



Hamilton Institute



**Maynooth
University**
National University
of Ireland Maynooth

The Curse of Hamilton's Chairs

Ahmed Shalaby

2nd year PhD

Supervisor: Damien Woods



European
Innovation
Council



Funded by
the European Union





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Thermodynamics of a multistranded one-dimension Scaffolded DNA Computer

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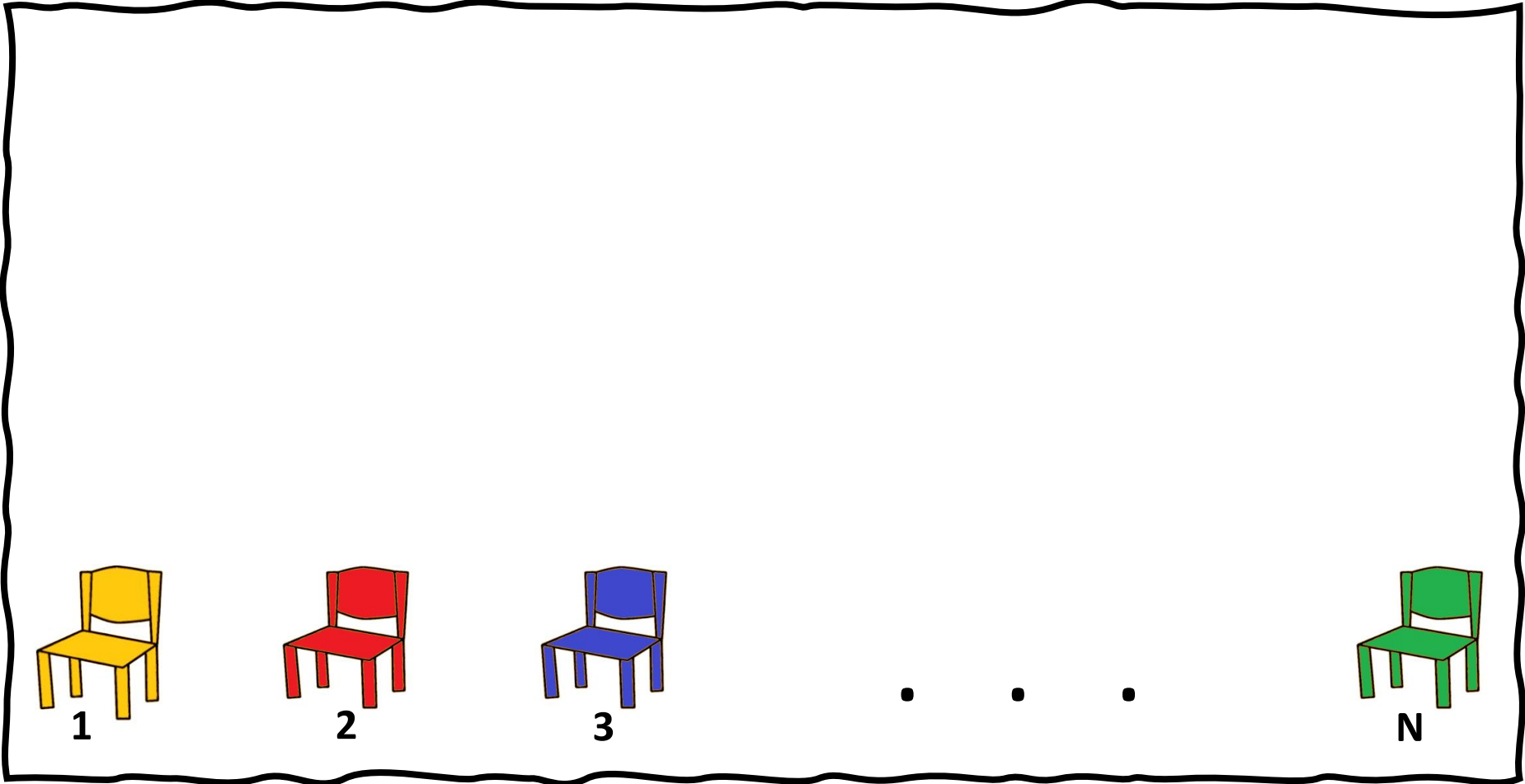
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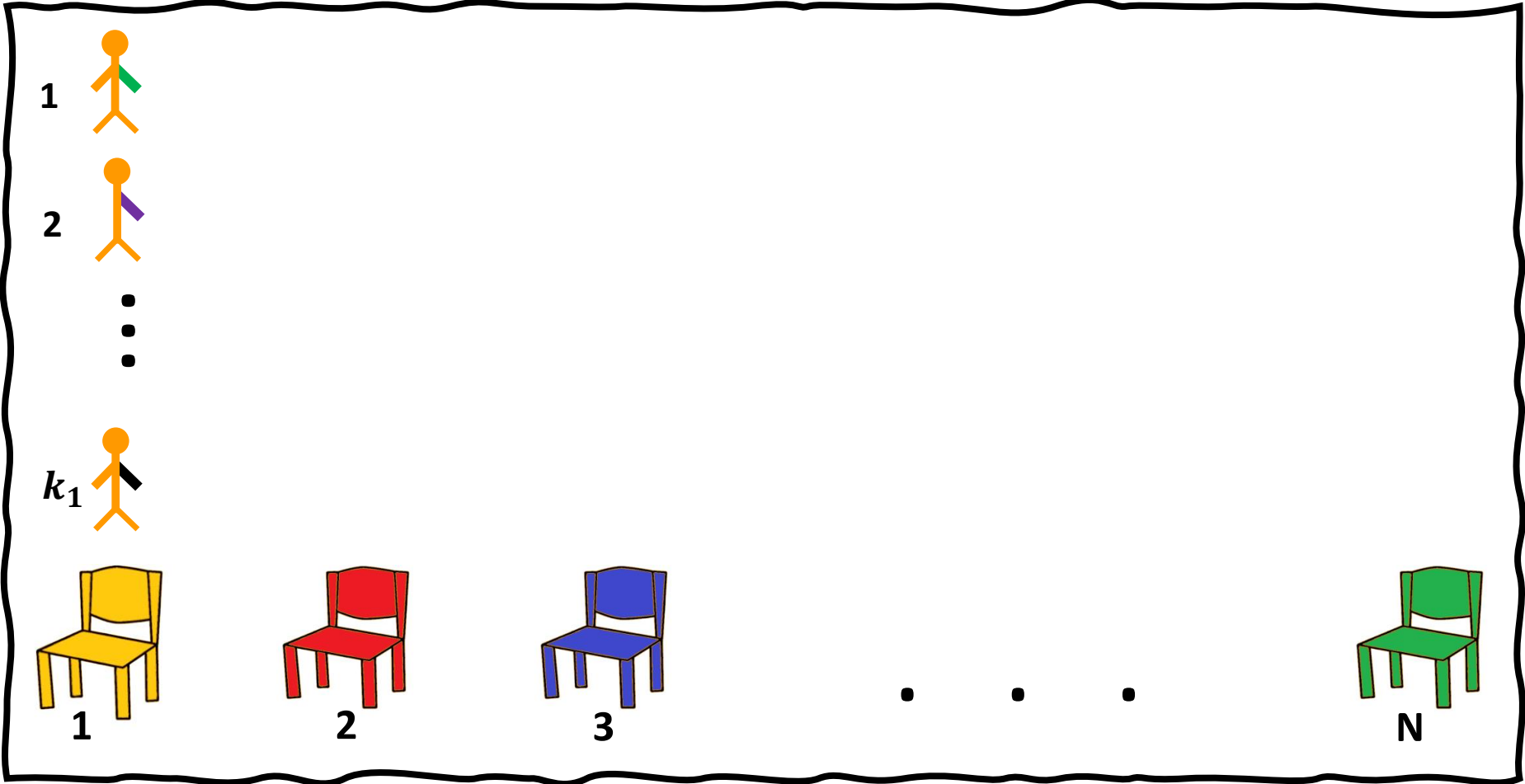




