On the Computational Strength of Calculi for (Bio)Chemistry

Based on joint works with:

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done within the UniBo Strategic Project CompReNDe
(Compositional and executable Representations of Nano Devices)

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$A \rightarrow^{r} C_1+\ldots+C_n \quad \Longleftrightarrow \quad A ::= \tau@r;C_1|\ldots|C_n + b@s;\mathbf{0}$

$A+B \rightarrow^{s} D_1+\ldots+D_m \quad \Longleftrightarrow \quad B ::= \overline{b}@s;D_1|\ldots|D_m$

What is the computational power of (Bio)Chemistry?

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Plan of the talk

- Chemistry as a Computational Model
  - ... not a new issue
- Chemical Ground Form (CGF) [Cardelli08]
  - ... a new way to analyze chemistry
- Computational Strength of Chemistry [Concur08]
  - Non Turing universal but...
  - Turing complete formalisms can be approximated with any degree of precision
- From Chemistry to...
  - Biochemistry: BGF [AB08]
  - Nano devices: nano-K [CMSB07,TCS08]
- Computational strength of BGF and K-calculi [CMSB09]
- Concluding remarks

Is Chemistry Turing powerful?

- Magnasco. ***Chemical Kinetics is Turing Universal***. *Phys Rev Lett*. 1997
  - Answer: **YES**… but justification not convincing (only Digital Computers with bounded memory are considered)
- Liekens and Fernando. ***Turing Complete Catalytic Particle Computers***. In Proc. *ECAL'07*. 2007
  - Answer: **YES**… but justification not convincing (only Minsky Machines with bounded computation are considered)
- Soloveichik et al. ***Computation with Finite Stochastic Chemical Reaction Networks***. *Nat. Computing*. 2008
  - Answer: **NO**… but all Minsky and Turing Machines can be at least approximated with any given degree of precision

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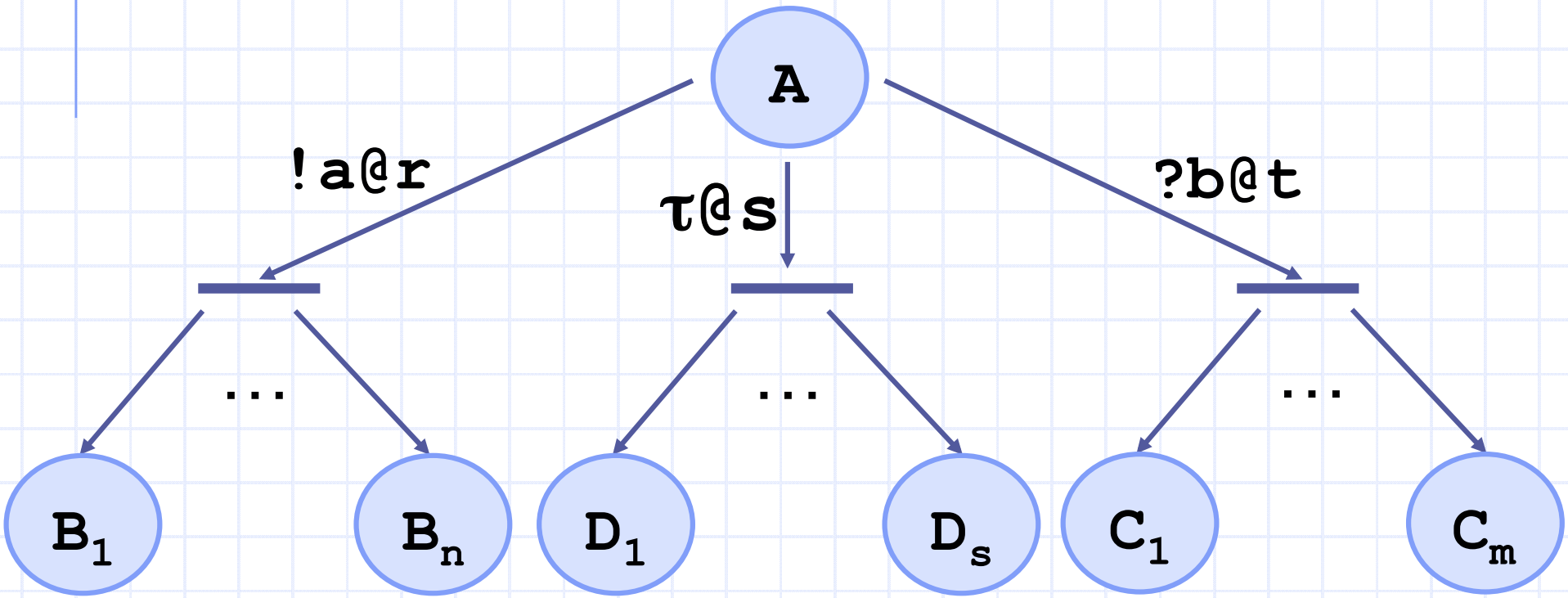
Chemical Ground Forms

- Stochastic variant of Milner's CCS, with an equivalent graphical notation (Stochastic Collective Automata)

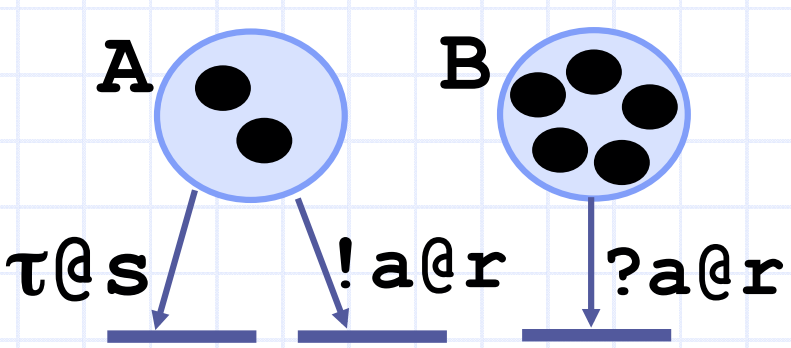


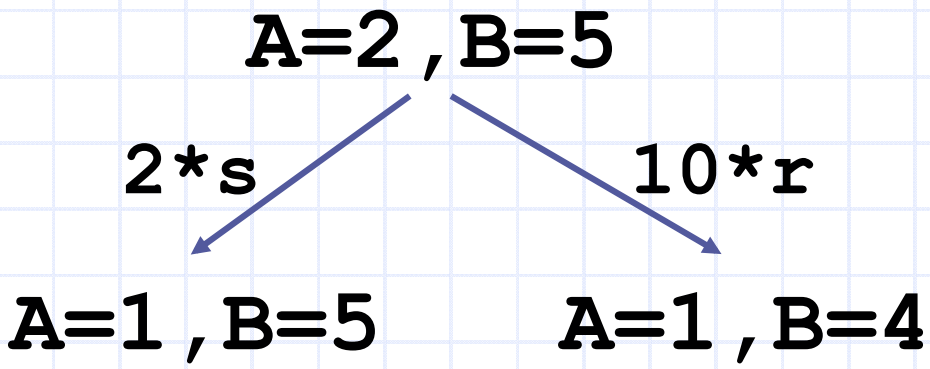
Stochastic semantics

- Actions take (an exponentially distributed amount of) time
  - Internal delay: **τ@r**
    - **Pr(internal delay < t) = 1-e^{-rt}**
  - Synchronization between complementary actions: **?a@r, !a@r**
    - **Pr(synchronization time < t) = 1-e^{-rt}**

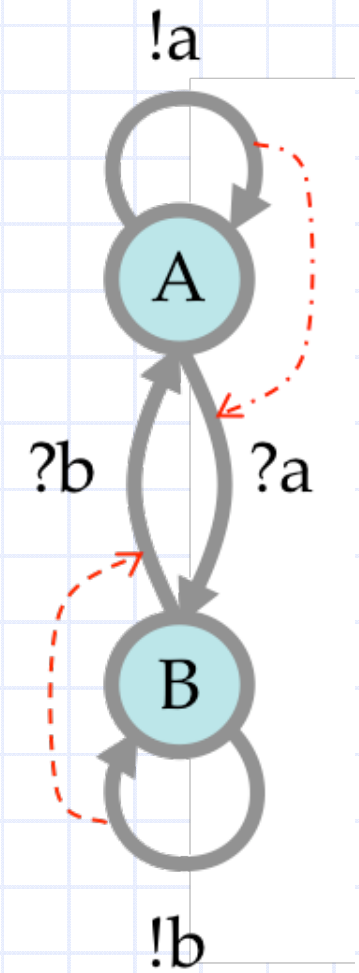
Collective stochastic semantics

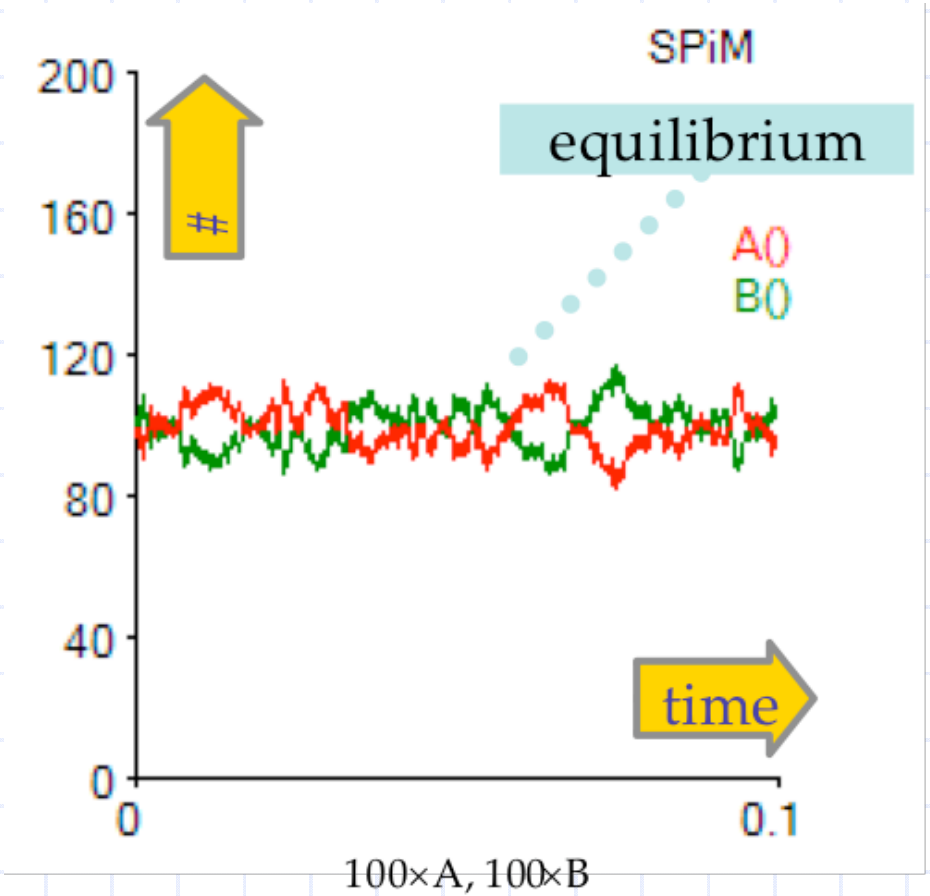
- To faithfully model chemistry, the rates of distinct transitions with the same effect **must be added**



