyoto Encyclopedia of Genes and Genomes
RCSB PDB
PROTEIN DATA BANK
UniProt

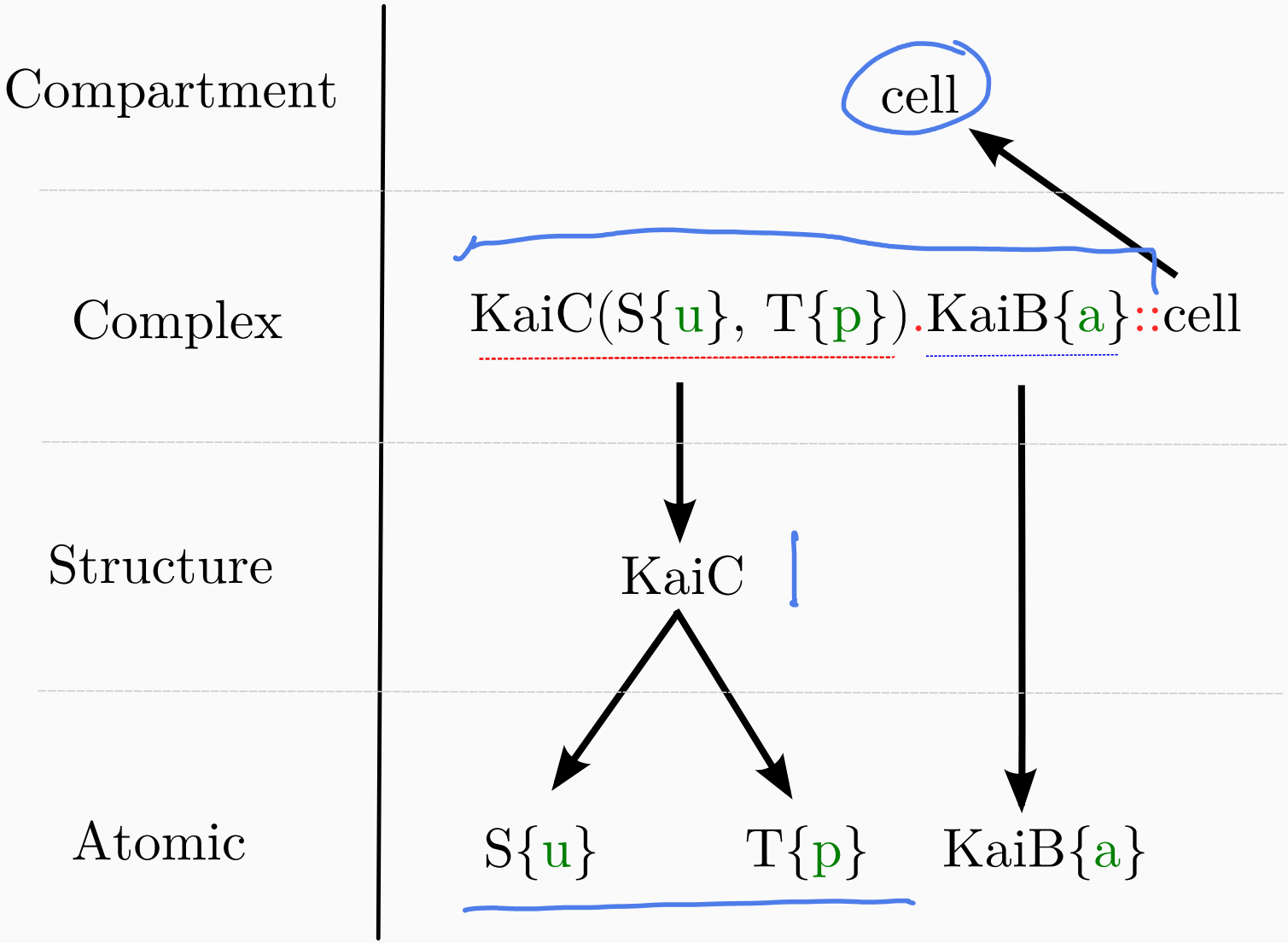
BioChemical Space Language (BCSL)

Important: the target users are outside of computer science (biology, mathematics, chemistry, . . .)