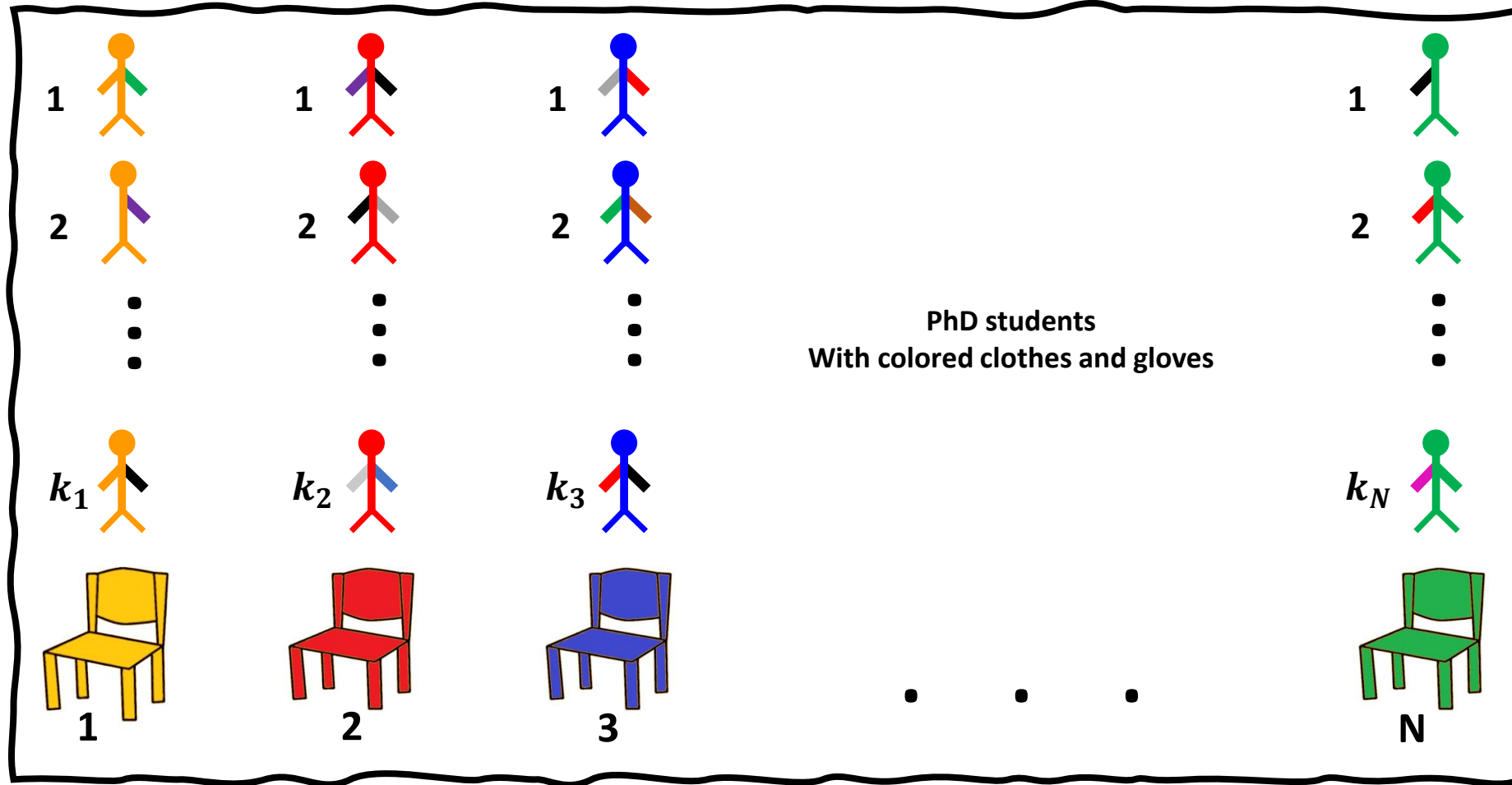
Let's discover the rules of the game



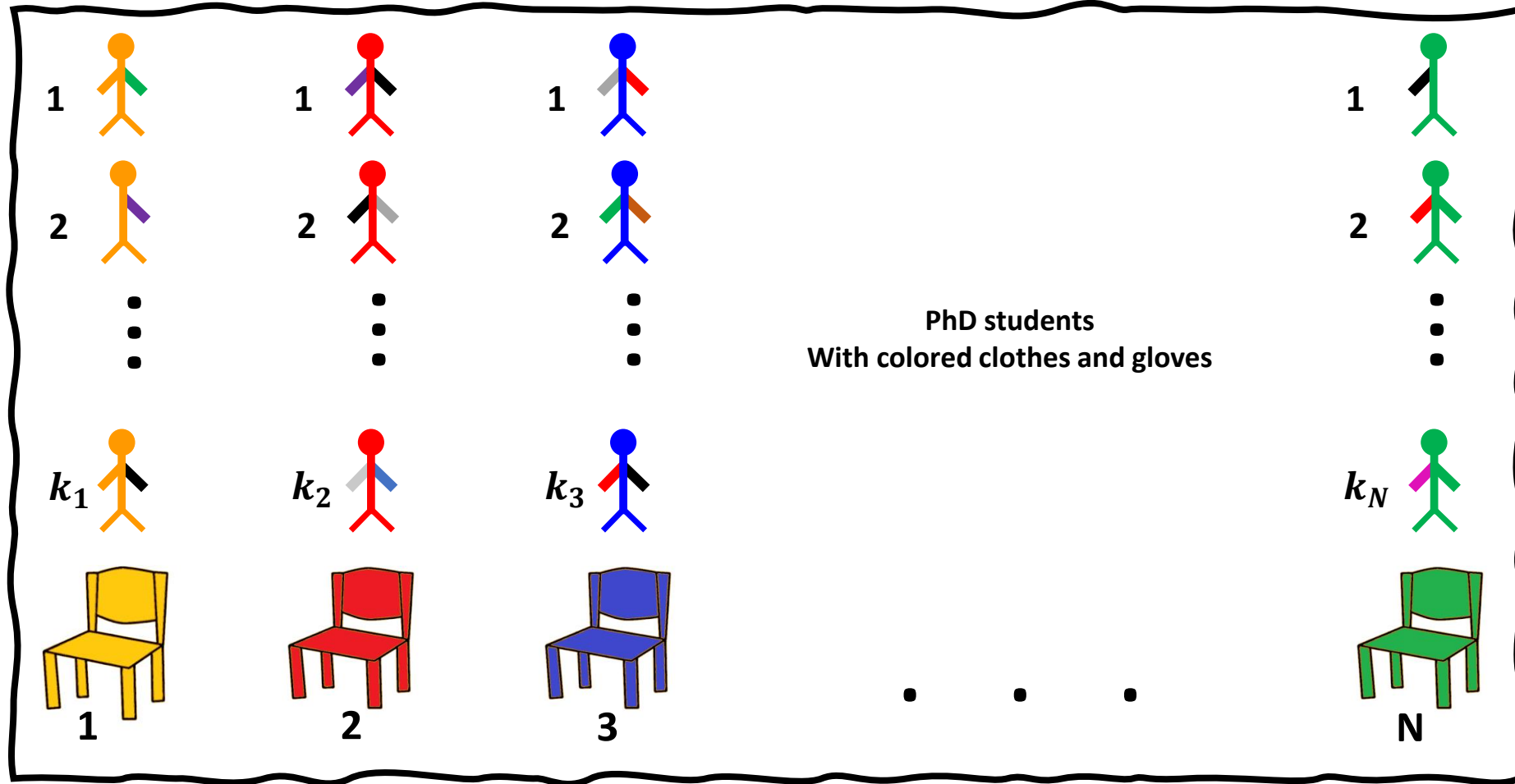
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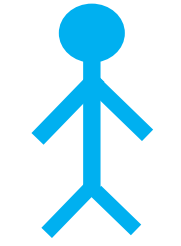
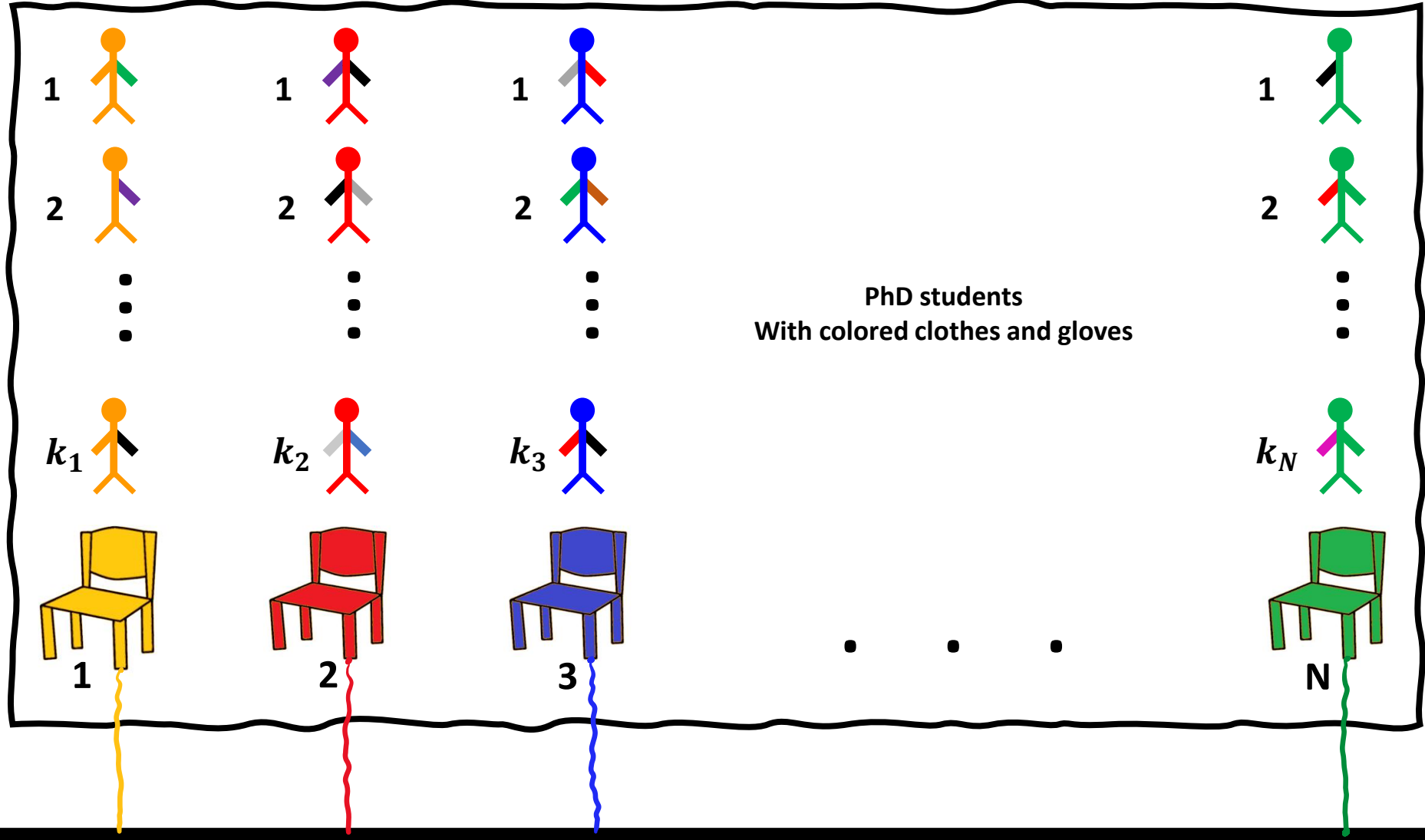


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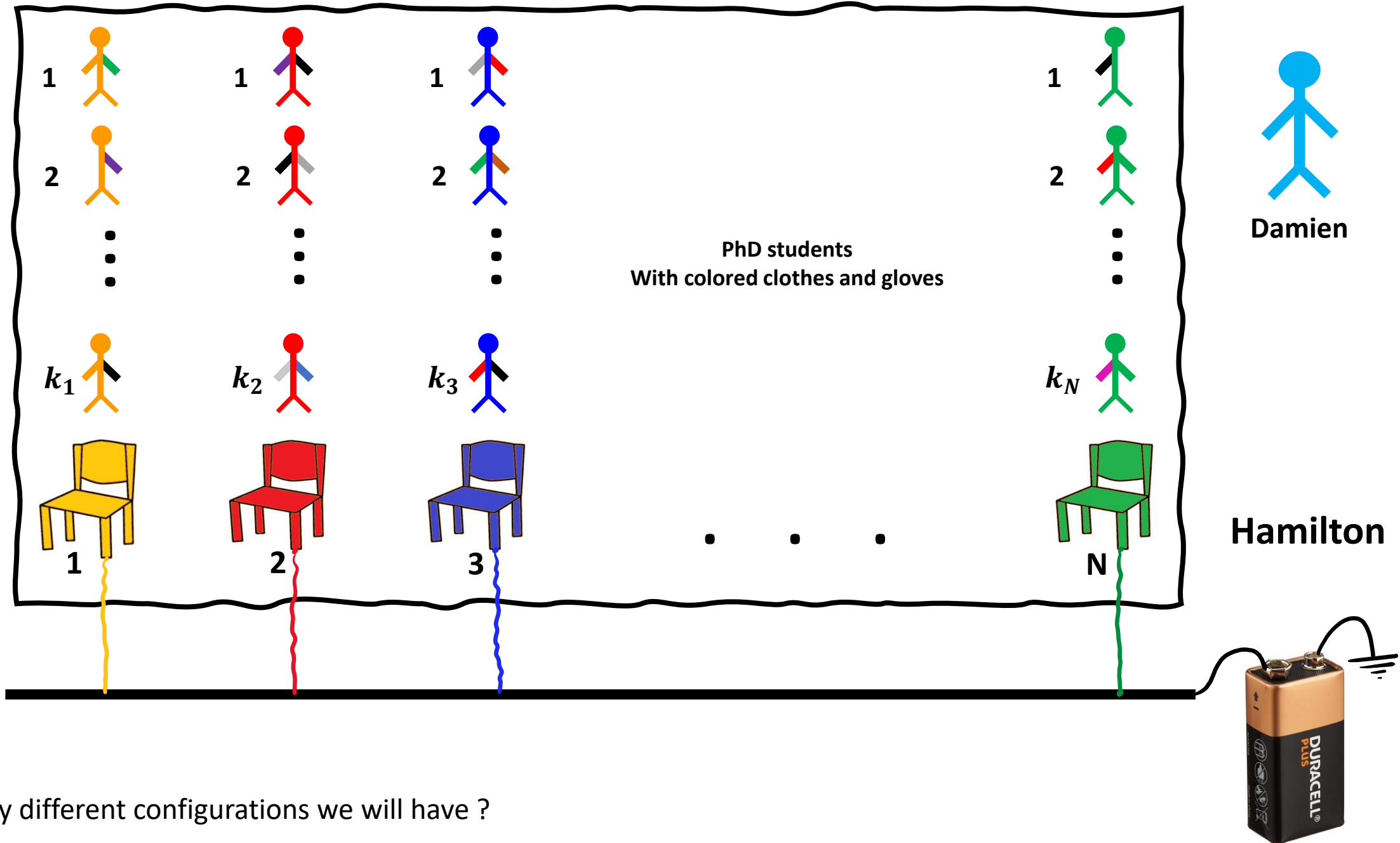




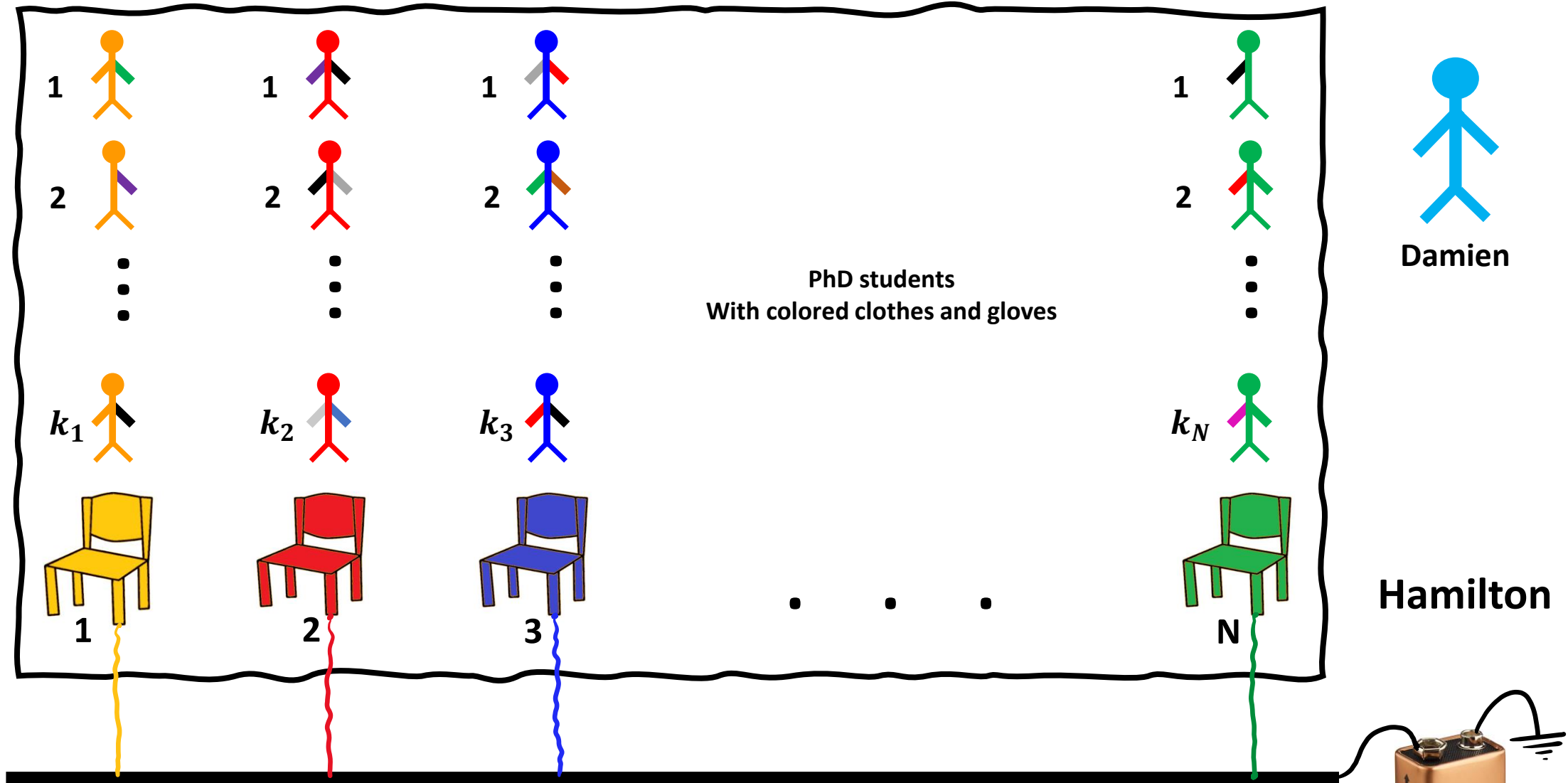
Damien

Hamilton





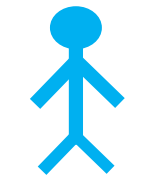
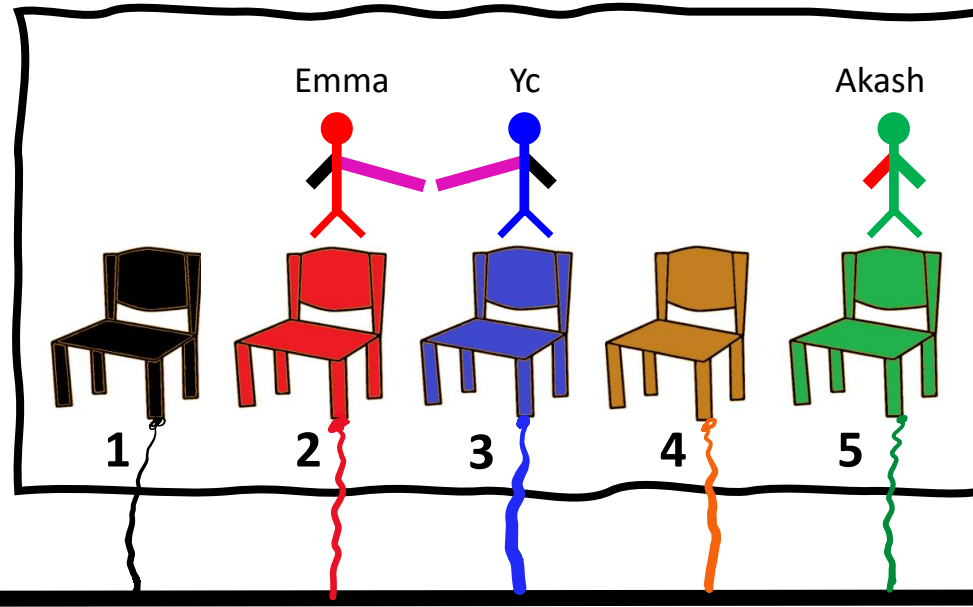
- How many different configurations we will have ?