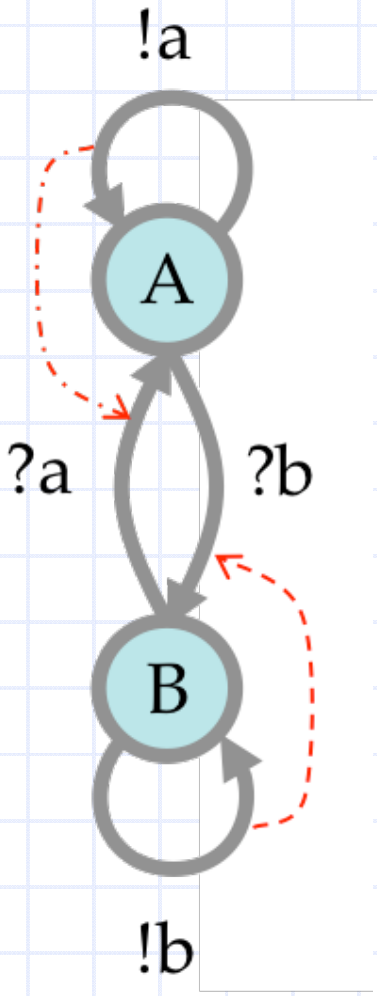


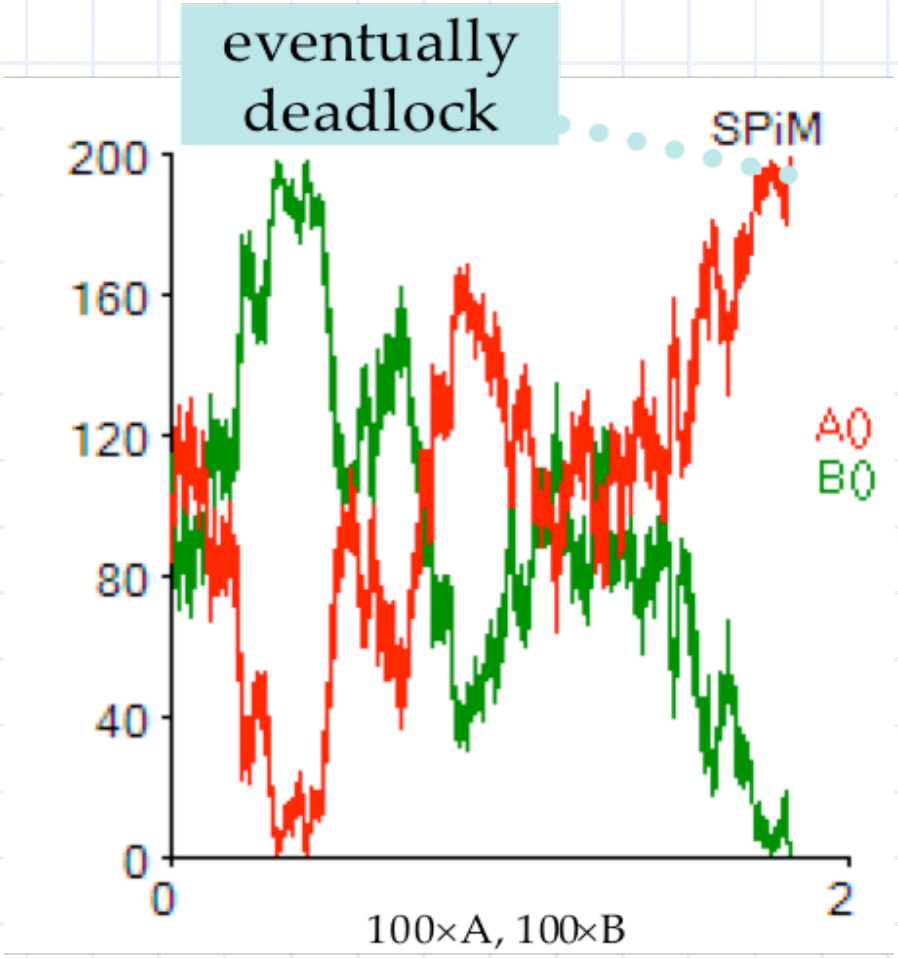
Example: Celebrities…



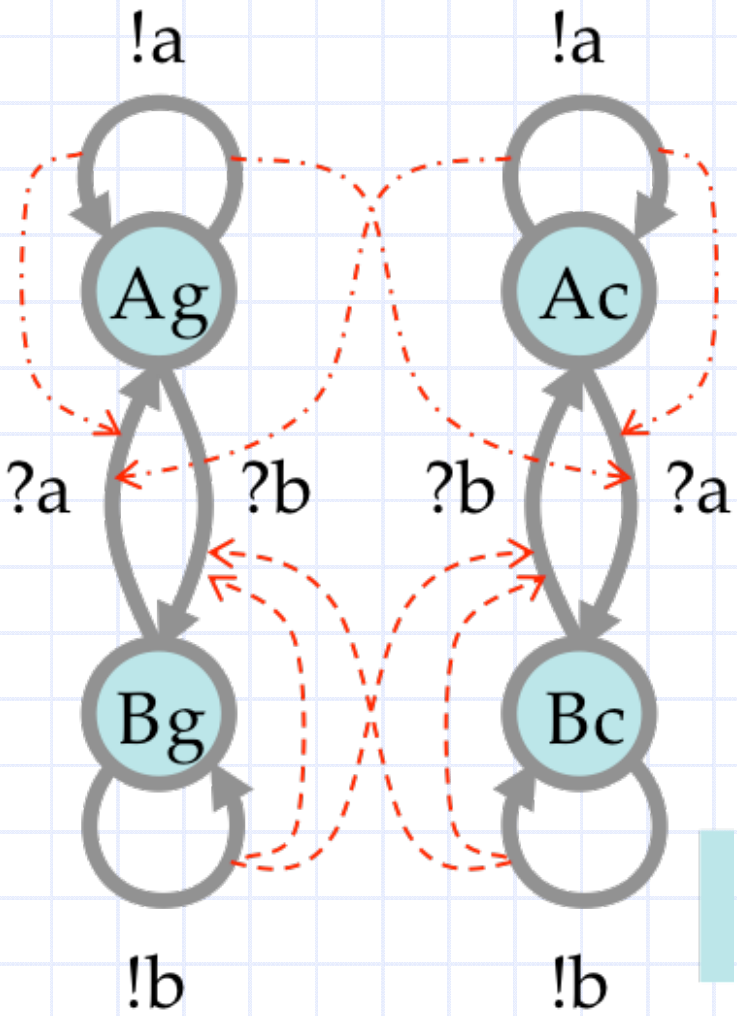


Example: Groupies...



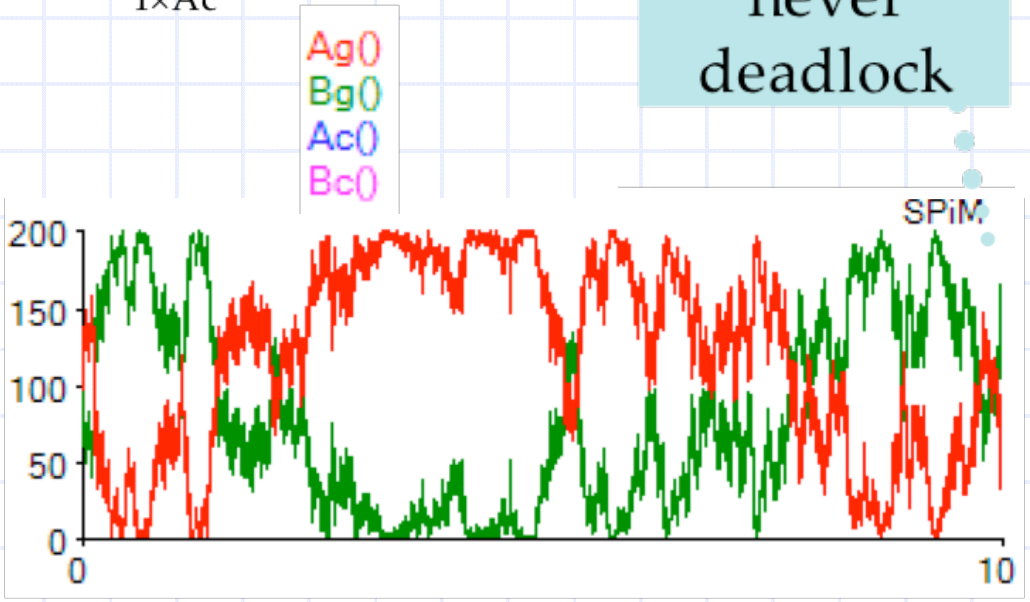


Example:
Groupies with one Celebrity…



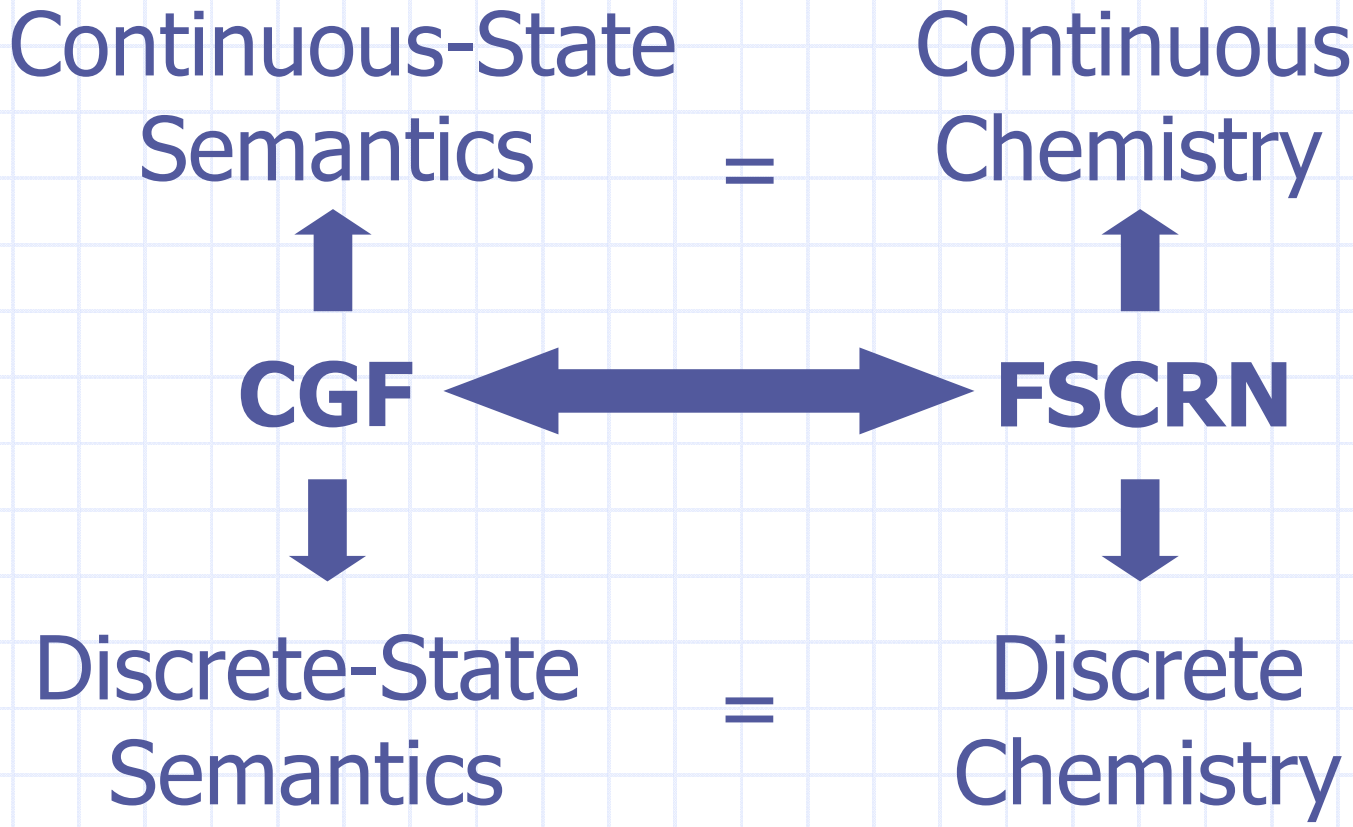
100×Ag, 100×Bg
1×Ac

never deadlock



CGF = FSCRN

[Cardelli08]



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Non Turing universality

- The (existential version of) the Halting problem is decidable in CGF
- **Proof**:
  - We first define an encoding of CGF into (nondeterministic) **Petri nets**
  - Theorem:
    Given a CGF process P, it can reach a halted configuration (with prob. > 0) **iff** the net that encodes P has a deadlock
  - **Deadlock is decidable** in Petri nets