BCSL combines the following aspects:

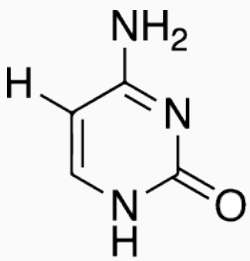
- **human-readability** (easy to read, write, and maintain),
- **rule-based** description – avoiding combinatorial explosion,
- unique level of **abstraction**,
- **hierarchy** – compositional assembly from simpler structures,
- **executability** – operational semantics allowing analysis.

The agents

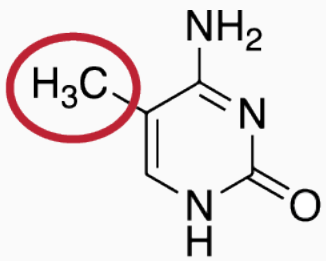

Compartment
Complex
Structure
Atomic
cell
KaiC(S{u}, T{p}).KaiB{a}::cell
KaiC
S{u}
T{p}
KaiB{a}

Atomic agents

- describe the most simple (biological) objects
- variable internal state
- level of abstraction



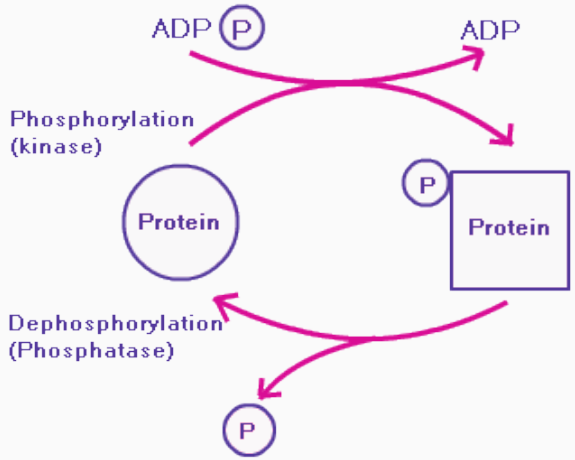
Cytosine



methylated Cytosine

amino acid metylation

`Cys{met}`, `Cys{active}`

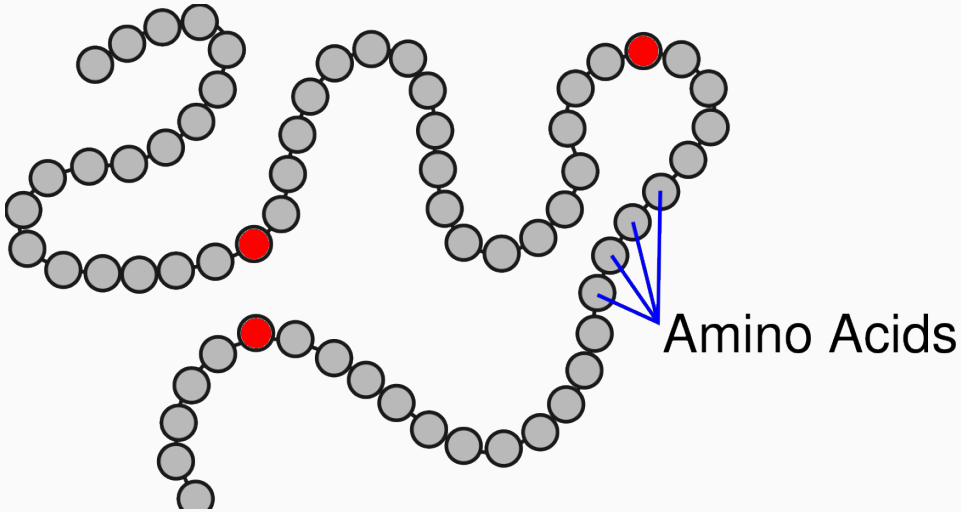


protein phosphorylation

`Prot{p}`, `Prot{u}`

Structure agents

- assigned set of unique atomic agents

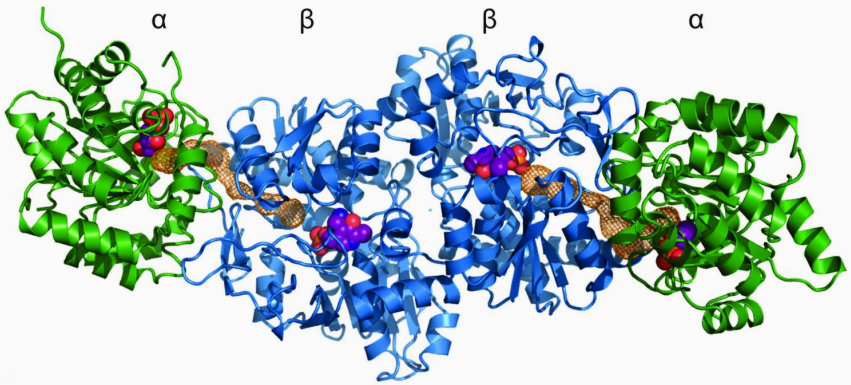


accessible AAs on a protein

```
Prot(Ser{p}, Cys{u})
```

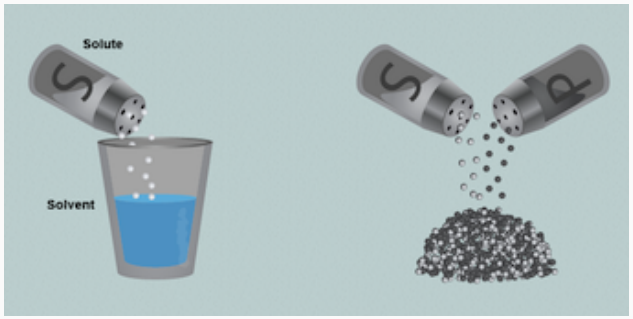
Complex agents

- composed of several atomic and/or structure agents
- abstraction – no particular order, i.e. no bonds
- assigned spatial position – compartment