- How many different configurations we will have ?

$(K + 1)^N$
(Exponential in the # of chairs)

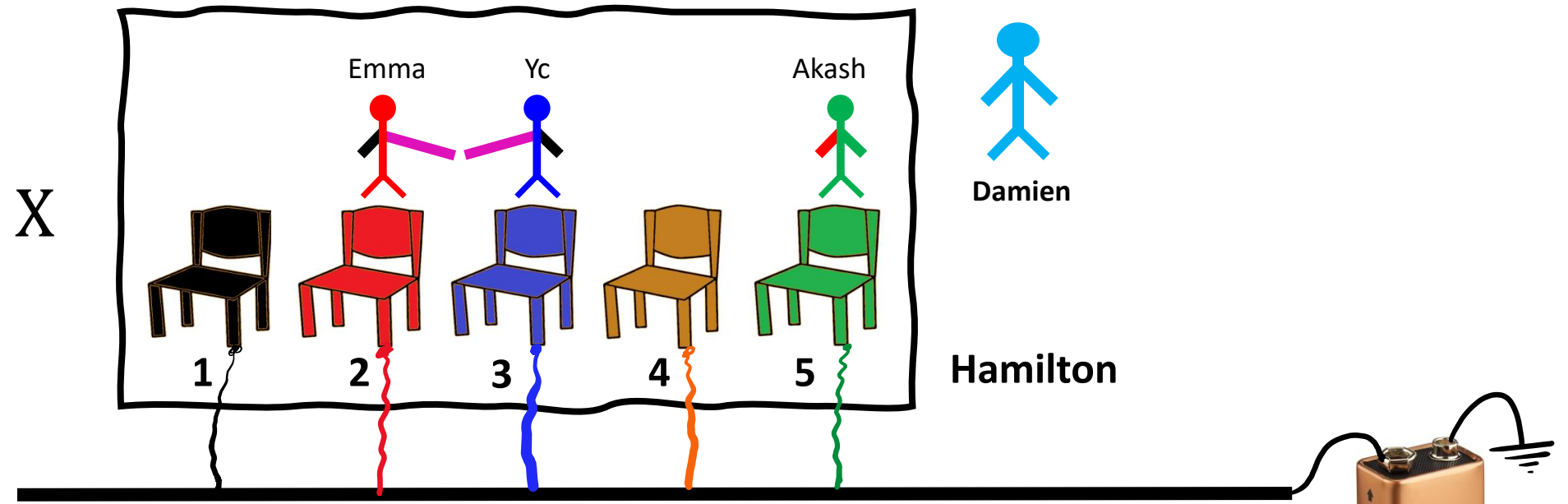
X



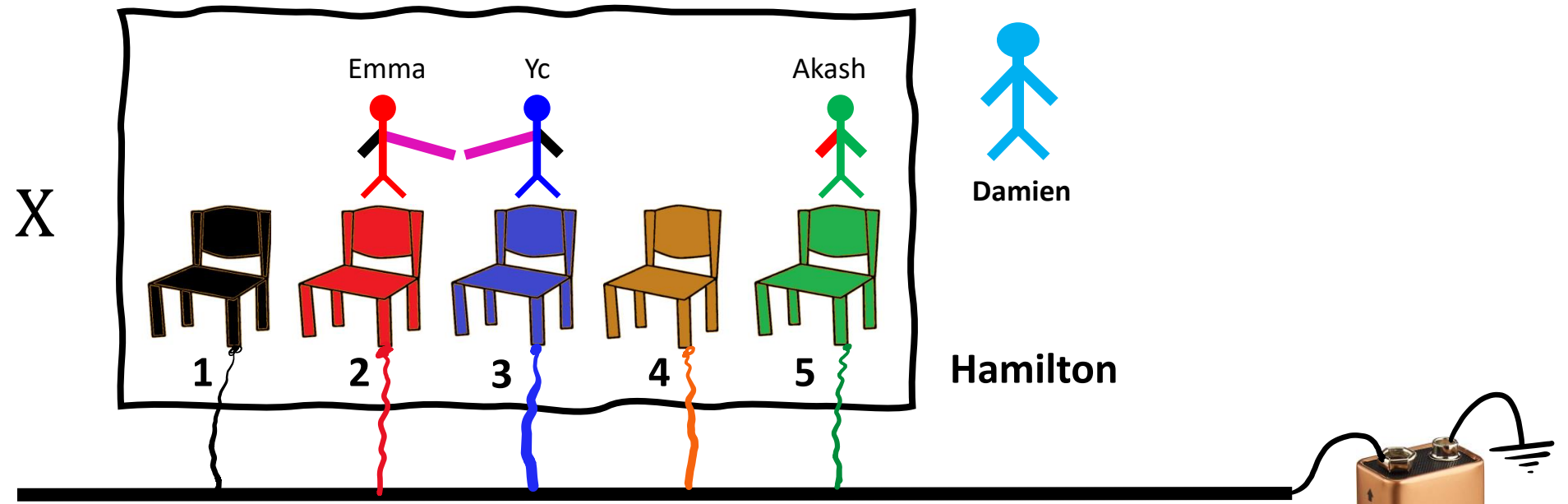
Damien

Hamilton





$$E(X) = \underset{+}{\text{sit(Emma)}} + \underset{+}{\text{sit(Yc)}} + \underset{+}{\text{sit(Akash)}} + \underset{+}{\text{handshake(Emma, Yc)}}$$



$$E(X) = \text{sit}(\text{Emma}) + \text{sit}(\text{Yc}) + \text{sit}(\text{Akash}) + \text{handshake}(\text{Emma}, \text{Yc}) + 3 * \text{sit_convincing_cost}.$$

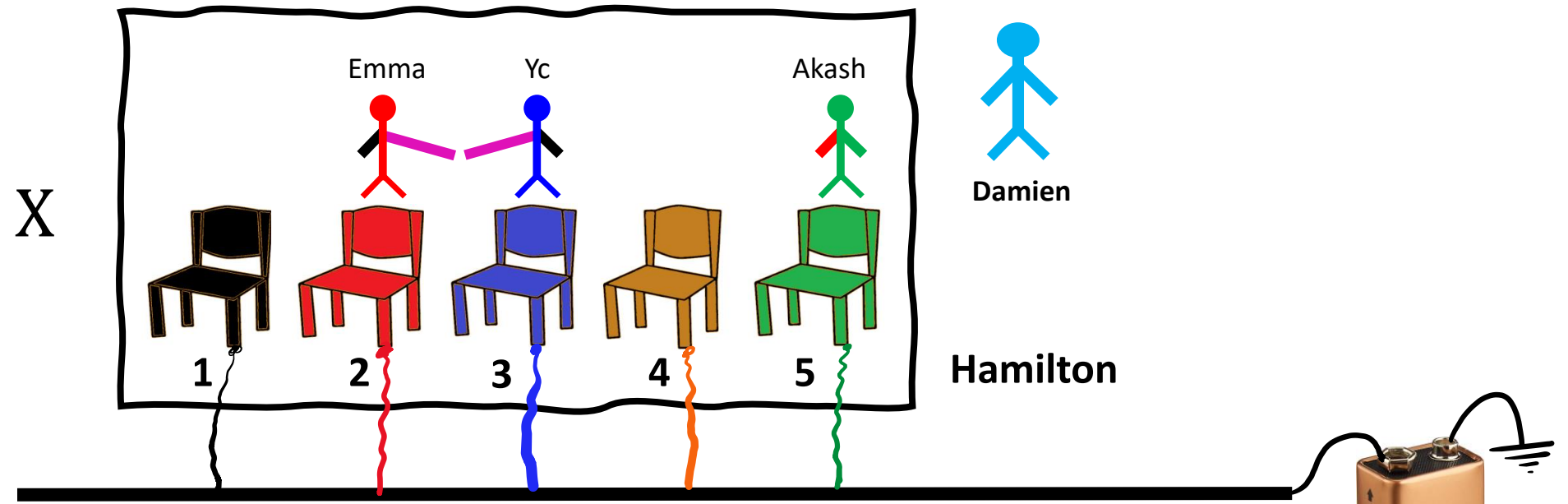
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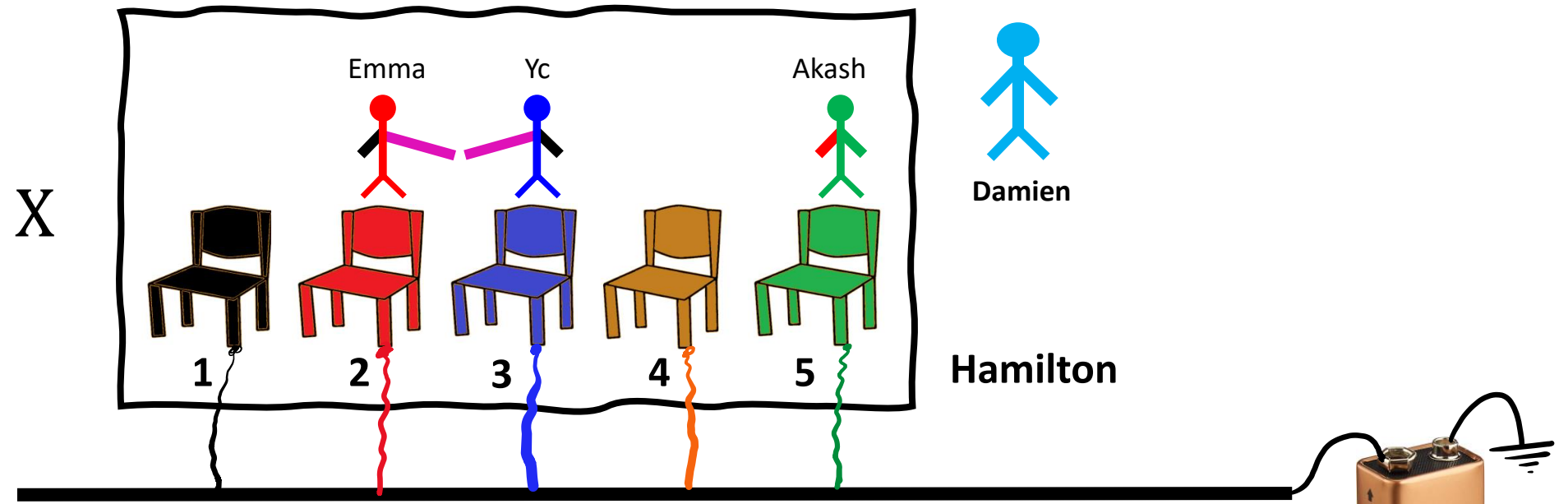
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$$E(X) = \underset{+}{\text{sit(Emma)}} + \underset{+}{\text{sit(Yc)}} + \underset{+}{\text{sit(Akash)}} + \underset{+}{\text{handshake(Emma, Yc)}} + \underset{-}{3 * \text{sit_convincing_cost}}.$$

We further assume the following:

- $|\text{sit}(p)| > |\text{sit_convincing_cost}|$. (Damien always gains by convincing a PhD student to sit)



$$E(X) = \underset{+}{\text{sit(Emma)}} + \underset{+}{\text{sit(Yc)}} + \underset{+}{\text{sit(Akash)}} + \underset{+}{\text{handshake(Emma, Yc)}} + \underset{-}{3 * \text{sit_convincing_cost}}.$$

$$E(X) = \sum_{p \in X} \text{sit}(p) + \sum_{p_i, p_{i+1} \in X} \text{handshake}(p_i, p_{i+1}) + l * \text{sit_convincing_cost}.$$

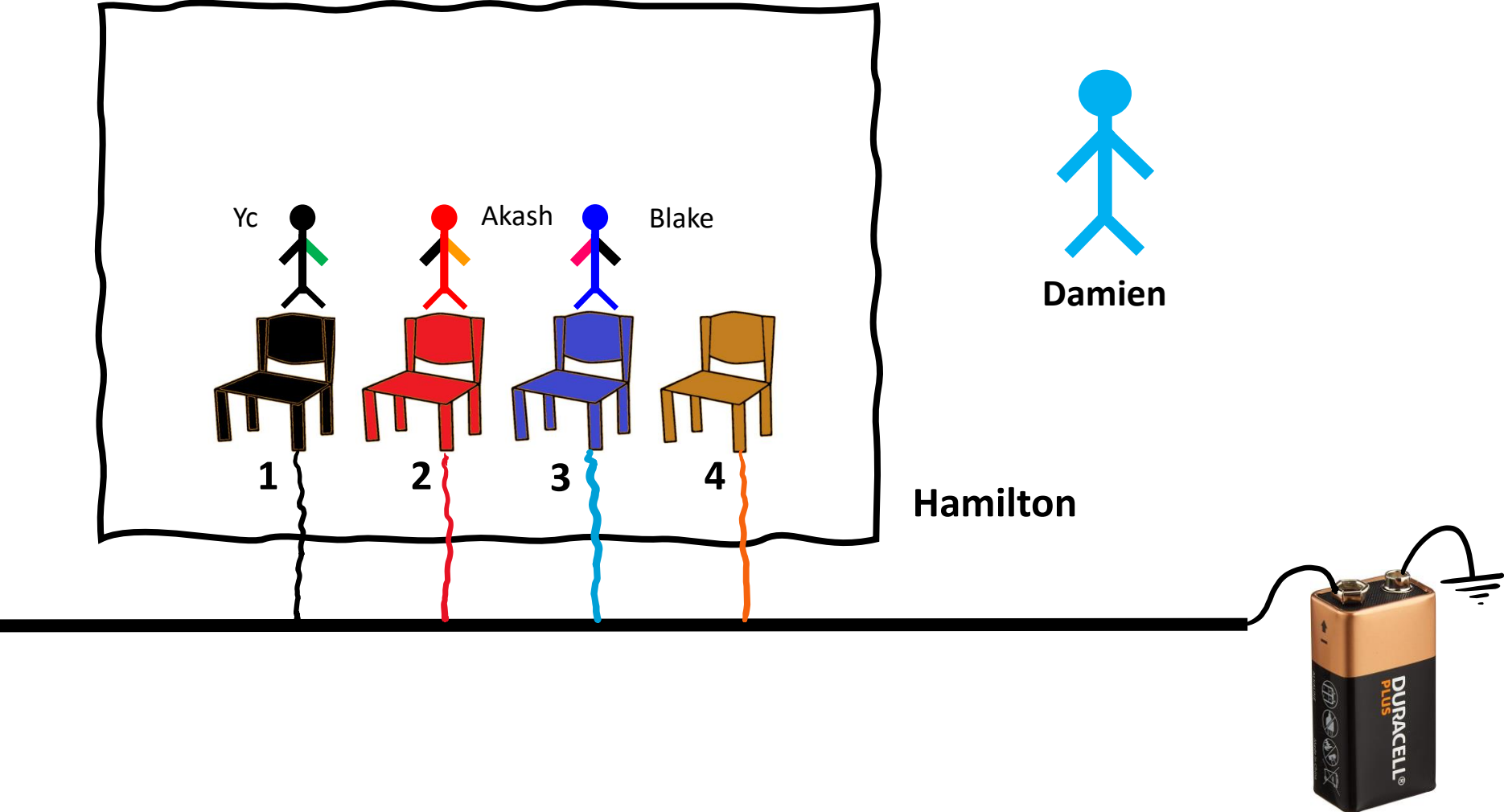
configuration X of size l PhD students

We further assume the following:

- $|\text{sit}(p)| > |\text{sit_convincing_cost}|$. (Damien always gains by convincing a PhD student to sit)

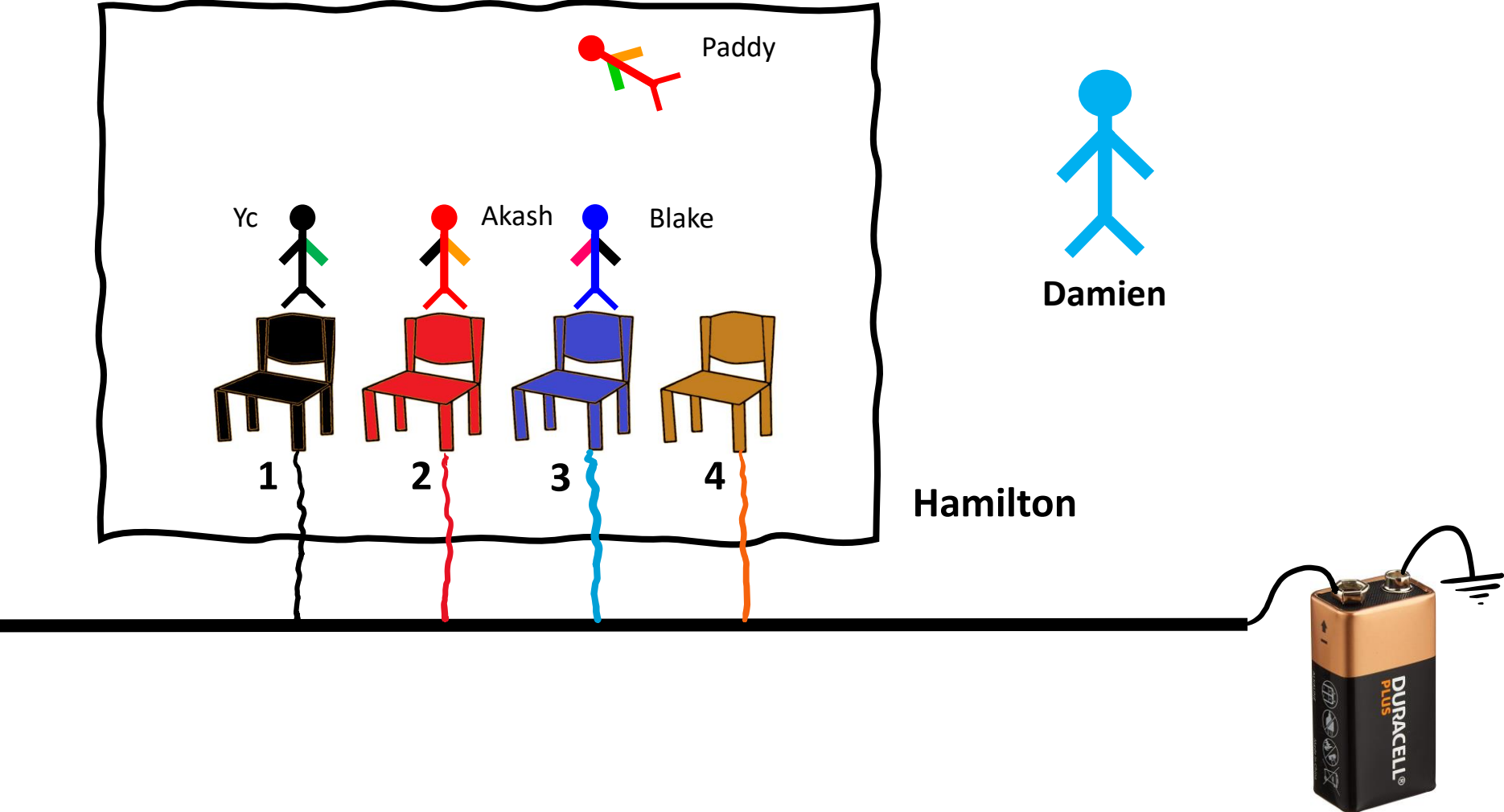
Built-in self improvement mechanism

PhD students' displacement system



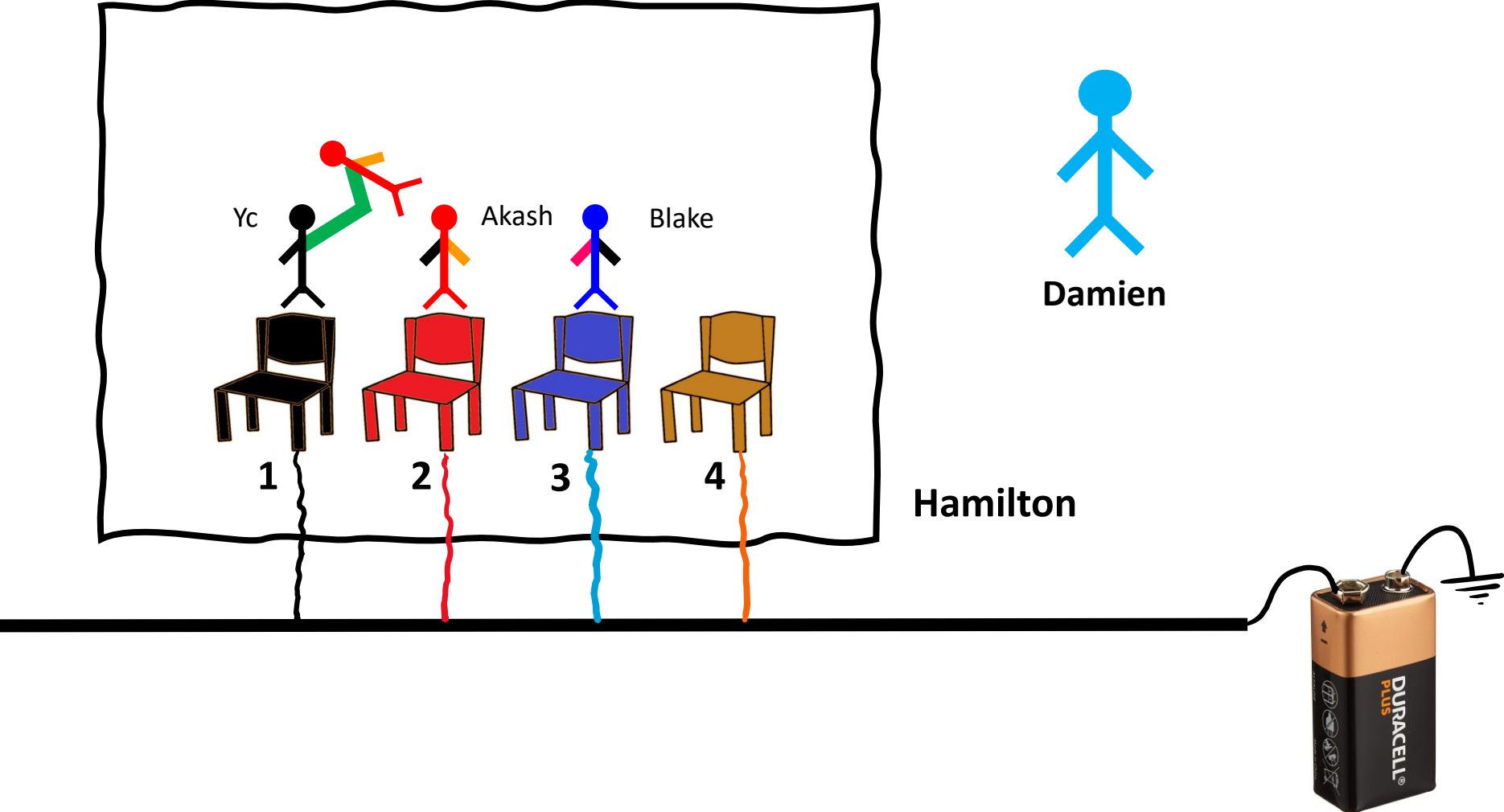
Built-in self improvement mechanism

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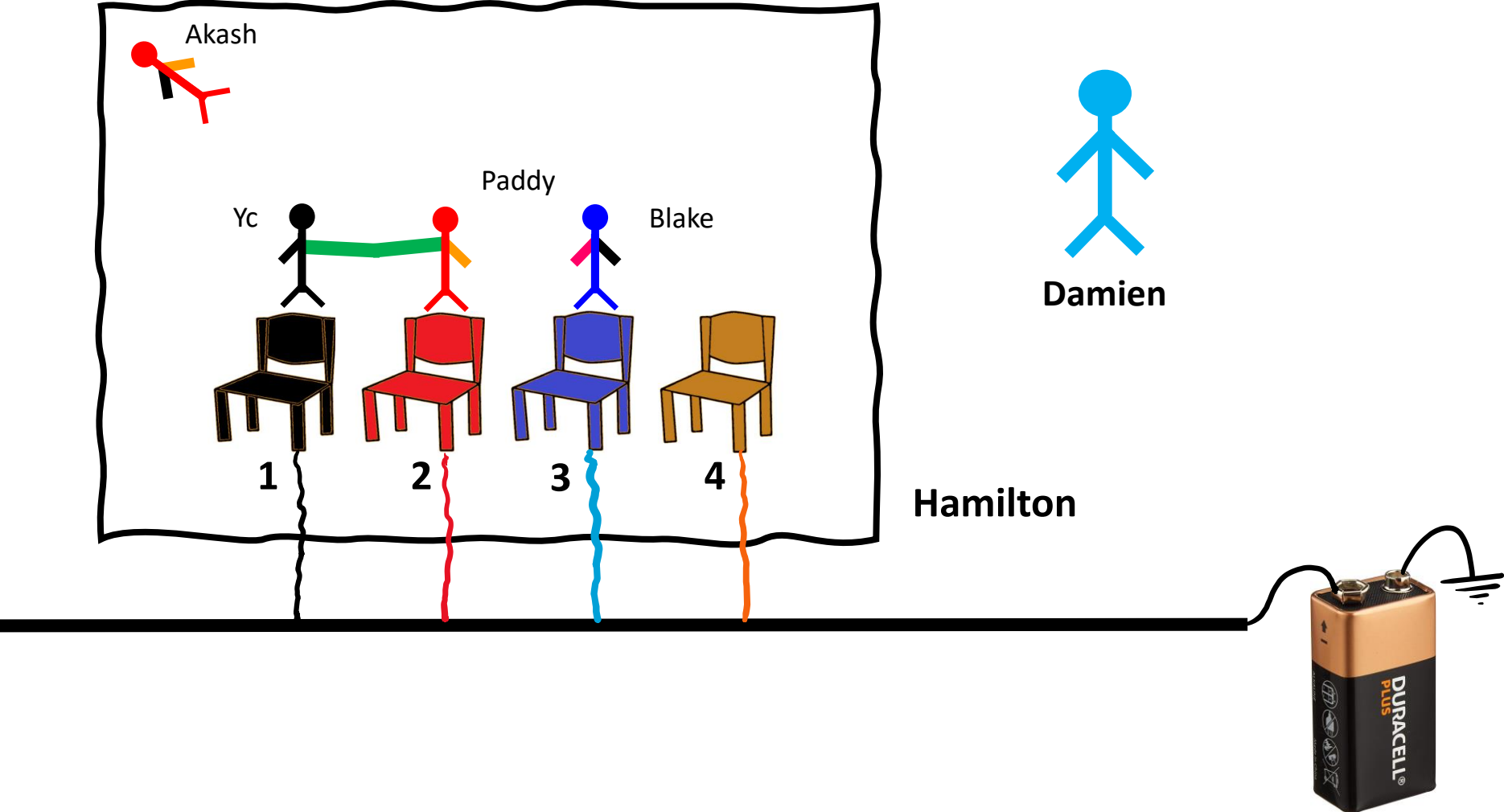
Built-in self improvement mechanism