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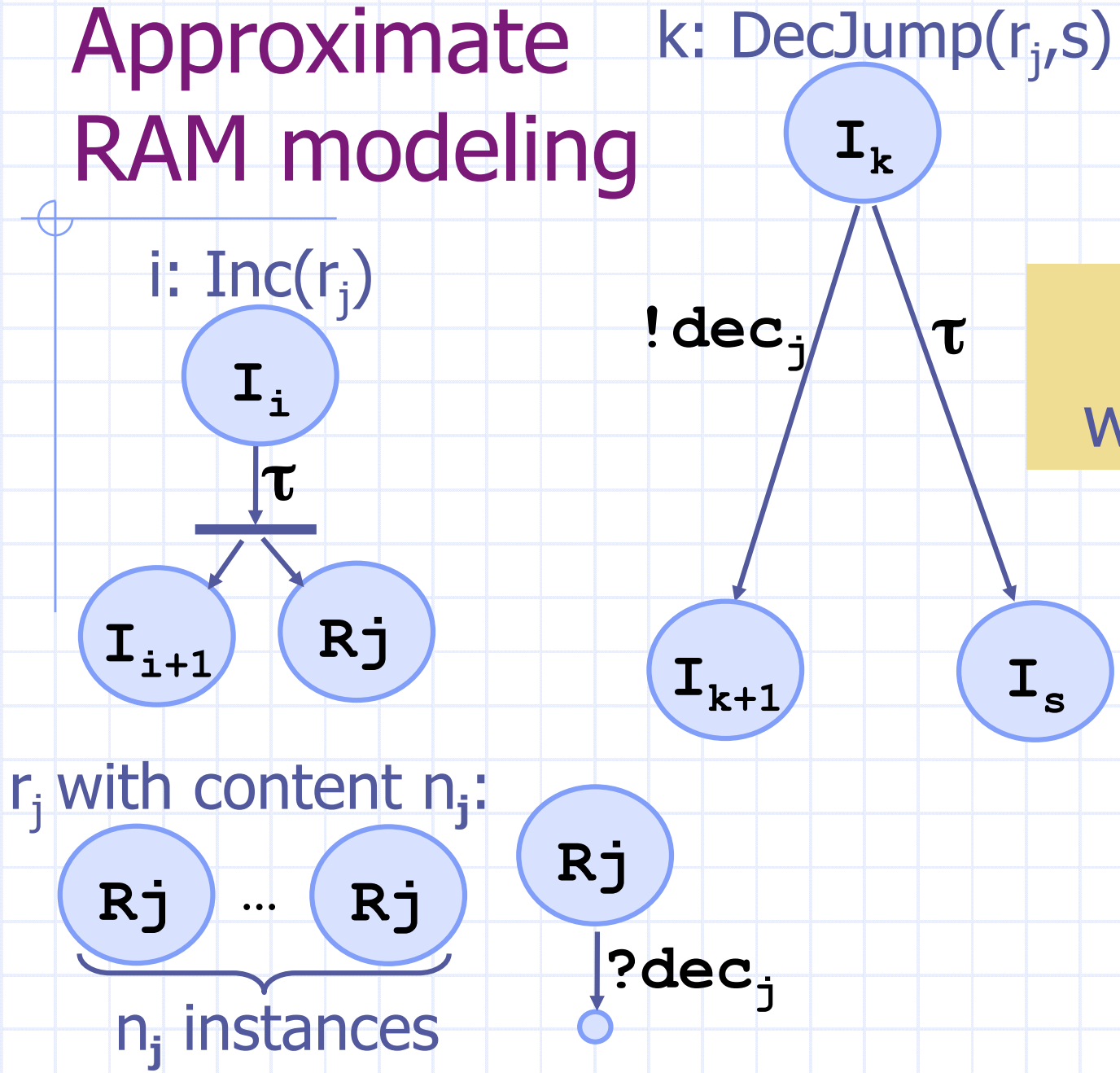
Approximation of Turing complete formalisms in CGF

- We approximate (for any degree of precision) **Random Access Machines** (RAMs)
- RAMs [Min67]:
  - **Registers**: r_1 ... r_n hold natural numbers
  - **Program**: sequence of indexed instructions
    - **i: Inc(r_j)**: add 1 to the content of r_j and go to the next instruction
    - **i: DecJump(r_j,s)**: if the content of r_j is not 0 then decrease by 1 and go to the next instruction; otherwise jump to instruction s

RAM encoding

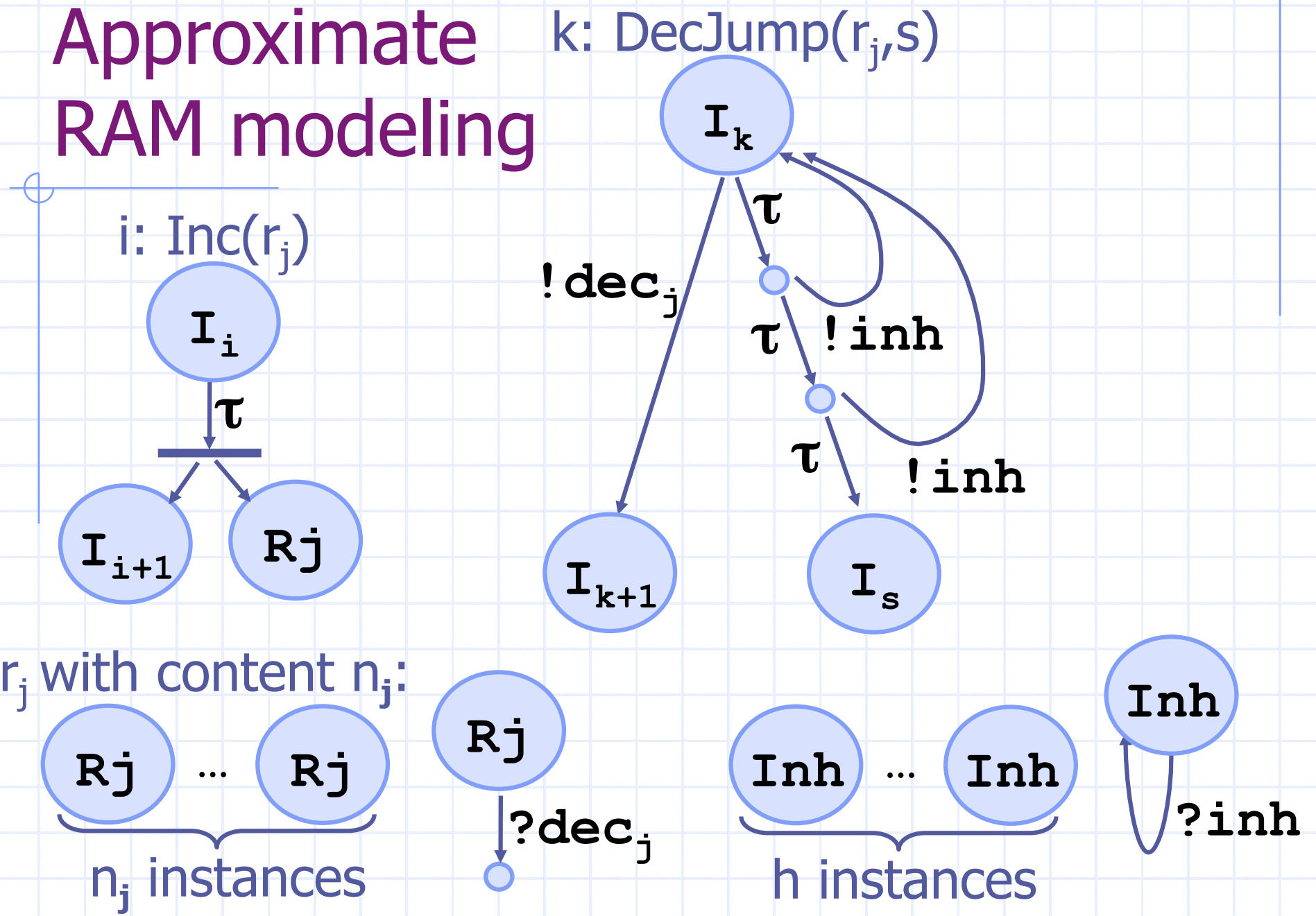
- RAMs **cannot** be faithfully modeled by a CGF process
  - otherwise (by decidability of existential term. in CGF) RAM termination is decidable
- **Main theorem:**
  Given $\varepsilon > 0$ and a RAM, it **can** be modeled by a CGF process that includes also wrong computations, but the probability a wrong computation is scheduled is smaller than ε

Approximate RAM modeling

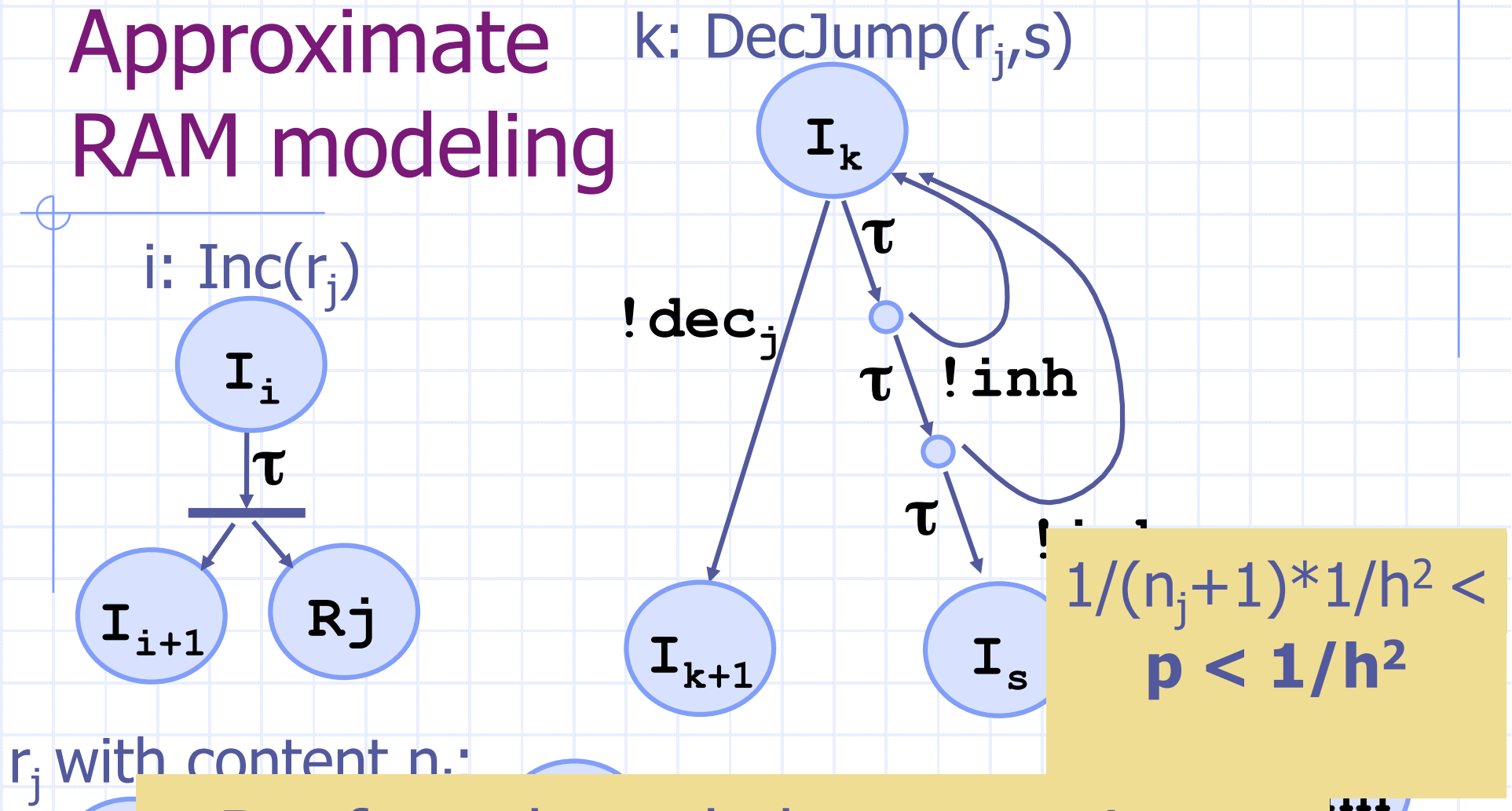


Problem:
wrong jump!