protein complex

$\alpha.\alpha.\beta.\beta$

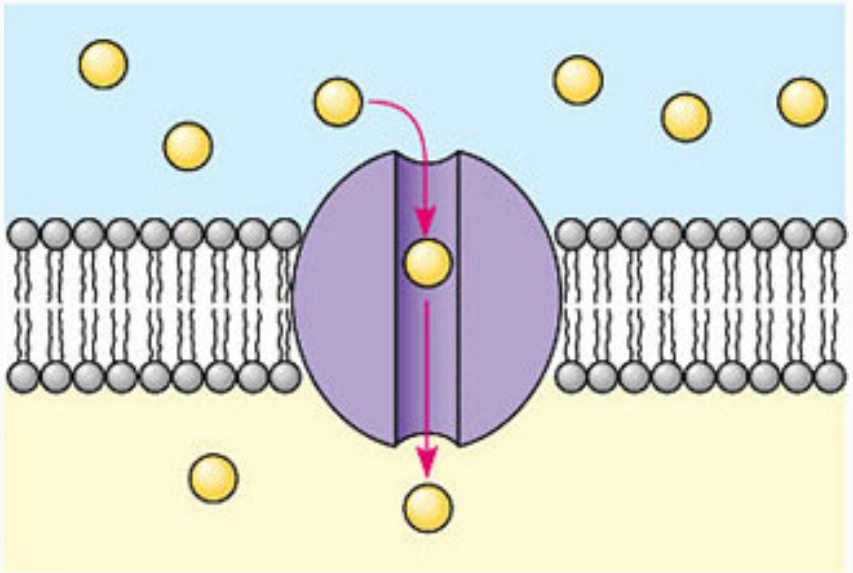


solution/mixture

$\mathtt{H_2O.NaCl}$

Compartments

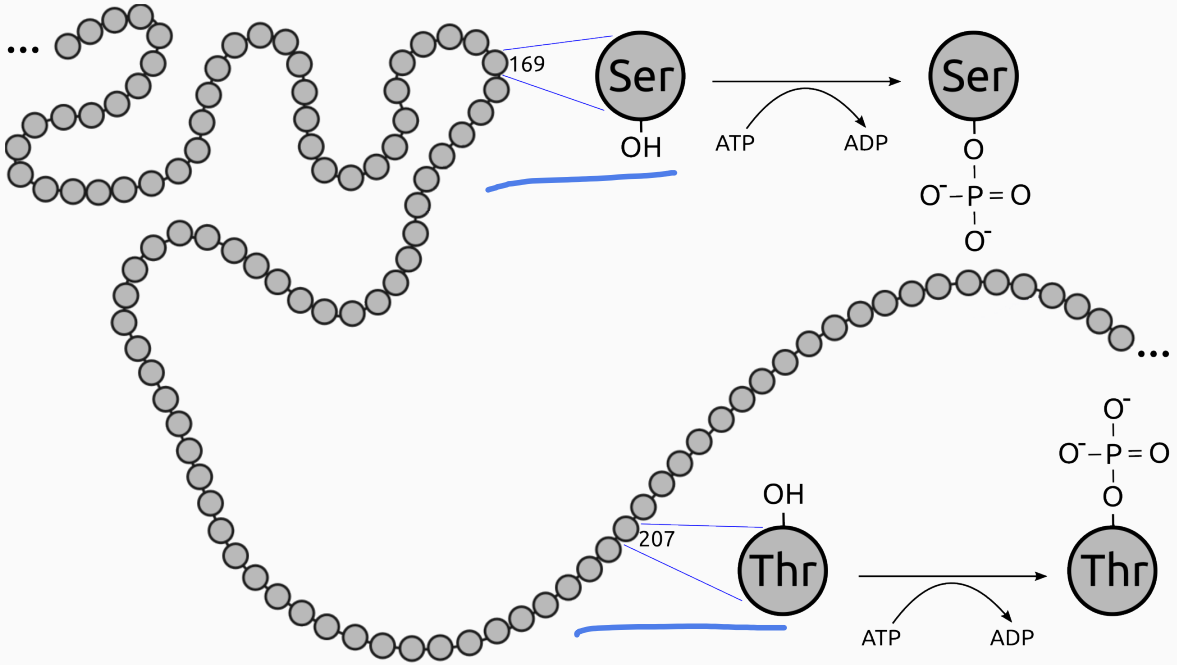
- determine spatial position of a complex
- other agents indirectly inherit compartment
- particularly useful for modelling of mass transport



$$\texttt{Prot::ext} \Rightarrow \texttt{Prot::cell}$$

Rules

- a rule describes a behavioural pattern
- generalised version of chemical reaction
- focus on particular substructure



$$\text{Prot}(\text{Ser}169\{u\})::\text{cell} \Rightarrow \text{Prot}(\text{Ser}169\{p\})::\text{cell}$$

$$\text{Prot}(\text{Thr}207\{u\})::\text{cell} \Rightarrow \text{Prot}(\text{Thr}207\{p\})::\text{cell}$$

Examples of rules

- **State change**

1. $\texttt{S\{u\}::cell} \Rightarrow \texttt{S\{p\}::cell} \ @ \ k_1 \times [\texttt{S\{u\}::cell}]$
2. $\texttt{E.S\{u\}::cell} \Rightarrow \texttt{E.S\{p\}::cell}$
3. $\texttt{R(active\{off\})::cyt} \Rightarrow \texttt{R(active\{on\})::cyt}$