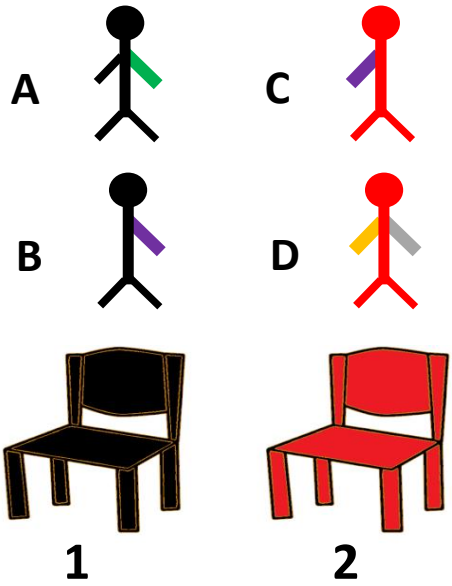
PhD students' displacement system



Built-in self improvement mechanism

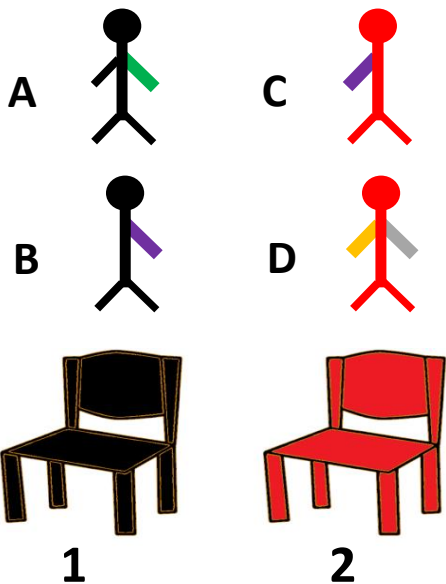
PhD students' displacement system



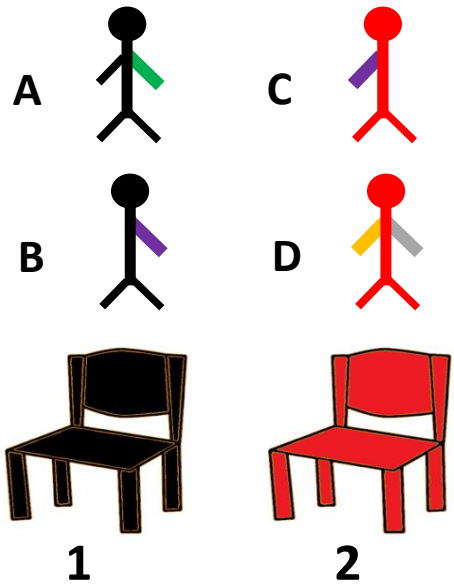


- $\text{sit}(A) = \text{sit}(B) = 3$
- $\text{sit}(C) = \text{sit}(D) = 3$
- $\text{handshake}(B, C) = 1$
- $\text{sit_convincing_cost} = -1$

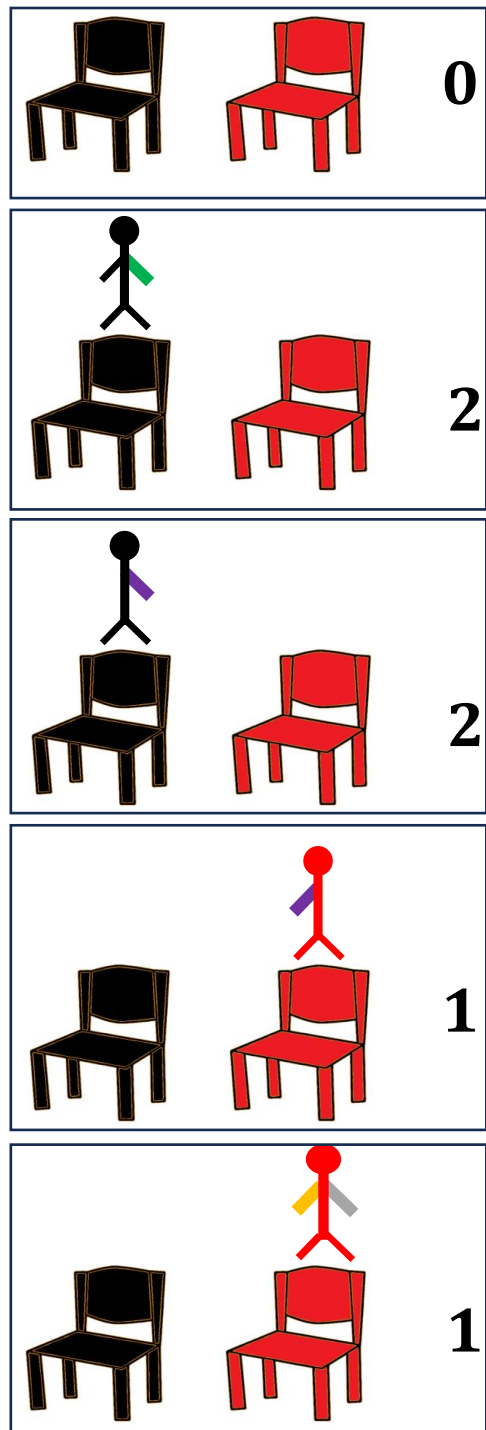
Ω



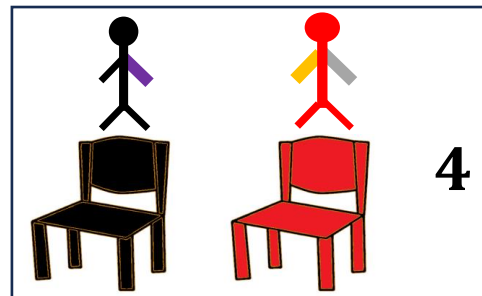
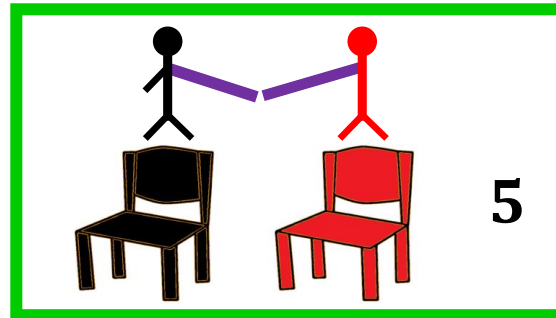
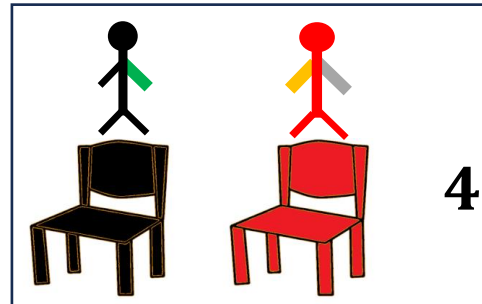
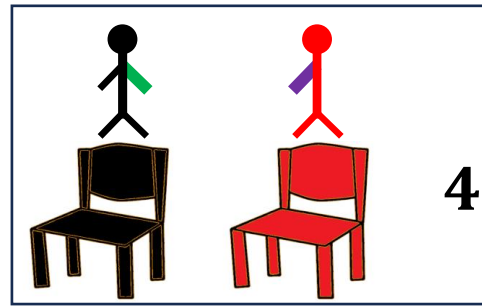
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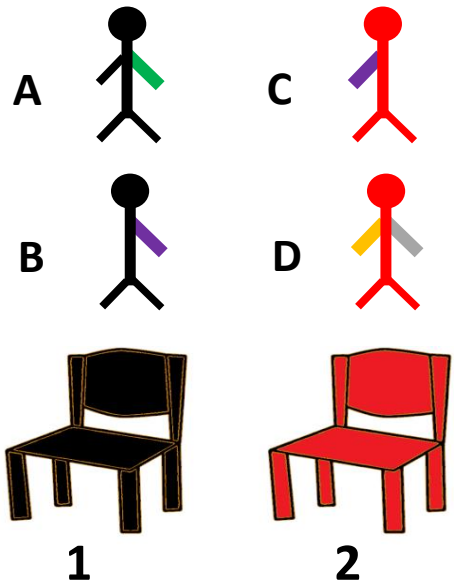


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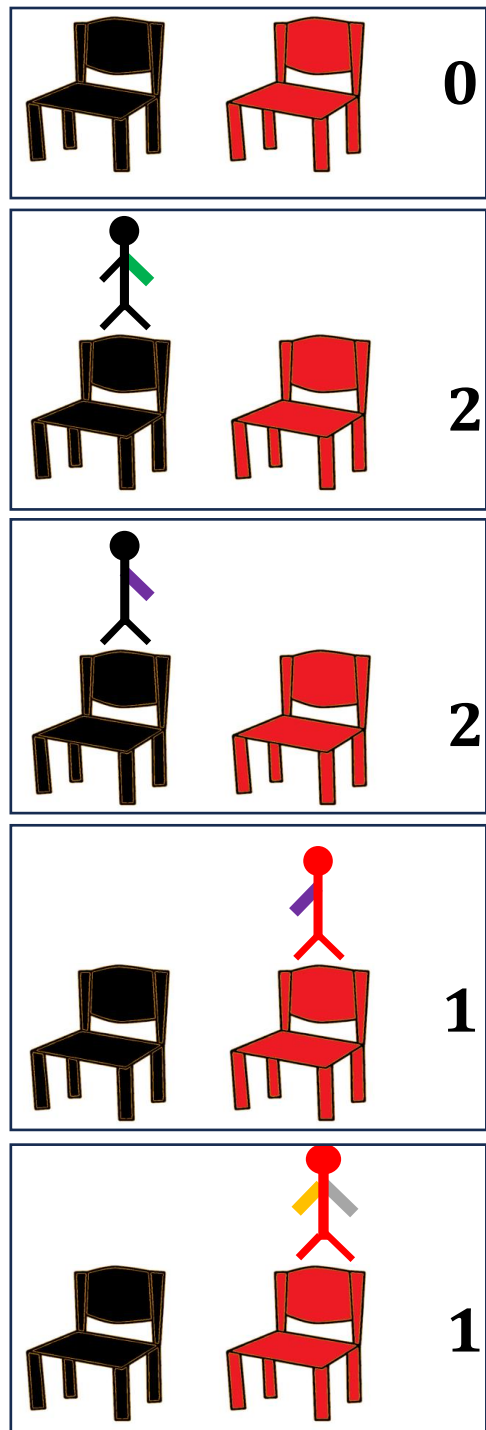


Ω

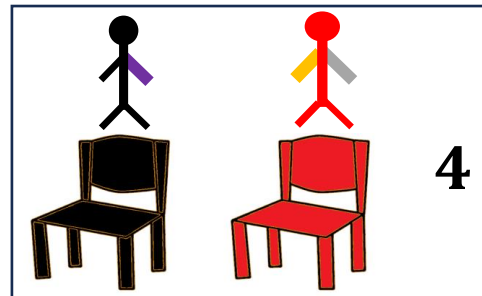
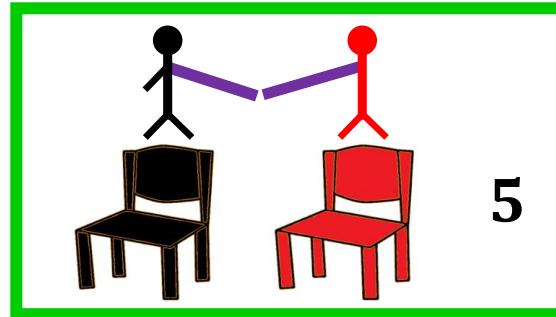
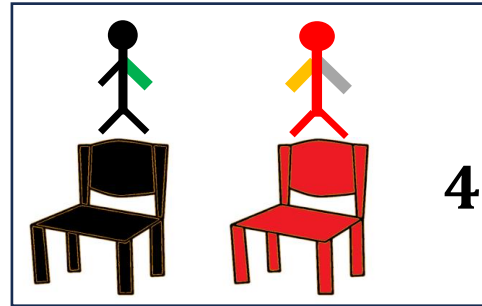
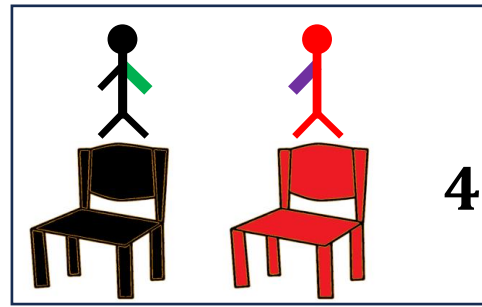




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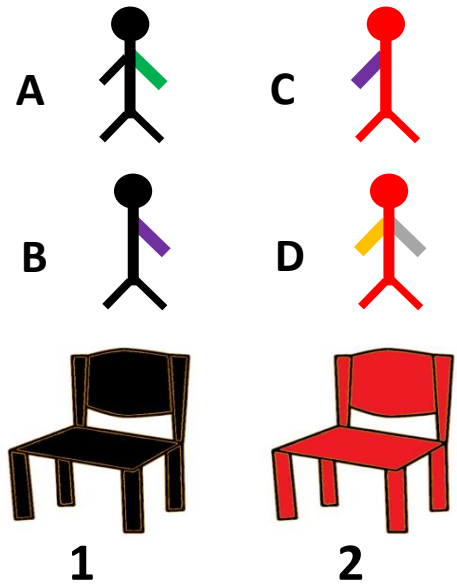


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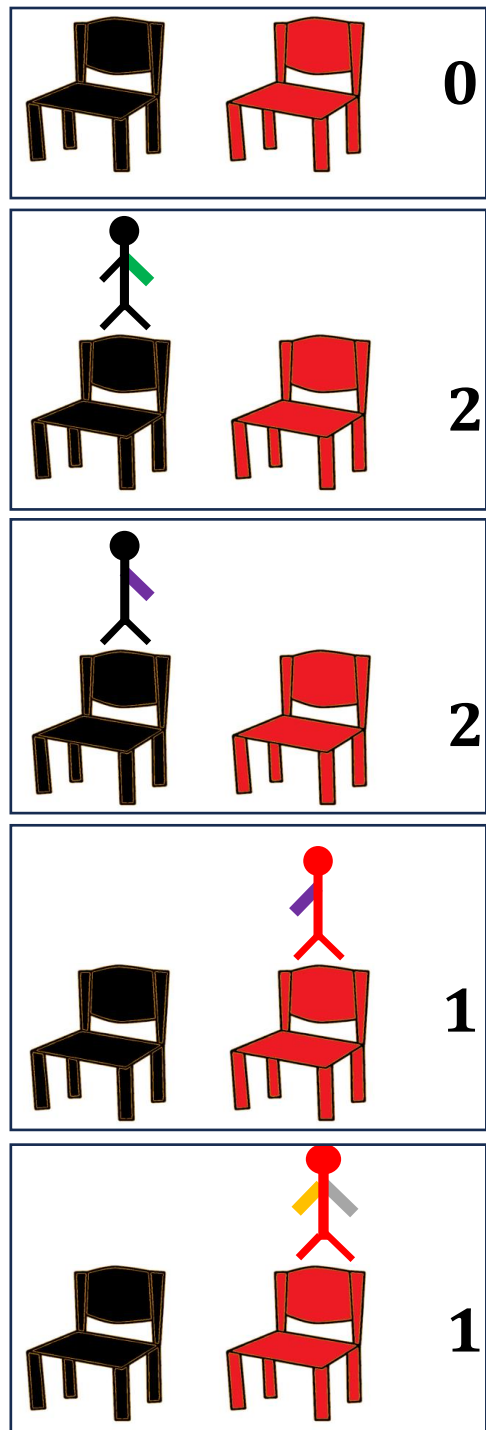