Approximate RAM modeling



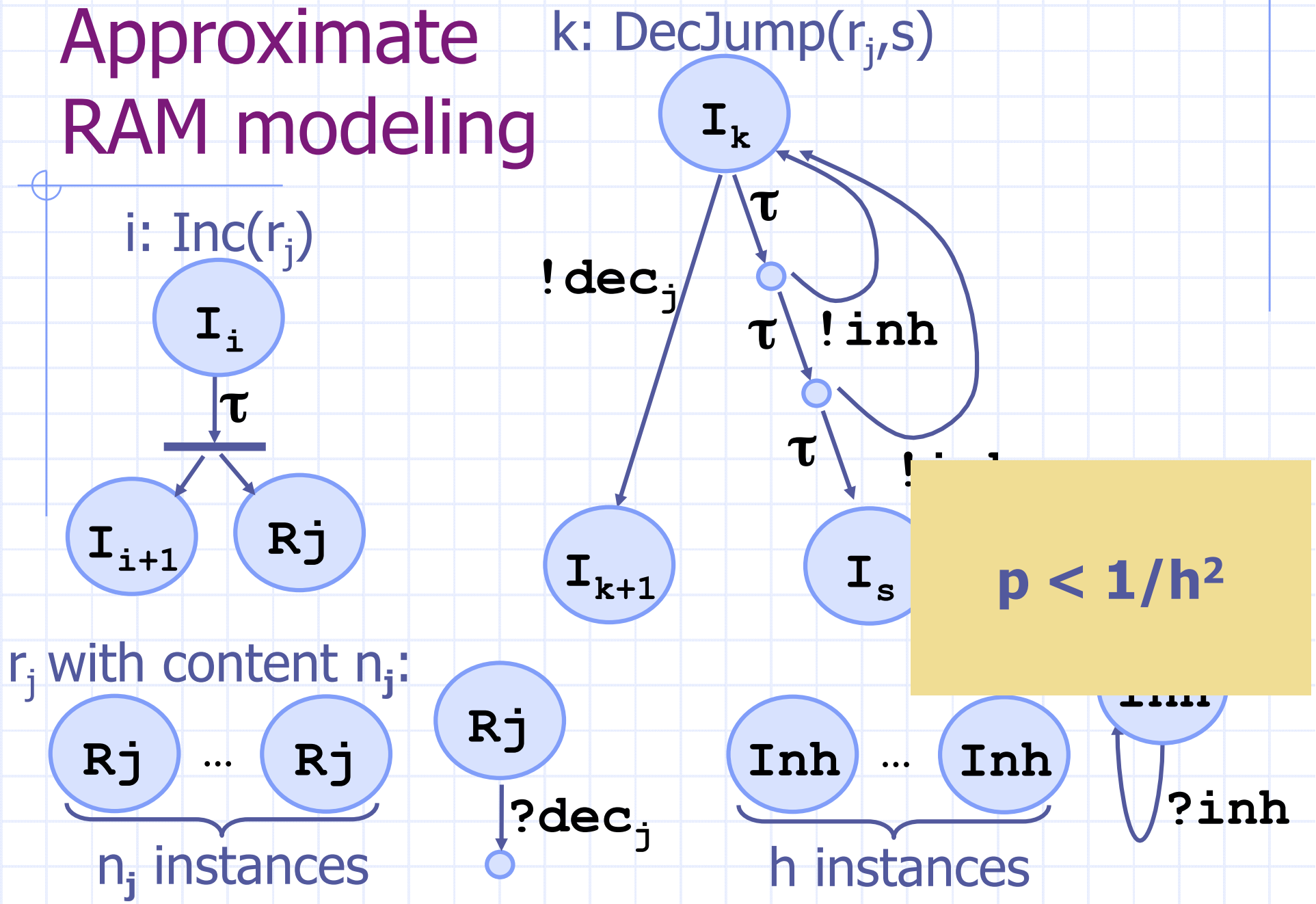
Approximate RAM modeling



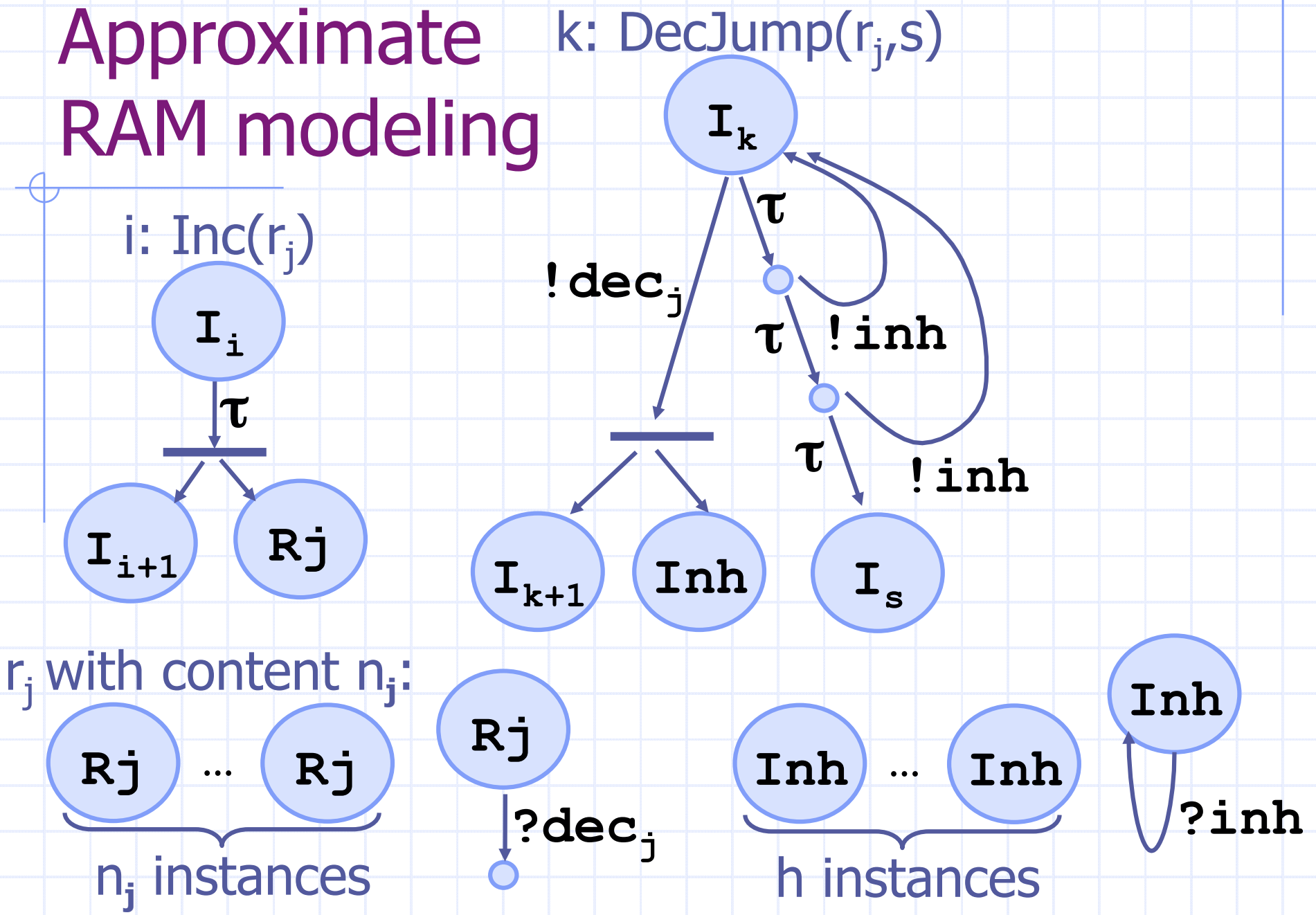
$1/(n_j+1)*1/h^2 < p < 1/h^2$

But for unbounded computations, with infinitely many decrements, the prob. of a wrong jump is 1