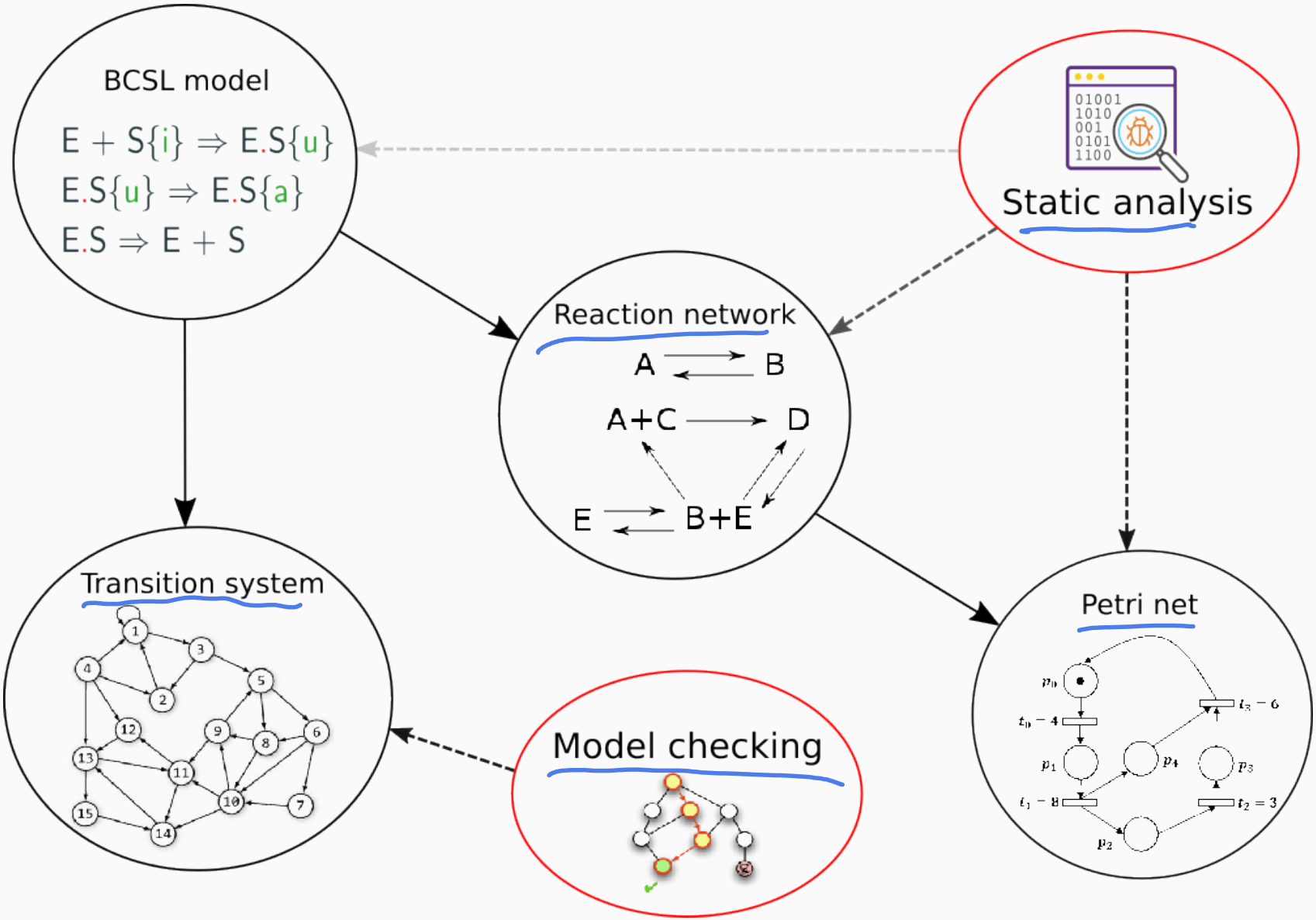
- **Complex formation**

4. $\texttt{E::cell} + \texttt{S\{u\}::cell} \Rightarrow \texttt{E.S\{u\}::cell}$
5. $\alpha.\alpha\texttt{::out} + \beta.\beta\texttt{::out} \Rightarrow \alpha.\alpha.\beta.\beta\texttt{::out}$

- **Transport**

6. $\texttt{Prot::cell} \Rightarrow \texttt{Prot::out}$
7. $\Rightarrow \texttt{mRNA::nuc}$

Executability and BCSL Models Analysis



BCSL Models Analysis

BCSgen – software support (CMSB 2020)

- online – `https://biodivine-vm.fi.muni.cz/galaxy`
- features
  - interactive editor
  - PCTL parameter synthesis and model checking (NFM 2020)
  - static analysis (consistency, redundancy)
  - simulation
  - interactive visualisation of results

Conclusions

Summary

- BCS as a format utilising the specific view on the biochemical structures and reactions
- integrating with annotation information

Future work

- focus on static analysis
- SBML-multi compatibility