The Maximum Energy M

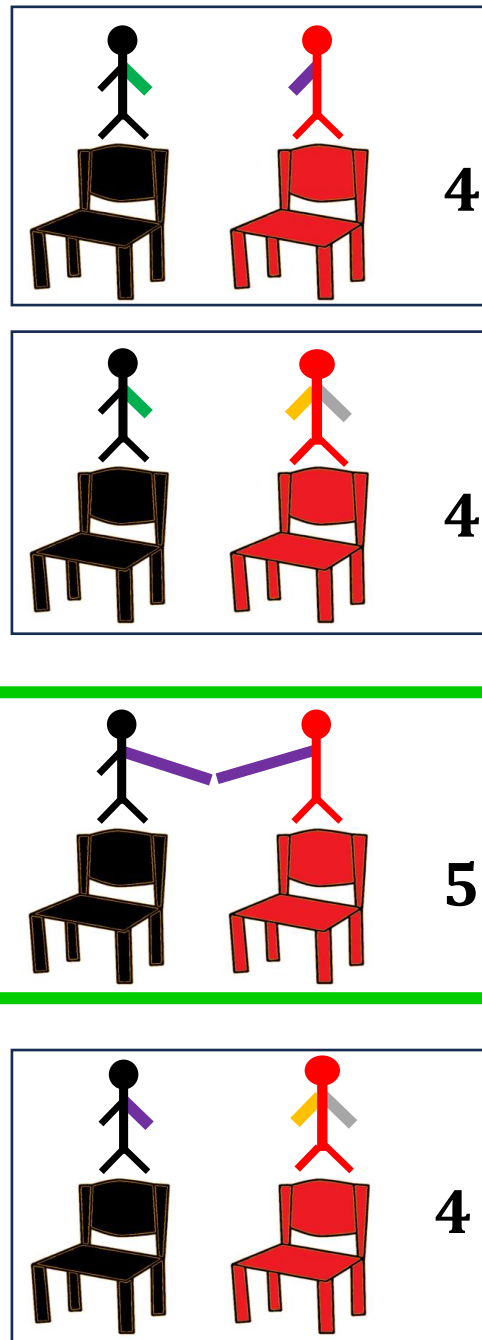
$$M := \max_{X \in \Omega} \{E(X)\}$$



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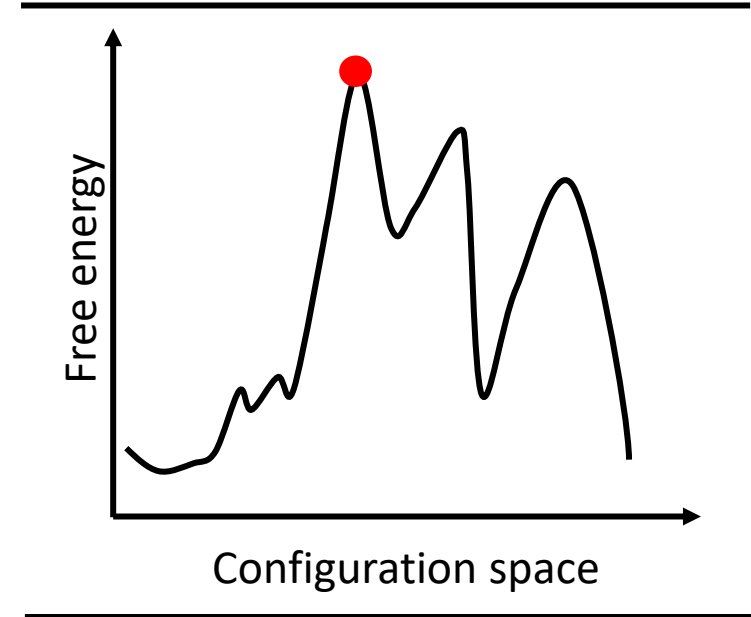


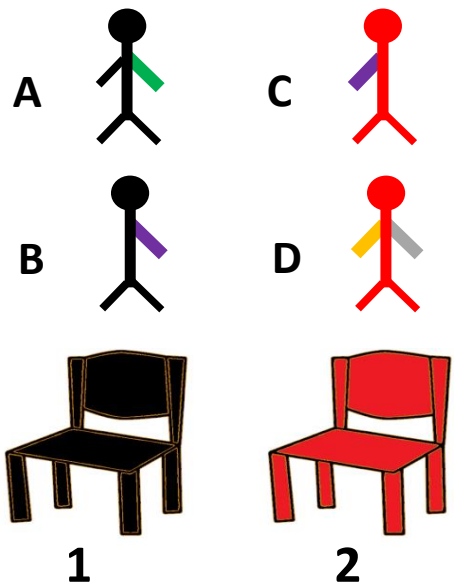
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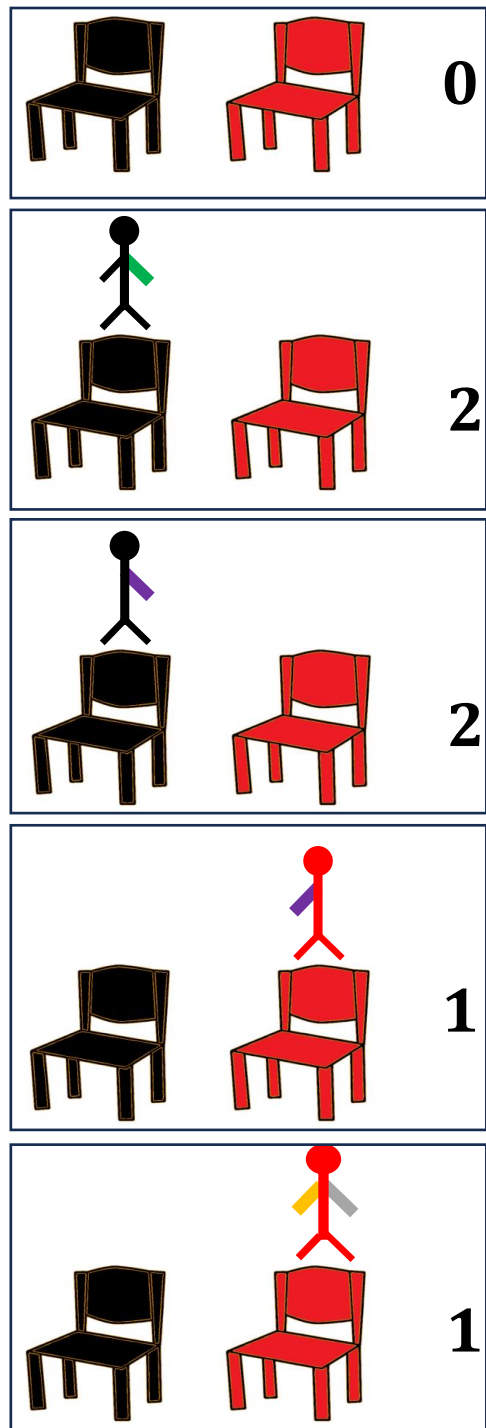
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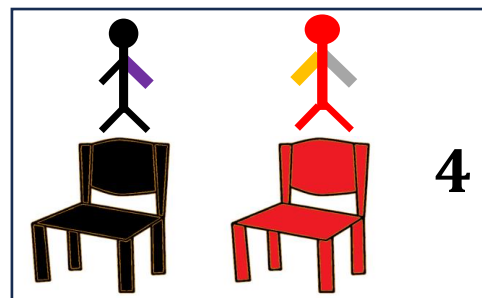
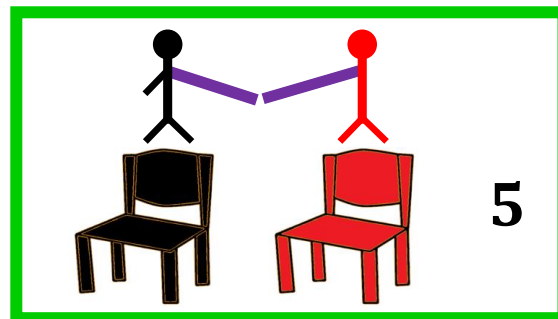
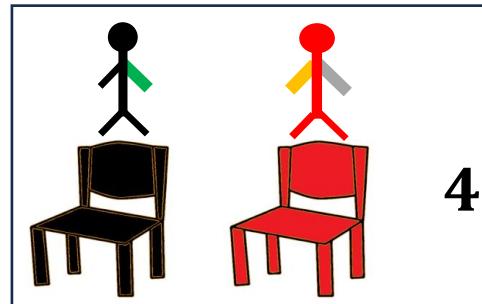
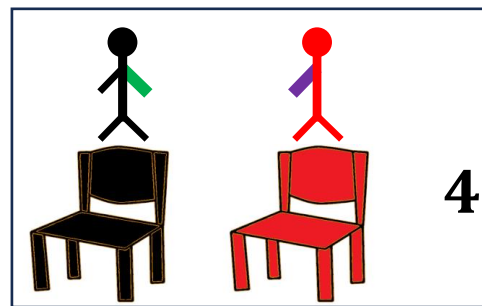




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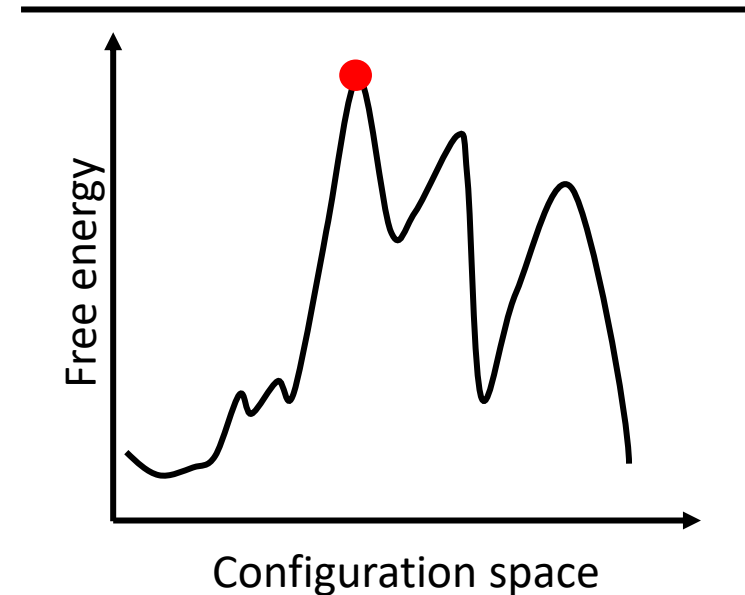


Ω



The Maximum Energy M

$$M := \max_{X \in \Omega} \{E(X)\}$$



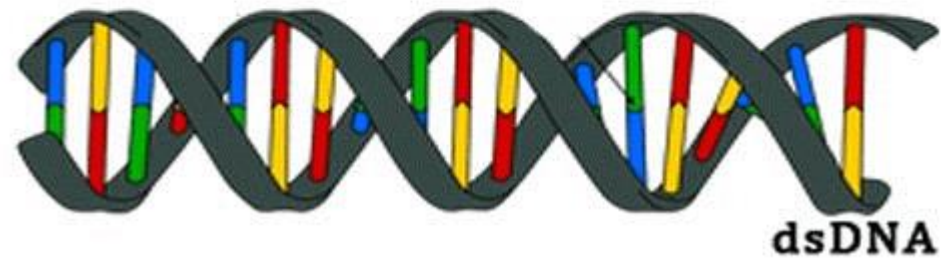
The Partition function Q

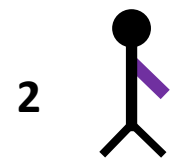
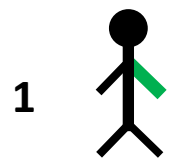
$$Q := \sum_{X \in \Omega} e^{\frac{E(X)}{c}}$$

Where c is some specific constant

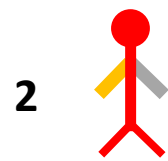
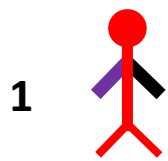
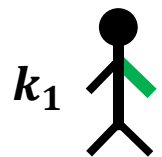
Why are we interested in this ?

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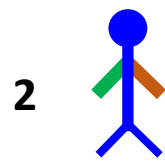
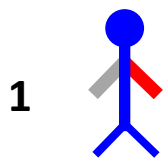
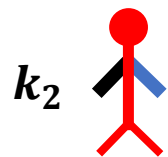




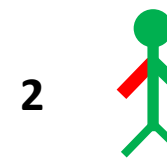
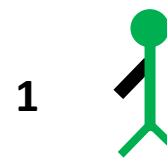
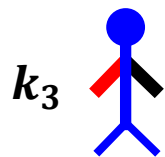
⋮



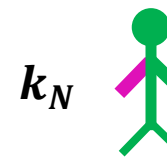
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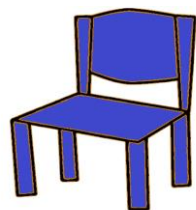
⋮