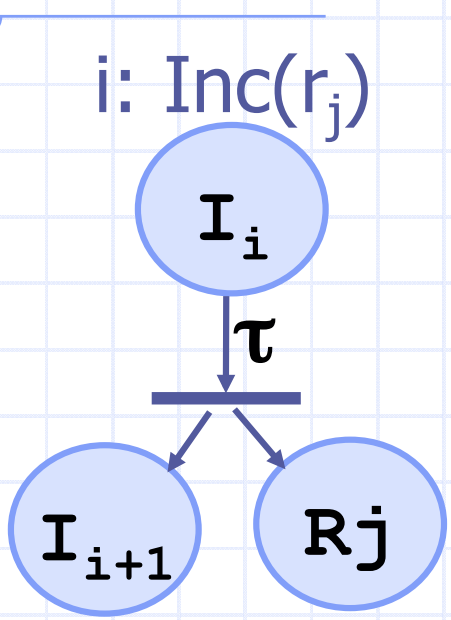
Approximate RAM modeling

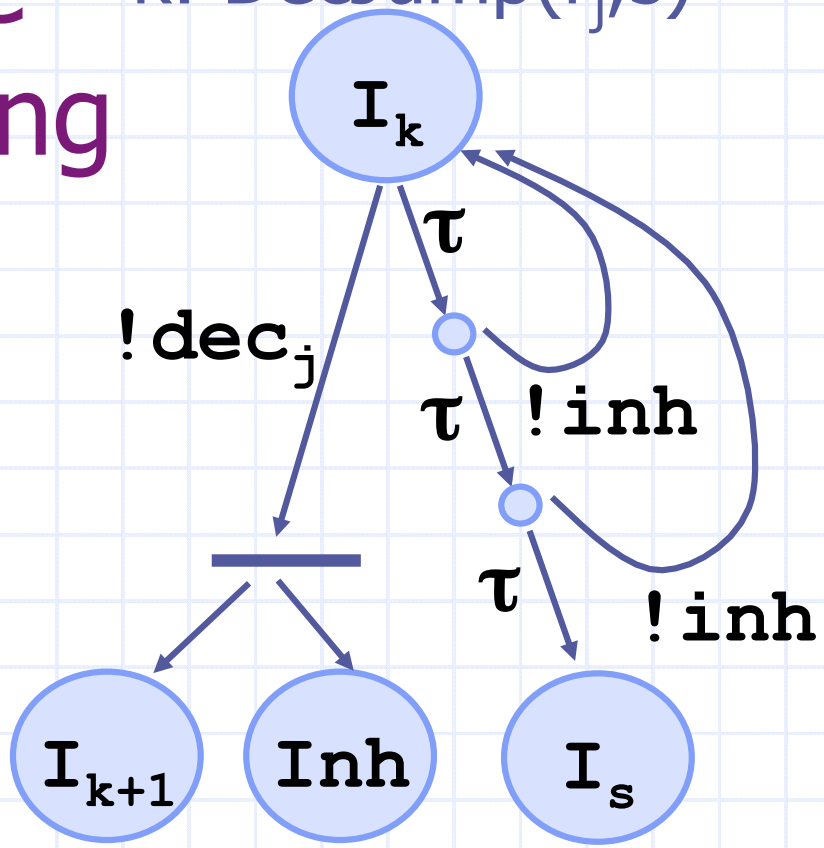


Approximate RAM modeling



Approximate RAM modeling





r_j wi

nh

Incrementing the occurrences of **Inh** the prob. a wrong jump is taken is

$$p < \Sigma_{i=inith...\infty} 1/i^2$$

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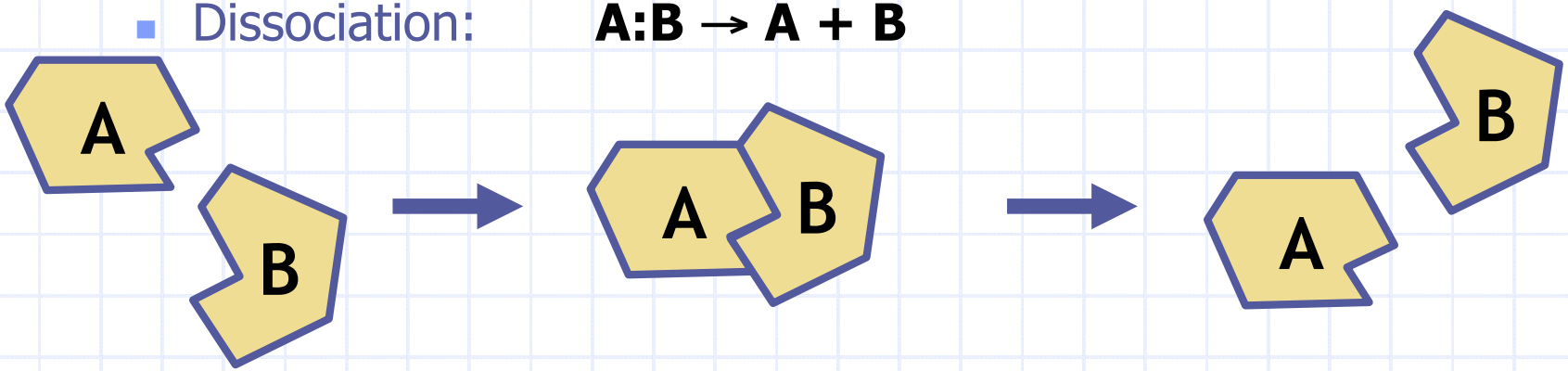
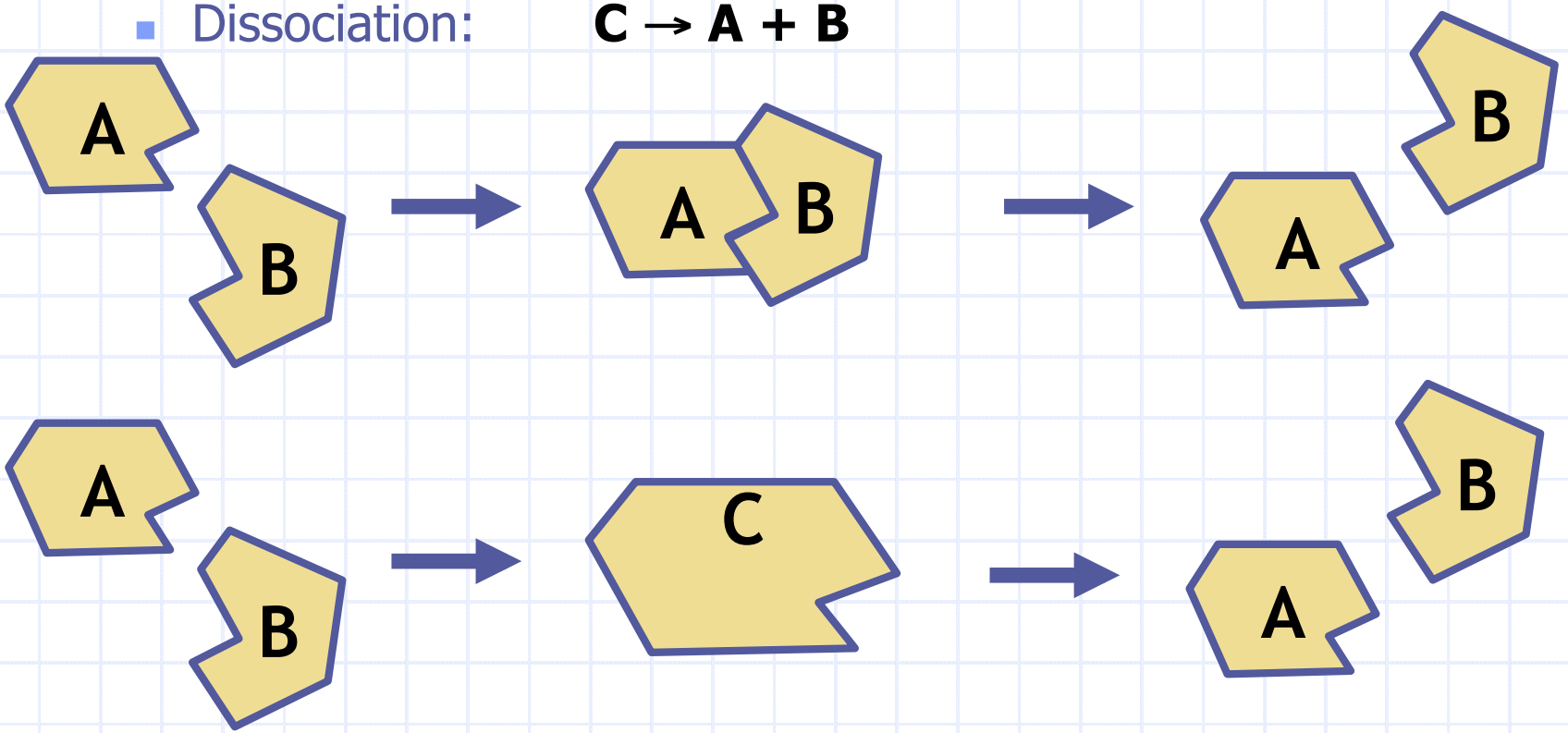
Basic Biochemistry

- Molecules may also form reversible complexes
  - Association: **A + B → A:B**
  - Dissociation: **A:B → A + B**

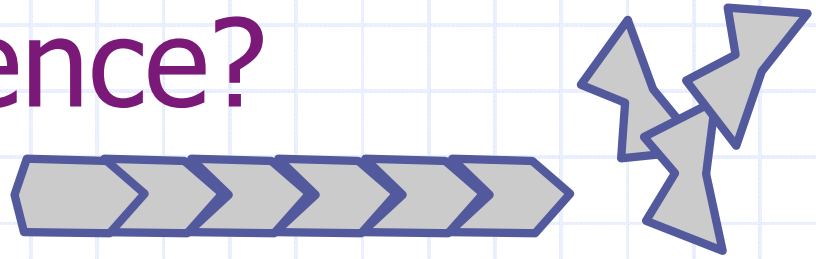


Basic Biochemistry

- Molecules may also form reversible complexes
  - Association: **A + B → C**
  - Dissociation: **C → A + B**



What's the Difference?



Consider linear polymerization:

The "chemical program" for polymerization:

$P_0 + M \rightarrow P_1$

$P_1 + M \rightarrow P_2$

$P_2 + M \rightarrow P_3$

....

an infinite (non-)program

an infinite set of species

$P_{10757} + M \rightarrow P_{10758}$

Such specificity is unreal

But "nature's program" for polymerization has to fit e.g. in the genome, so it cannot be infinite! Clearly, nature must be using a different "language" than basic chemistry:

molecule with convex patch +

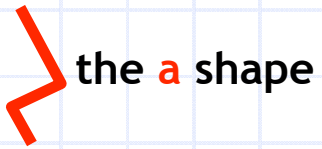
molecule with concave patch →

molecule with convex patch

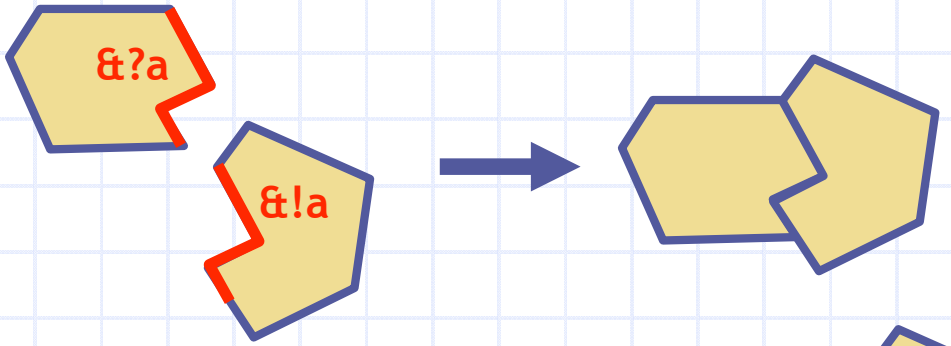
Finite program composed of local rules

Biochemical Ground Form= CGF + Association and Dissociation

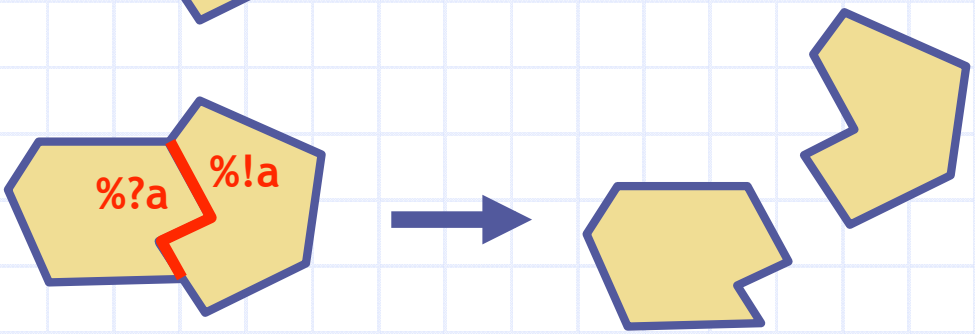
- Association patches are named



- & – association
  - &?a associate
  - &!a co-associate



- % – dissociation
  - %?a dissociate
  - %!a co-dissociate



- A given patch can *hold* only one association at a time
- Two molecules can dissociate only if *they* are associated

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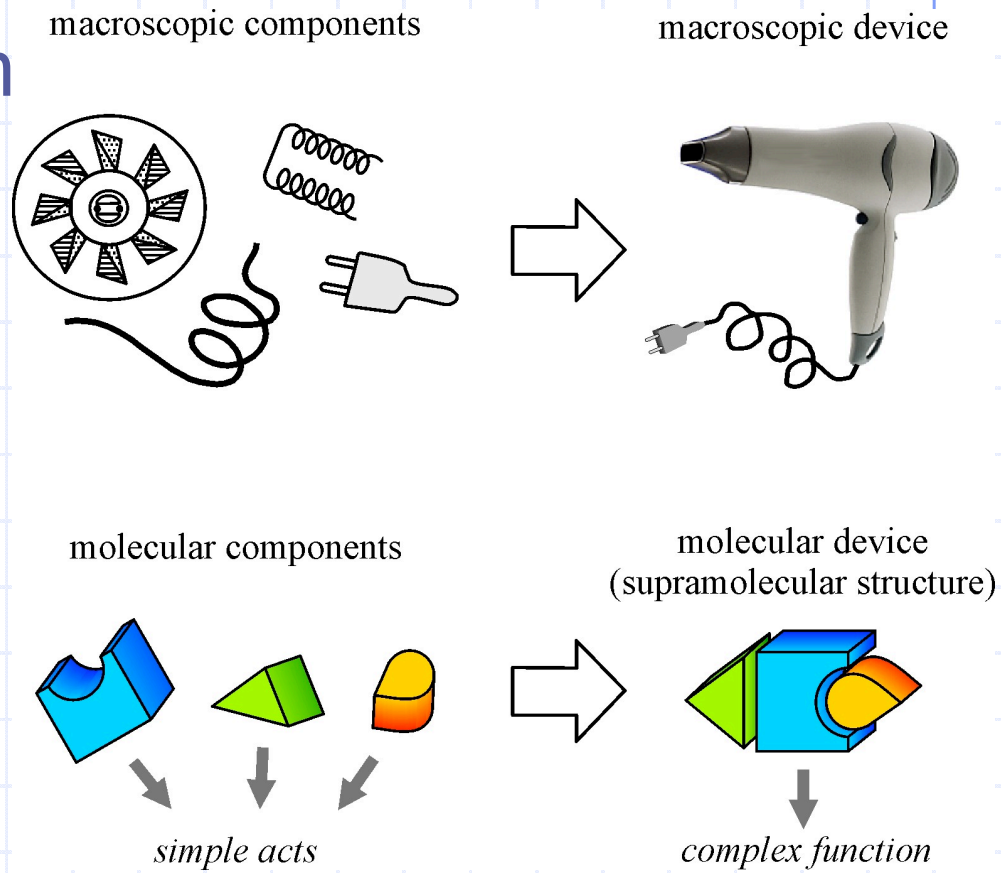
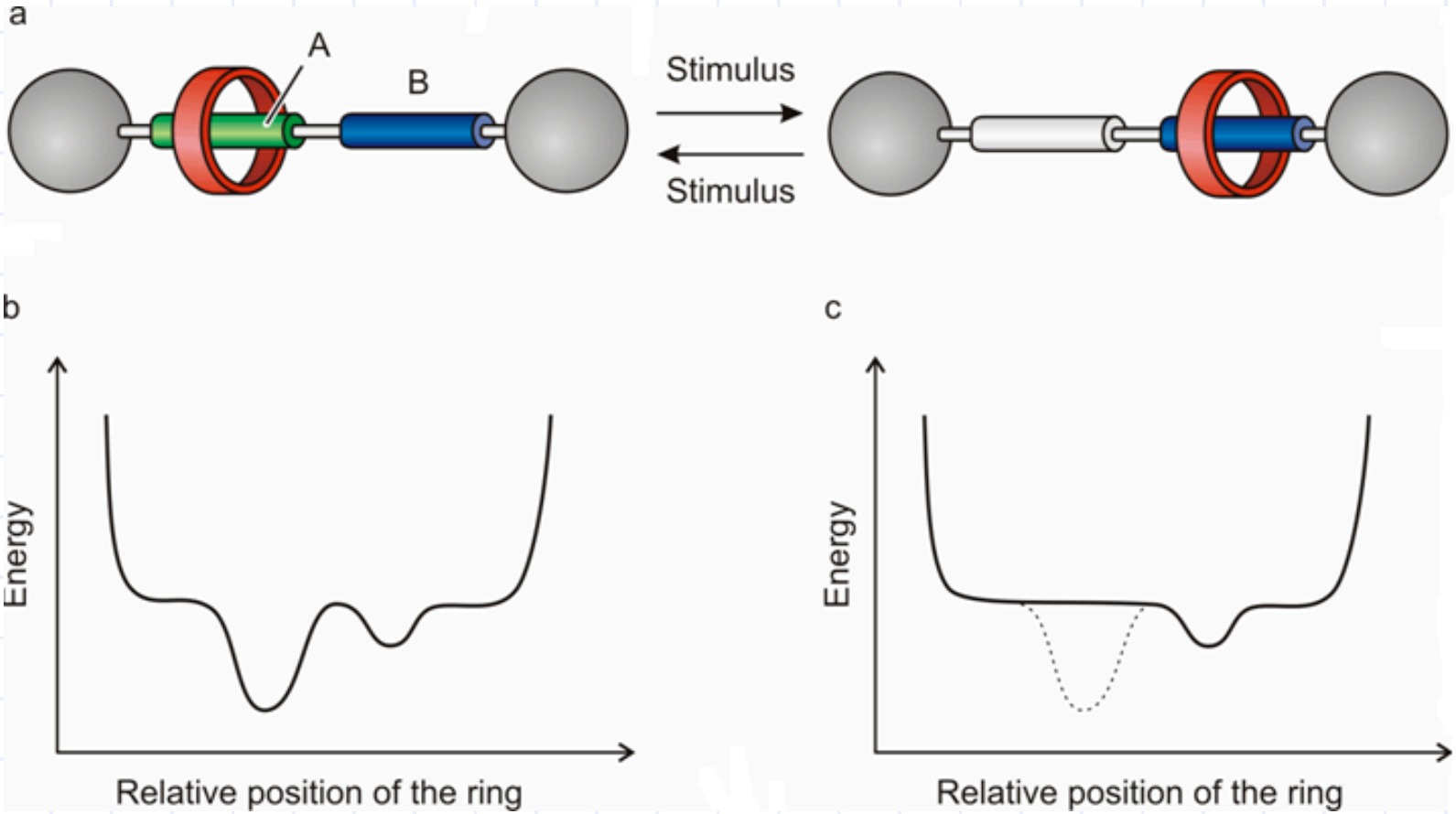
Nano Devices