1



2

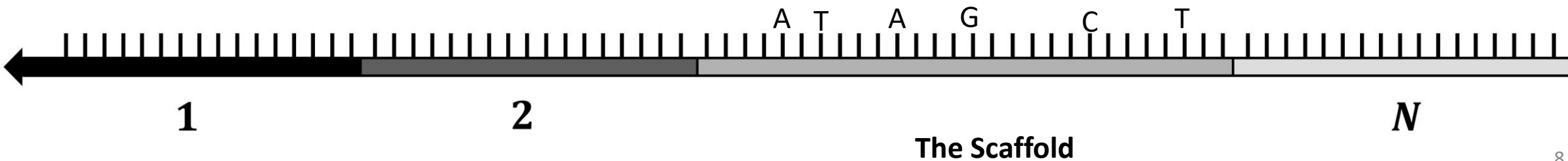
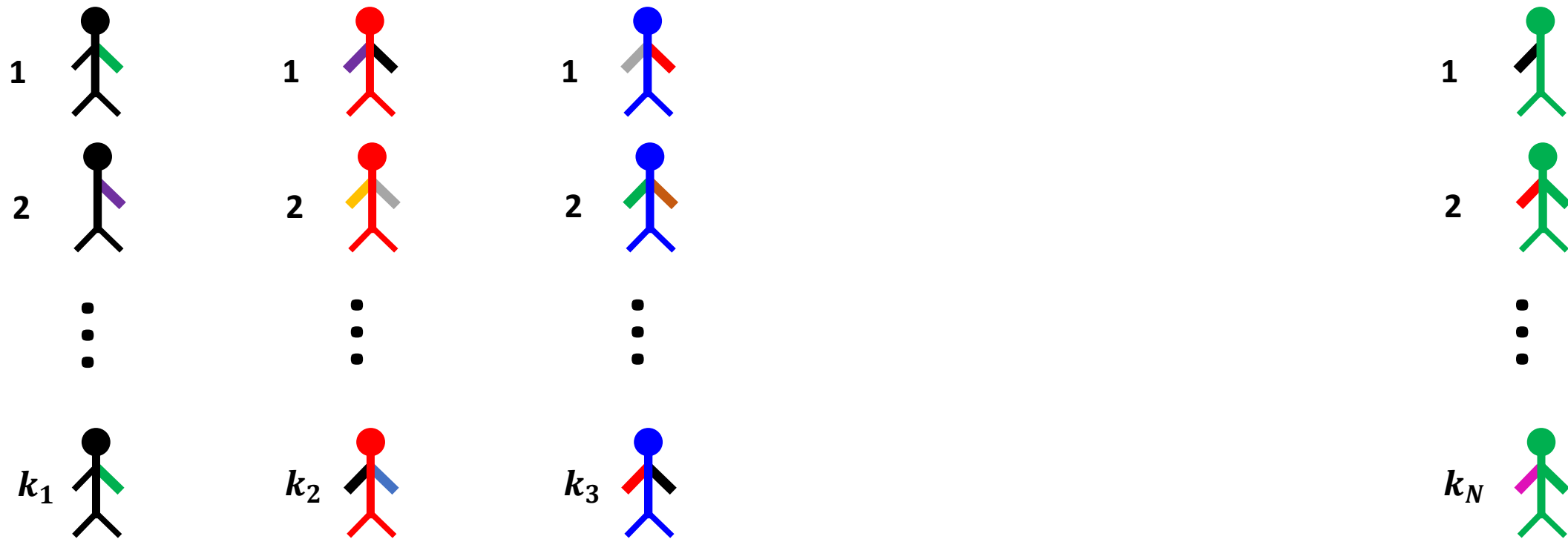


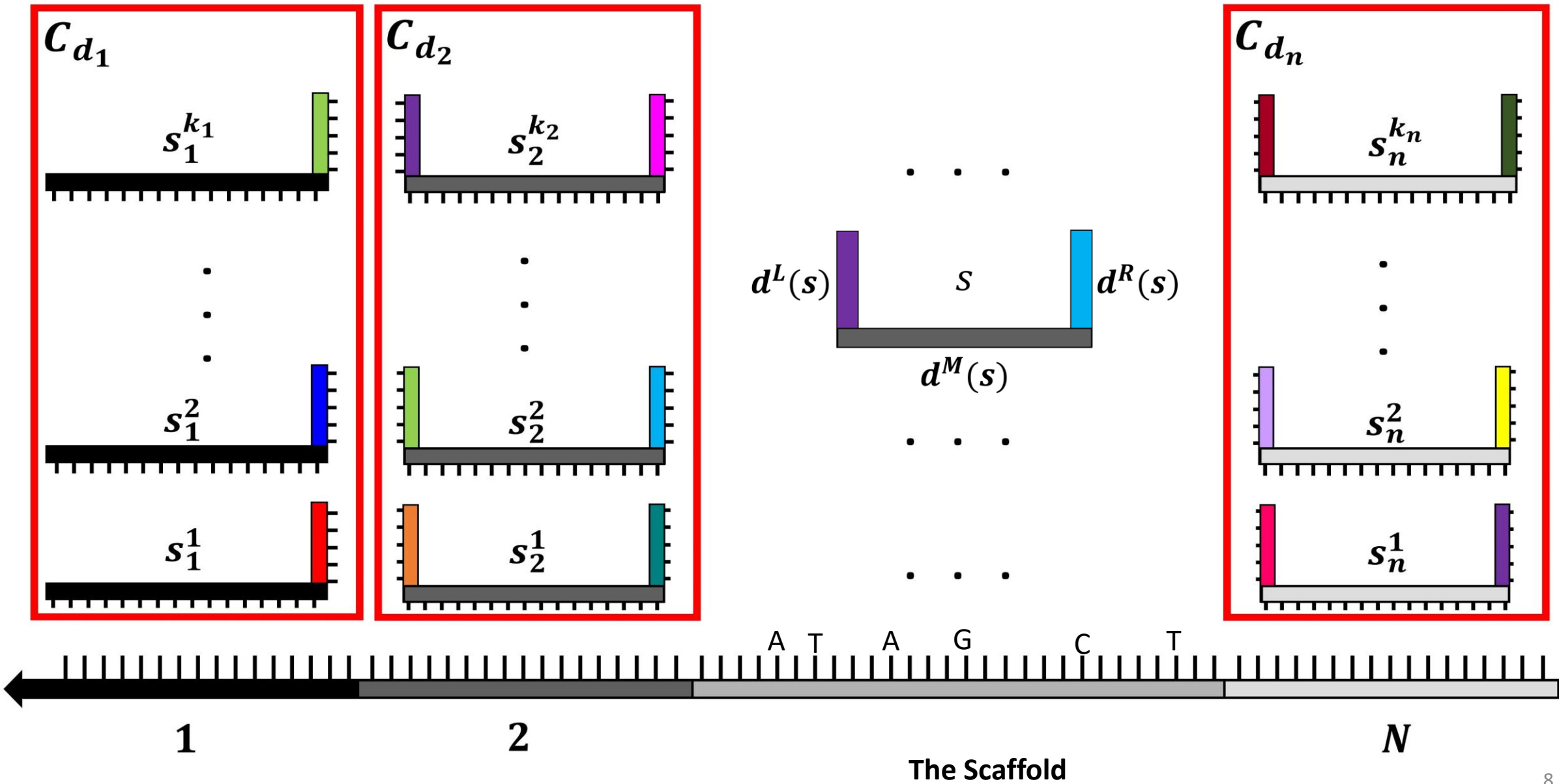
3

⋮

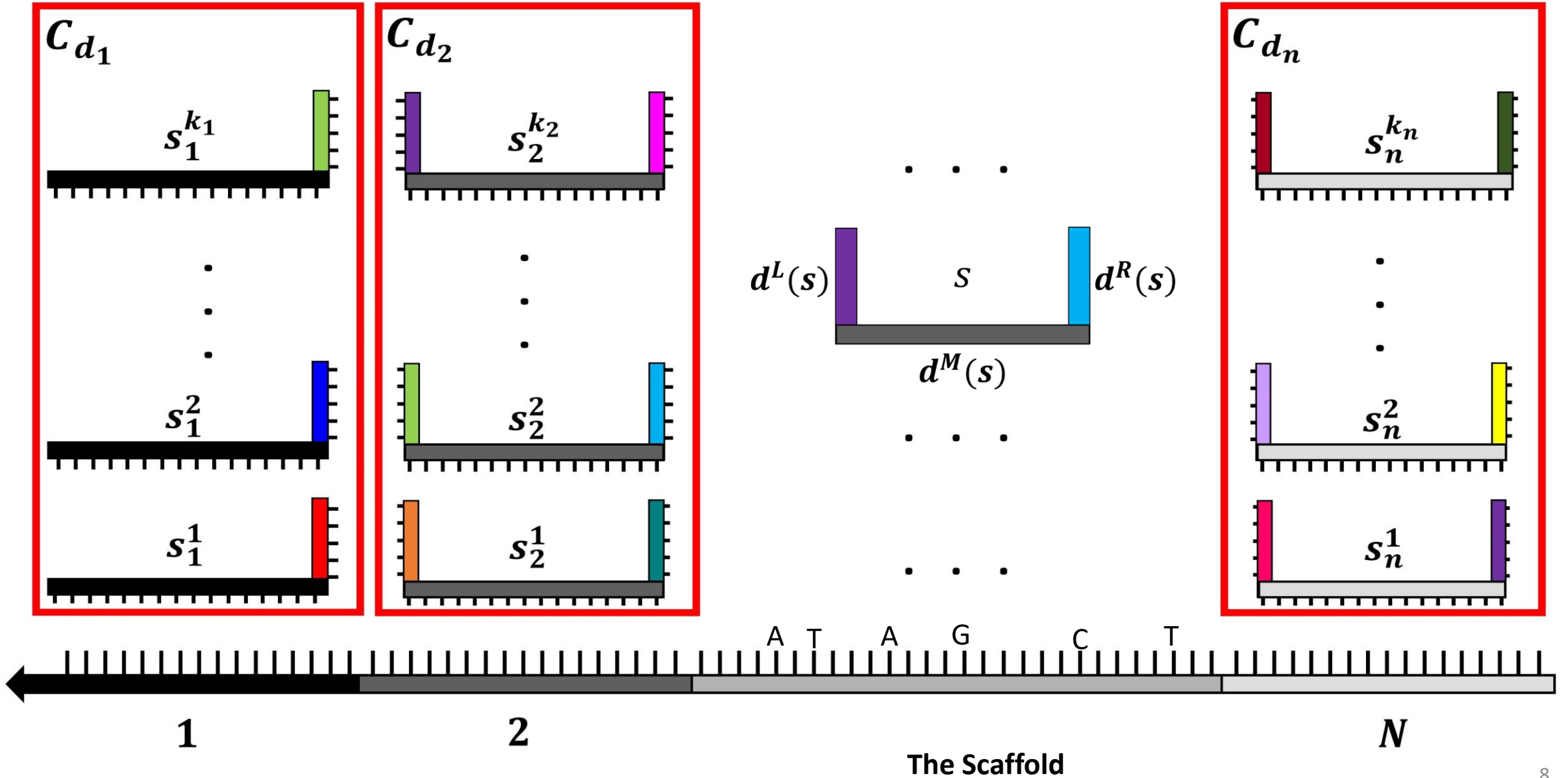


N





This is 1D Scaffolded DNA Computer



Built-in algorithmic self correction mechanism

DNA strand displacement

Built-in algorithmic self correction mechanism

DNA strand displacement

Microsoft Research

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1D Scaffolded DNA Computer Energy model and thermodynamic features

For any configuration X of size l :

Chair
$$E(X) = \sum_{p \in X} \text{sit}(p) + l * \text{sitcost} + \sum_{p_i, p_{i+1} \in X} \text{handshake}(p_i, p_{i+1}).$$

1D Scaffolded DNA Computer Energy model and thermodynamic features

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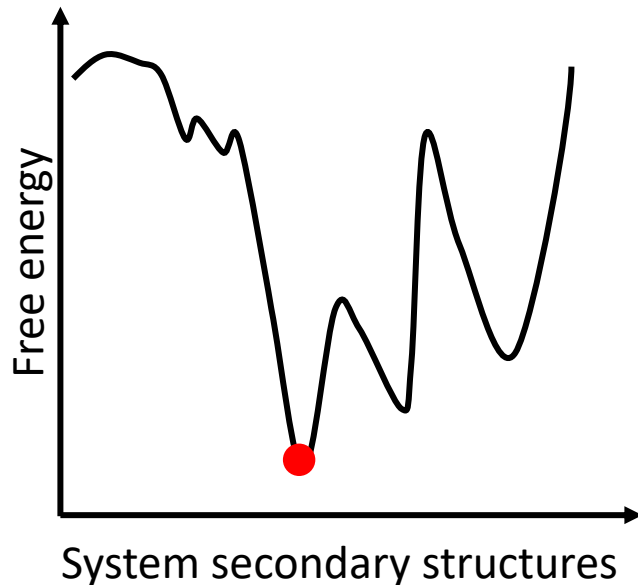
DNA $\Delta G^S(X) = \sum_{s \in X} \Delta G(d^M(s)) + l \cdot \Delta G^{\text{assoc}} + \sum_{s_i, s_{i+1} \in X} \Delta G(d^R(s_i), d^L(s_{i+1})).$

1D Scaffolded DNA Computer Energy model and thermodynamic features

For any configuration X of size l :

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$$\text{MFE} = \min_{S \in \Omega} \Delta G(S)$$

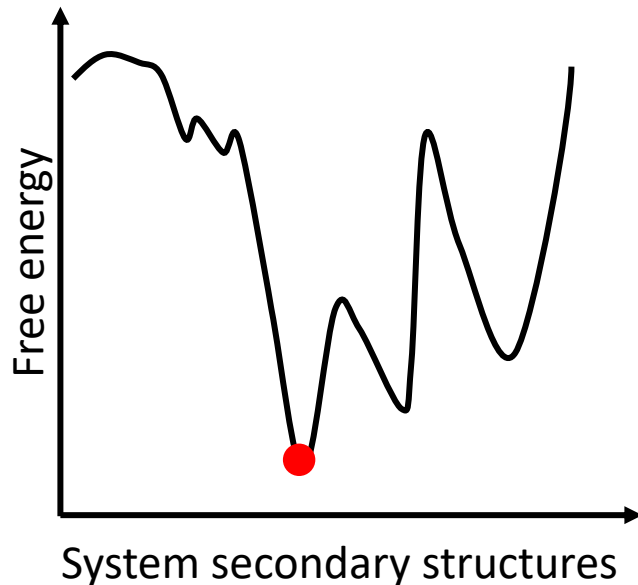
Minimum Free Energy

1D Scaffolded DNA Computer Energy model and thermodynamic features

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$$\text{MFE} = \min_{S \in \Omega} \Delta G(S)$$

Minimum Free Energy

Boltzmann weighted sum

$$Q = \sum_{S \in \Omega} e^{-\Delta G(S)/k_B T}$$

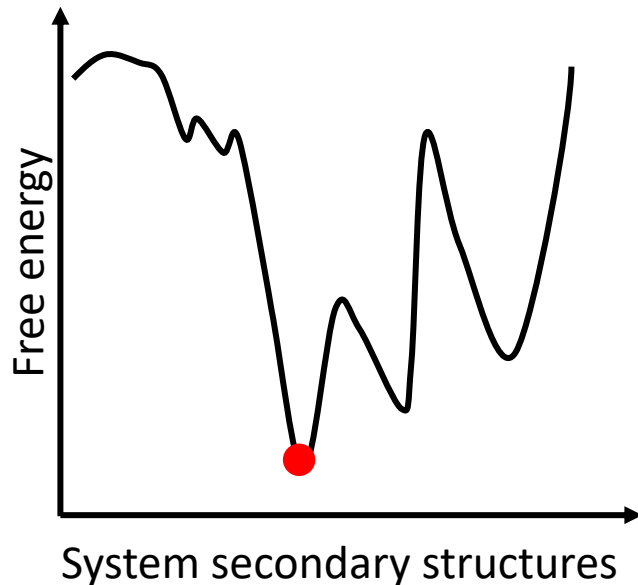
Partition Function

1D Scaffolded DNA Computer Energy model and thermodynamic features

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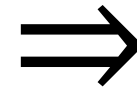
$$\text{MFE} = \min_{S \in \Omega} \Delta G(S)$$