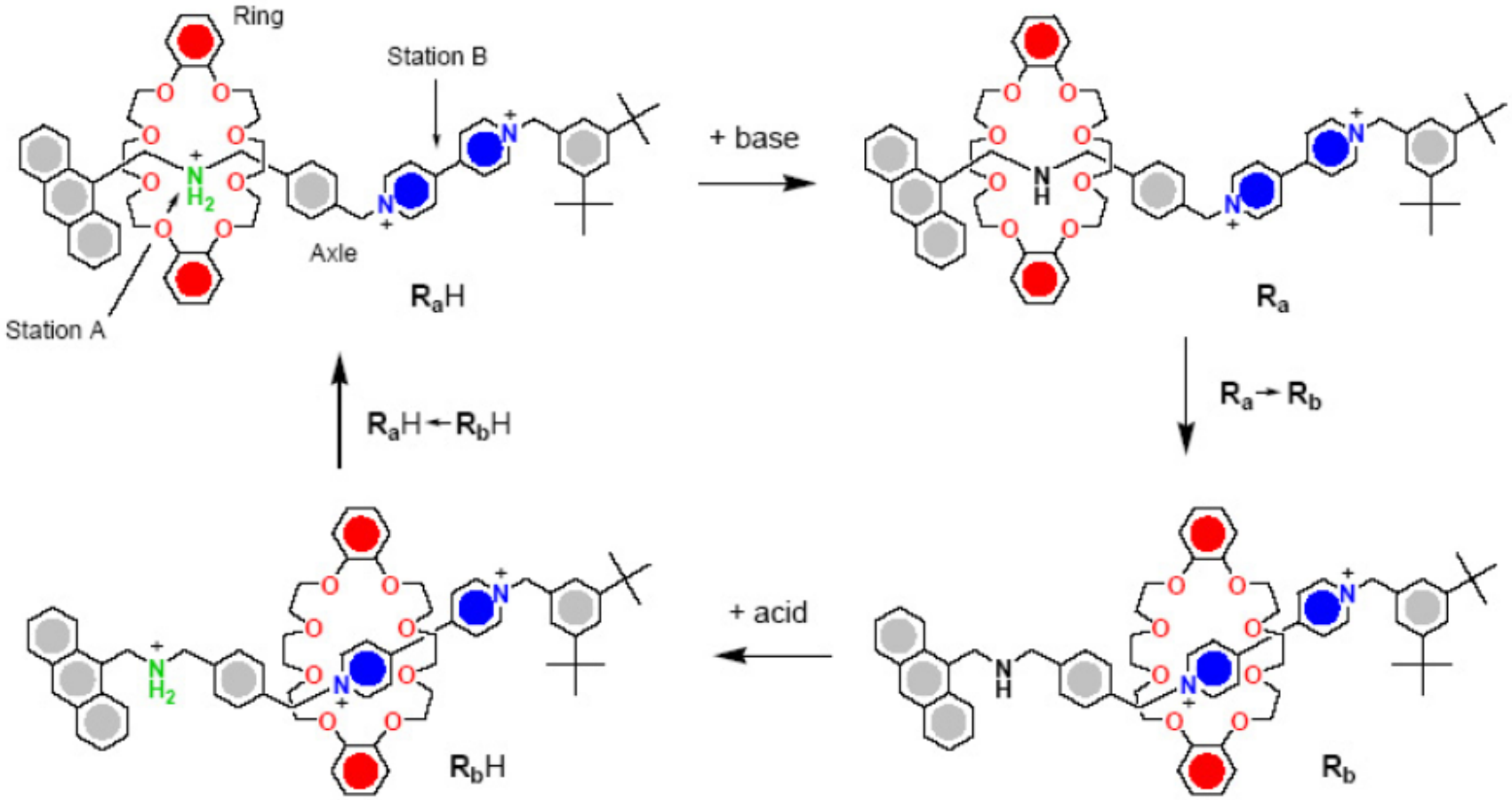
- Supramolecular system
  - Built **bottom-up**: assembling molecular components
  - Used to "implement" basic **functionalities**: binary memories, basic logic gates, mechanical movements, …



Example: [2]rotaxane

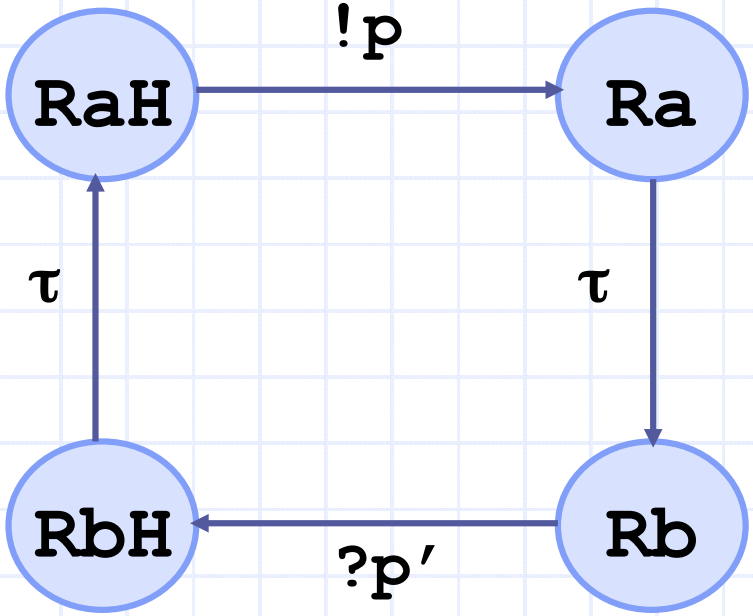


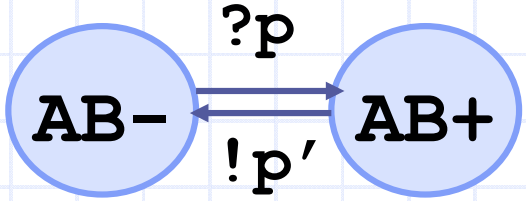
Rotaxane RaH



Modeling RaH in CGF

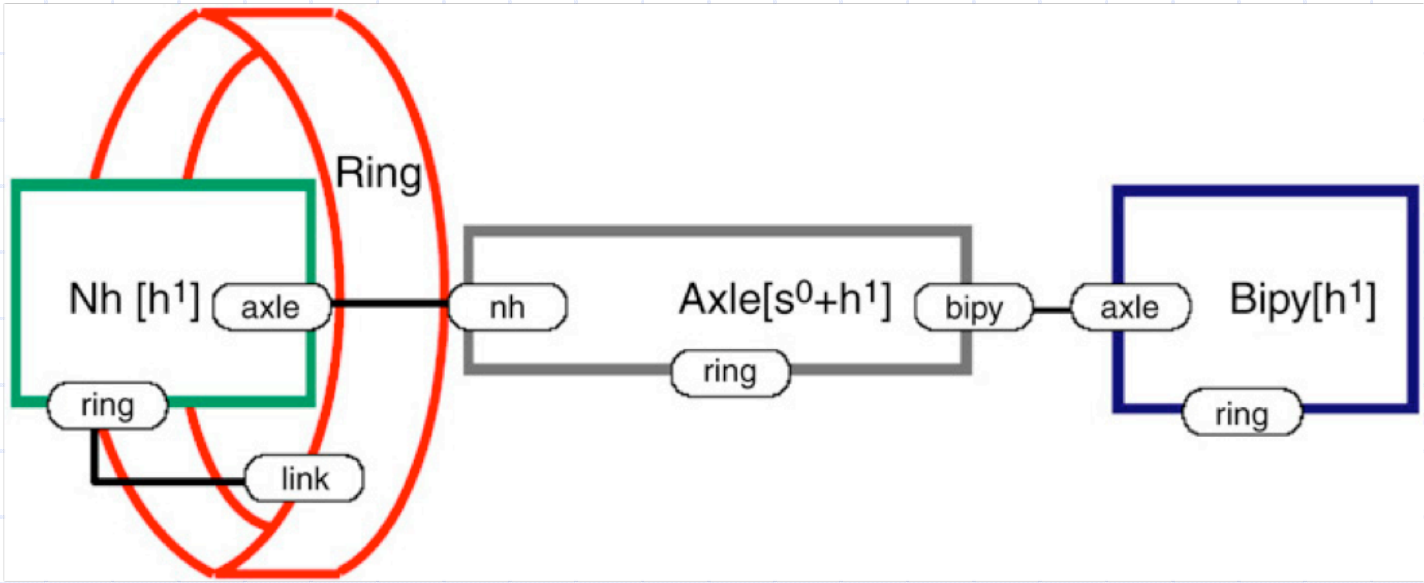
- The RaH process calculus definition





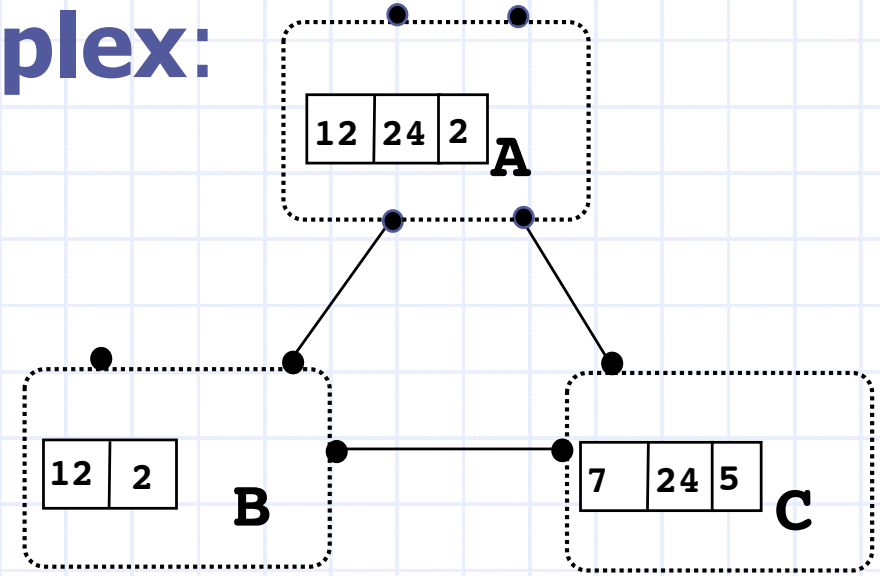
Towards a compositional representation

- In this representation there is no indication of the exploited **components**!
- **Solution**: follow the approach of K-calculi



K-calculi: the nodes

- K is a **graph-rewriting** system where nodes
  - carry **state information** (about phosphorilation, shape,...)
  - have **sites** through which they bind other nodes
- A **complex**:



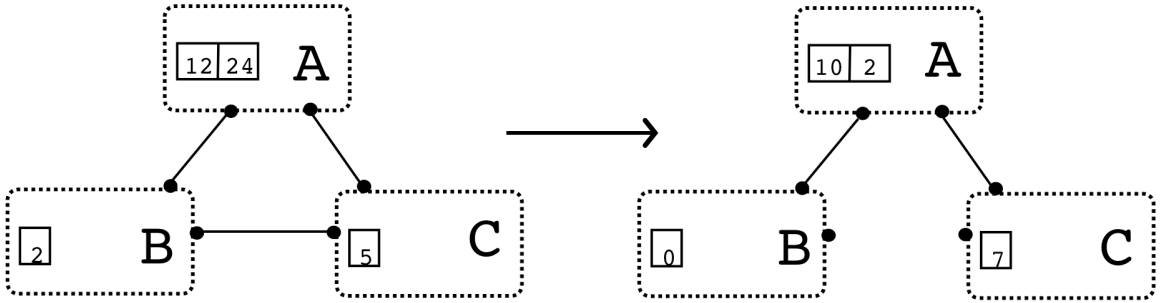
and its syntactic description:

K-calculi: the reactions

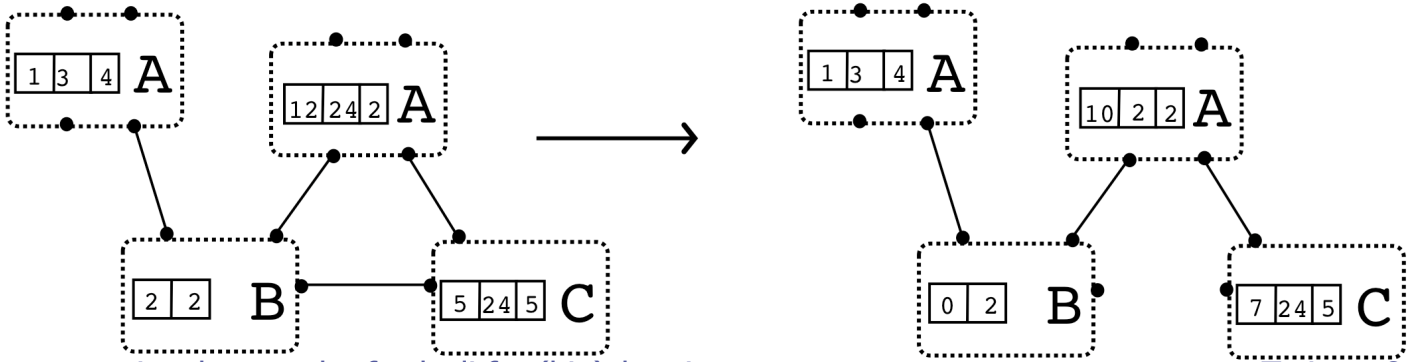
- A reaction rule:

$$A[1^{12}+2^{24}](1^{x}+2^{y}),\ B[1^{2}](2^{x}+3^{z}),\ C[1^{5}](1^{z}+2^{y})$$

$$\rightarrow A[1^{10}+2^{2}](1^{x}+2^{y}),\ B[1^{0}](2^{x}+3),\ C[1^{7}](1+2^{y})$$

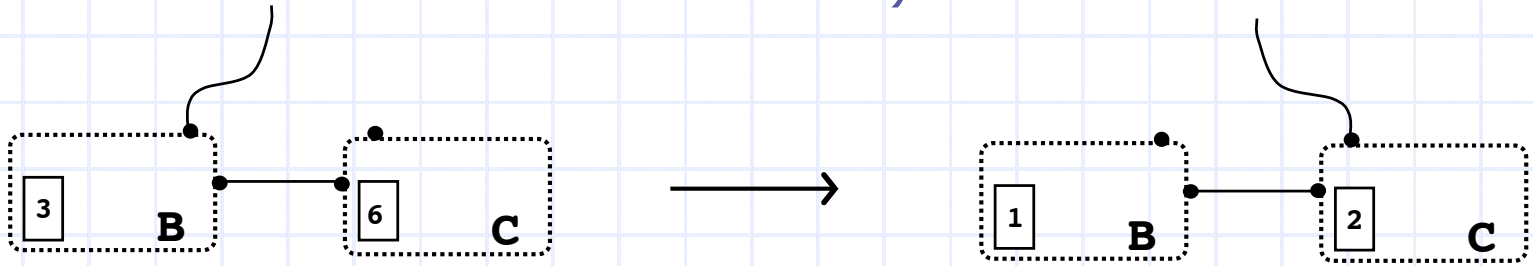


and a possible instantiation:

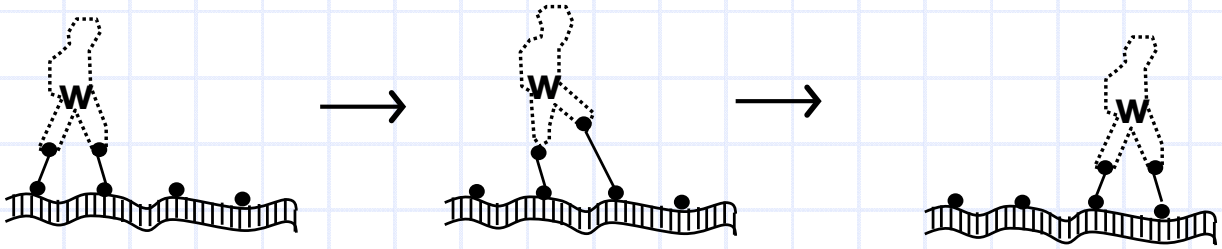


Three types of reactions: creations, destructions and bond flipping

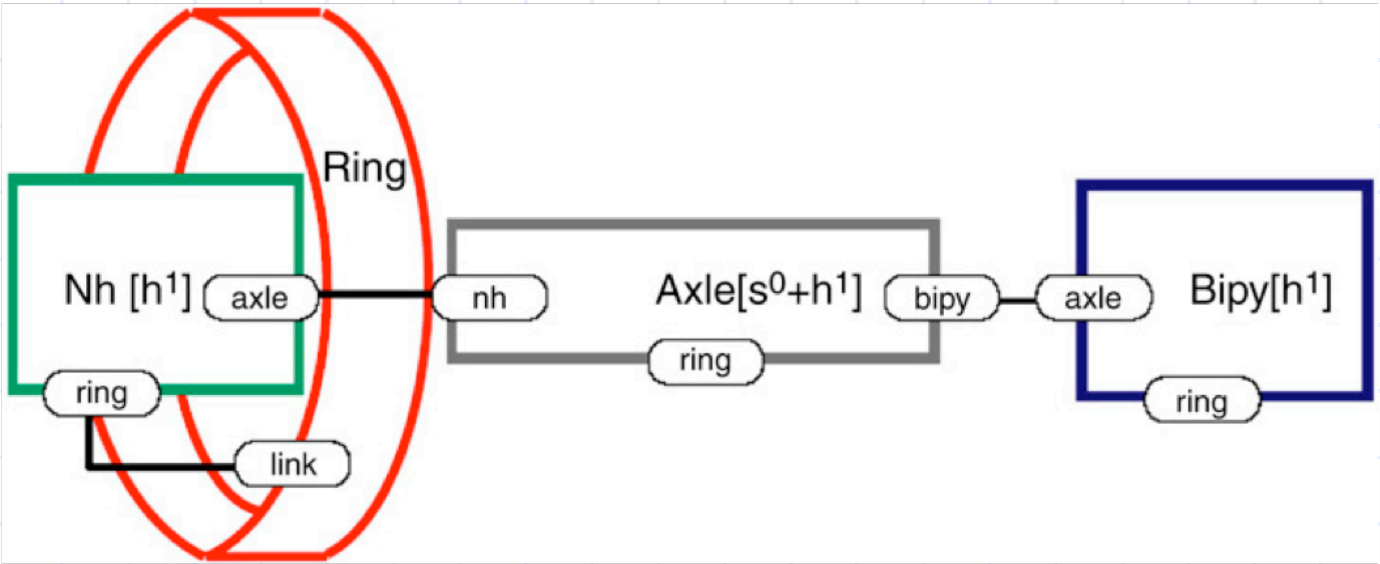
- Reactions are monotone:
  - either **creations** (bonds and/or proteins are created)
  - or **destructions** (bonds and/or proteins are removed)
  - or (extension of k) **bond flippings** (an edge of a bond may be moved from one molecule to another)



suggested by the bipedal movement on a DNA strand



RaH modeled in K: the initial state



$$Nh[h^1](axle^s + ring^x),\qquad Axle[s^0 + h^1](nh^s + bipy^r + ring),$$
$$Bipy[h^1](axle^r + ring),\qquad Ring\,(link^x)$$

RaH modeled in K: some reaction rules

- Deprotonation:

$$Nh[h^1], Base[h^0] \underset{base\_nh}{\overset{nh\_base}{\rightleftarrows}} Nh[h^0], Base[h^1]$$

- Disconnection:

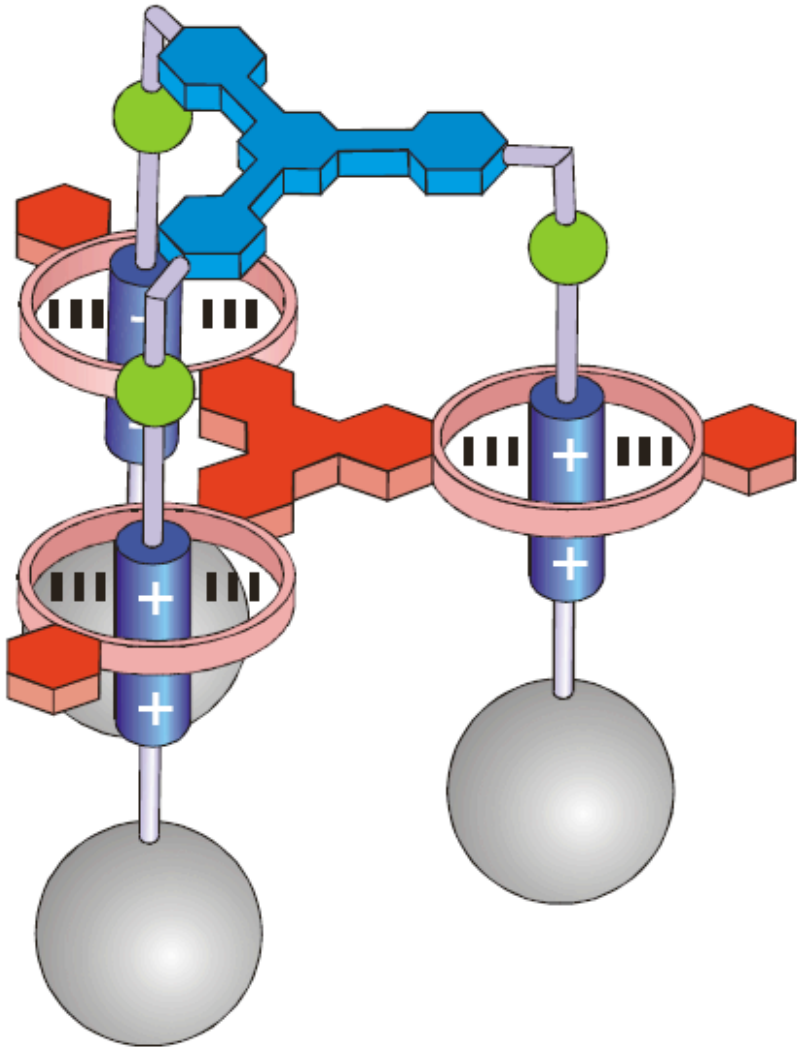
$$Nh[h^0](axle^s + ring^x), Axle[s^0](nh^s + ring) \overset{\infty}{\rightarrow} Nh[h^0](axle^s + ring), Axle[s^0](nh^s + ring^x)$$

- Connection:

$$Axle[s^0](bipy^r + ring^x), Bipy[h^0](axle^r + ring) \underset{unlink\_bipy}{\overset{link\_bipy}{\rightleftarrows}} Axle[s^1](bipy^r + ring), Bipy[h^0](axle^r + ring^x)$$

From the rotaxane to the nano-elevator

- **Nano-elevator**: three joined rotaxanes with a platform connected to the rings
- We plan to **re-use** the modeling of the rotaxane also for the nano-elevator (adding two new species: top & platform)
- **Monolithic approach**: exponential explosion of the species: $\mathbf{4^3 = 64}$

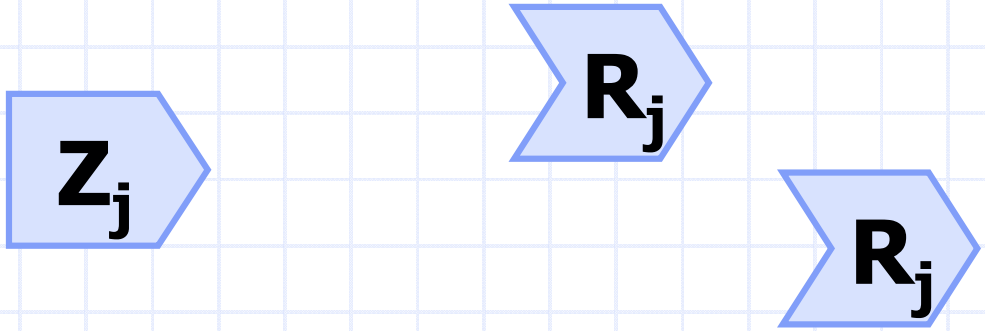


Plan of the talk

- Chemistry as a Computational Model
  - ... not a new issue
- Chemical Ground Form (CGF) [Cardelli08]
  - ... a new way to analyze chemistry
- Computational Strength of Chemistry [Concur08]
  - Non Turing universal but...
  - Turing complete formalisms can be approximated with any degree of precision
- From Chemistry to...
  - Biochemistry: BGF [AB08]
  - Nano devices: nano-K [CMSB07,TCS08]
- **Computational strength of BGF and K-calculi** [CMSB09]
- Concluding remarks

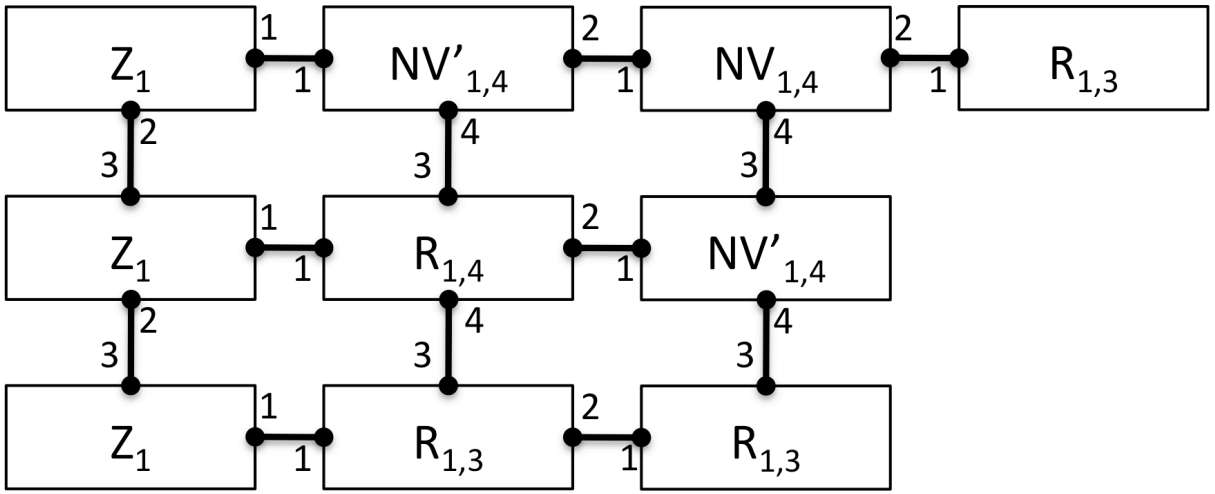
Turing completeness of BGF

- BGF=CGF+association+dissociation
  - This calculus is Turing complete
- **Proof**: RAMs can be faithfully modeled representing registers as polymers



Turing completeness of K-calculi

- K without **destructions** and **internal state** is already Turing complete
- **Proof**: RAMs can be faithfully modeled representing registers as grids



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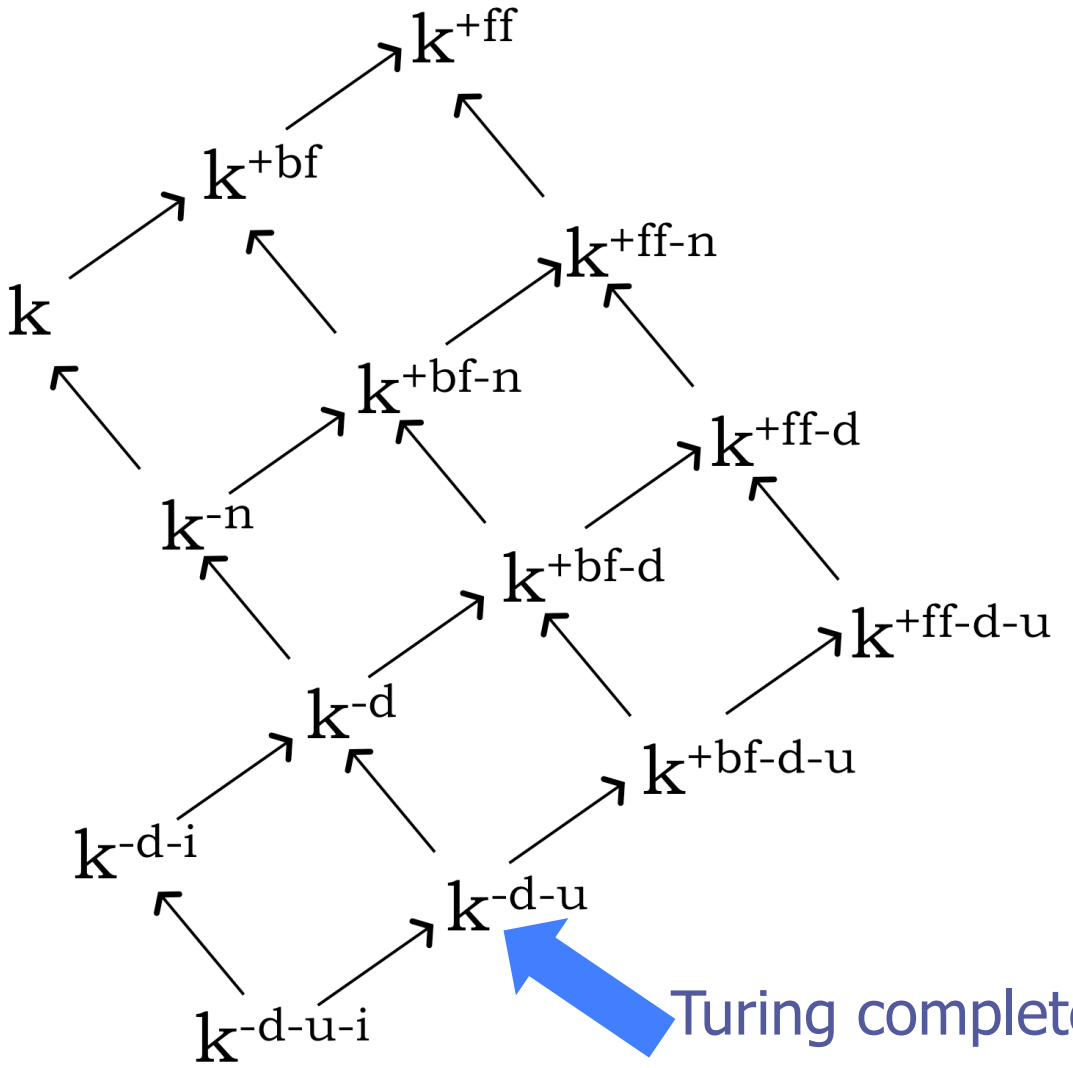
Conclusion

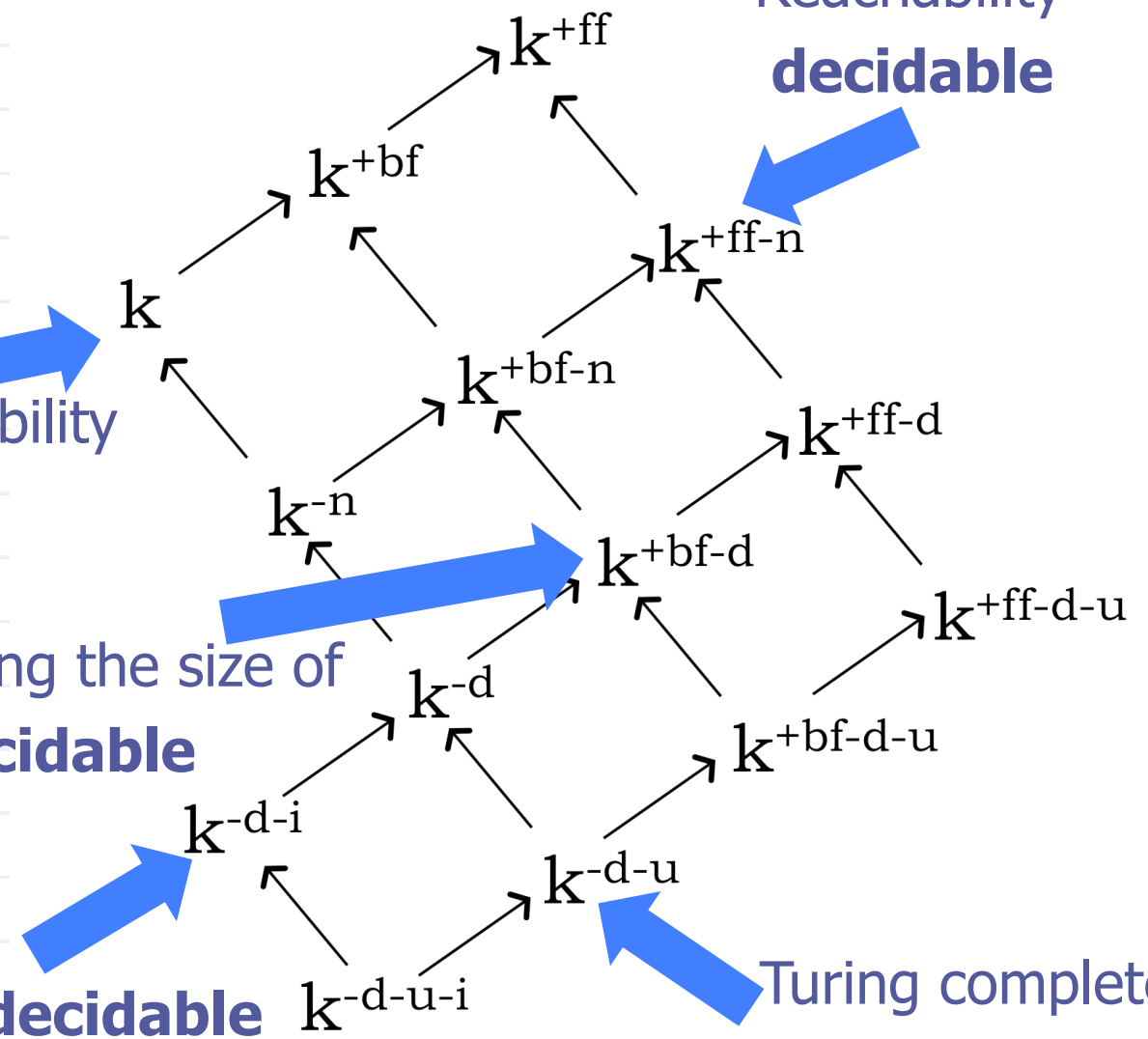
- CGF, the calculus for chemistry, is not Turing powerful…
  - …but Turing complete formalisms can be **approximated** with any given degree of precision
- Molecule complexation "Turifies" chemistry
  - BGF includes a **basic** mechanism for association/ dissociation, which is also biologically **realistic**, that makes CGF Turing complete

K-calculi: the lattice

- The ordering is the subcalculus relation
- Dialects are inspired by **biological** phenomena



K-calculi: the lattice



Reachability **decidable**

Reachability/Coverability **undecidable**

Coverability (limiting the size of complexes) **decidable**

Coverability **decidable**

Turing complete

Coverability **undecidable**

Future work

- Understand better the actual importance of molecule dissociation/bond destruction
  - K without **bond destruction** is Turing complete while BGF without **dissocation** is not!
  - Possible motivations: **multimolecular reactions** of K, test of the **entire interface** in K, ...
- **Quantitative** analysis
  - The approximated Turing completeness of CGF suggests that quantitative analysis is **undecidable**
    (is a molecule/complex reachable with prob. greater than P?)
  - As done for qualitative analysis, we plan to capture **fragments** of these calculi in which also quantitive analysis is possible

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