Minimum Free Energy

Boltzmann weighted sum

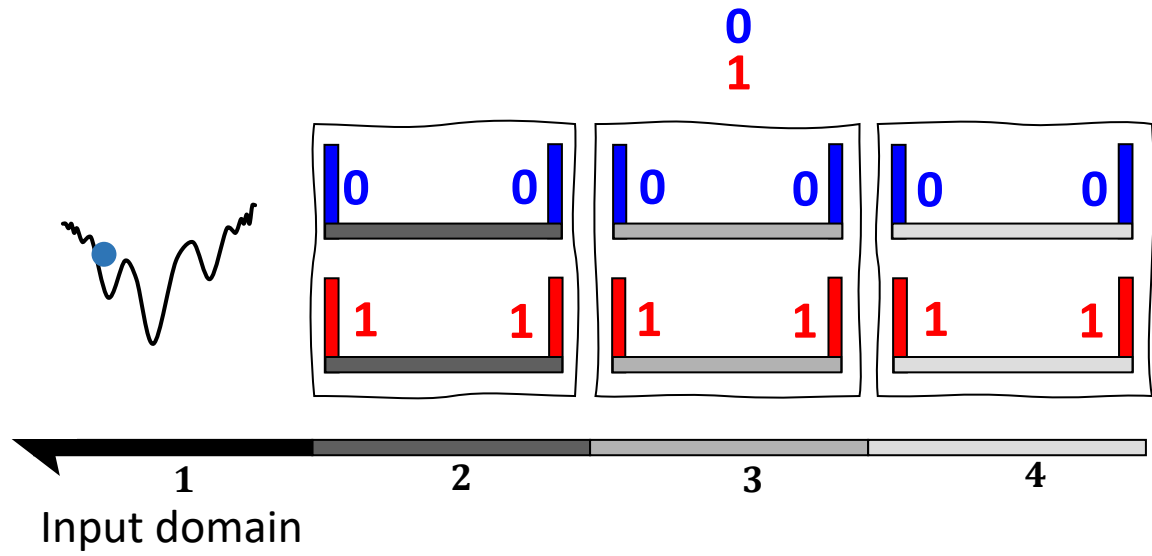
$$Q = \sum_{S \in \Omega} e^{-\Delta G(S)/k_B T}$$

Partition Function

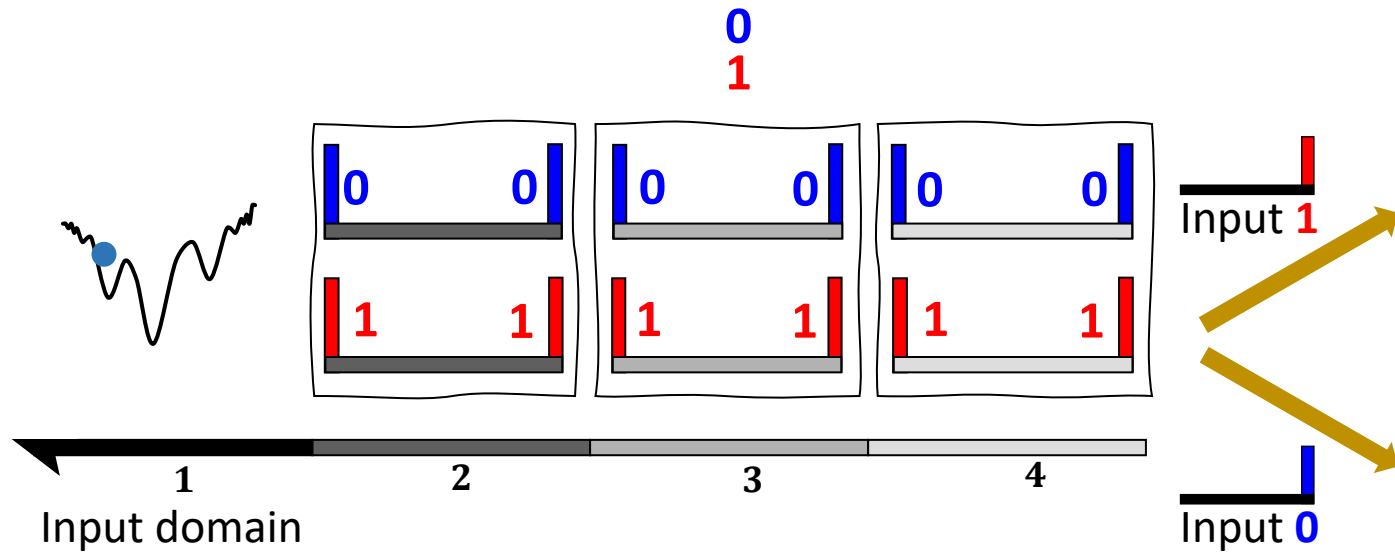


$$\text{Pr}[S] = \frac{e^{-\Delta G(S)/k_B T}}{Q}$$

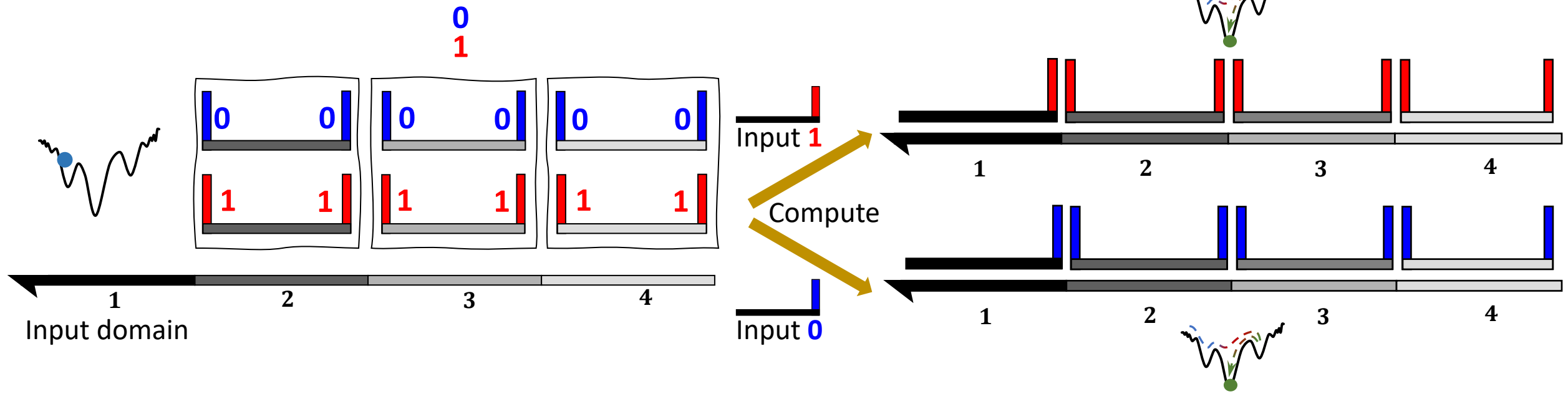
Scaffolded DNA Computer example: Bit-Copy



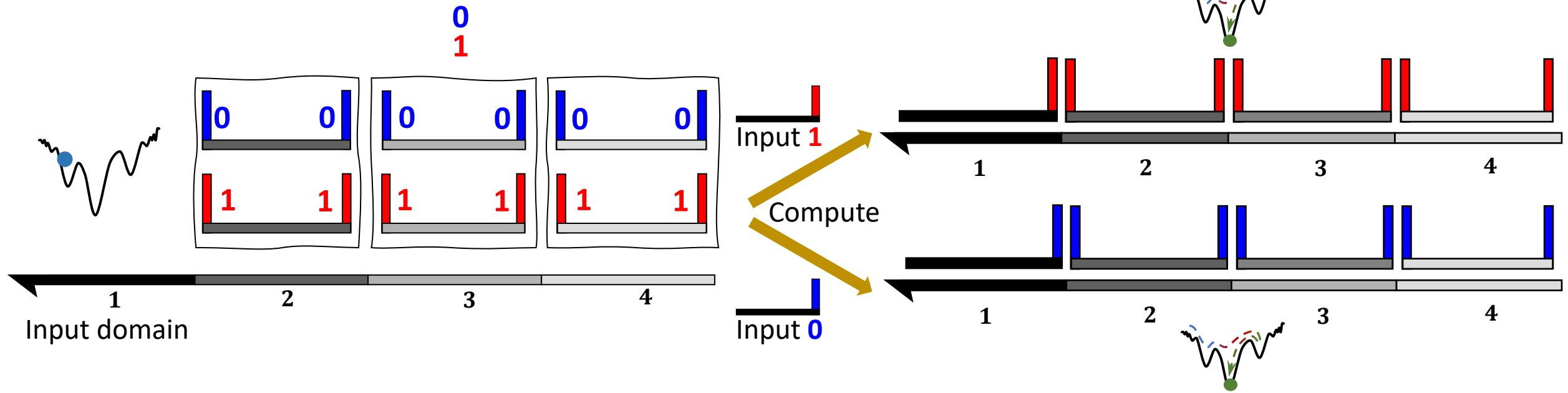
Scaffolded DNA Computer example: Bit-Copy



Scaffolded DNA Computer example: Bit-Copy



Scaffolded DNA Computer example: Bit-Copy



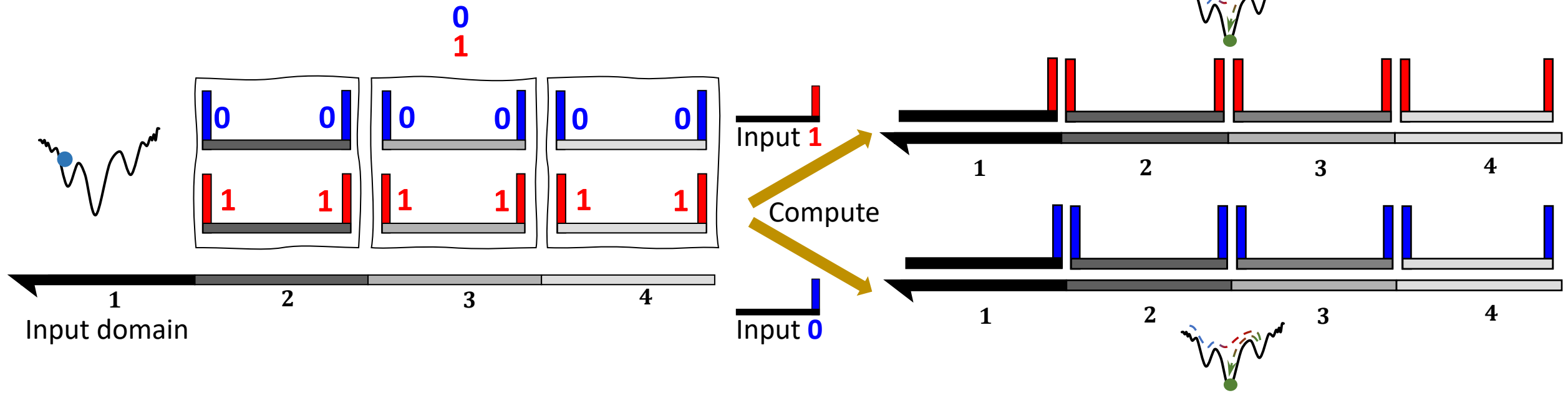
GOAL

$$\Pr\left[\begin{array}{c} \text{[Diagram of a DNA strand with red bars on top and blue bars on bottom]} \\ \text{[Diagram of a probe binding to the strand]} \end{array}\right] \gg \sum_c \Pr[c : \textit{is another configuration}]$$

[Diagram of a DNA strand with red and blue bars]

At equilibrium

Scaffolded DNA Computer example: Bit-Copy



GOAL

$$\Pr\left[\left\langle \begin{array}{c} \text{Target Configuration} \\ \text{Scaffold} \end{array} \right\rangle\right] \gg \sum_c \Pr[c : \text{is another configuration}]$$

At equilibrium

$$\Pr[\text{target}] = \frac{e^{-\text{MFE} / k_B T}}{Q}$$

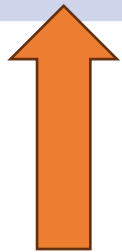
Computational complexity of Minimum Free Energy and the Partition Function

Input Type	MFE	Partition Function
Single Strand	$O(n^3)$	$O(n^3)$
Multiple Strands, Bounded ($\leq s$)	?	$O(n^3)(s - 1)!$
Multiple Strands, Unbounded	NP – Complete	?

n bases, s strands

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n bases, s strands

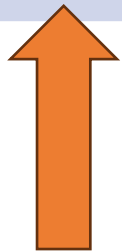
GOAL

At equilibrium

$\Pr \left[\text{Diagram of a single strand configuration} \right] \gg \sum_c \Pr [c : \text{is another configuration}]$

Computational complexity of Minimum Free Energy and the Partition Function

Input Type	MFE	Partition Function
Single Strand	$O(n^3)$	$O(n^3)$
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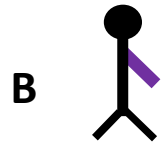
n bases, s strands

GOAL

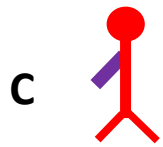
At equilibrium

$\Pr \left[\left[\text{Diagram of a single strand with four red vertical bars representing potential binding sites} \right] \right] \gg \sum_c \Pr [c : \text{is another configuration}]$

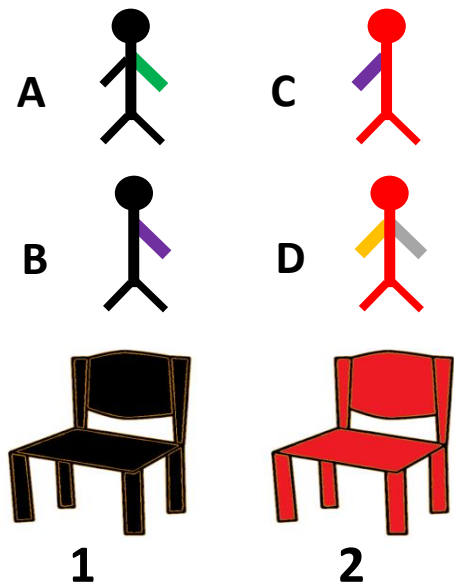
Efficiently



1

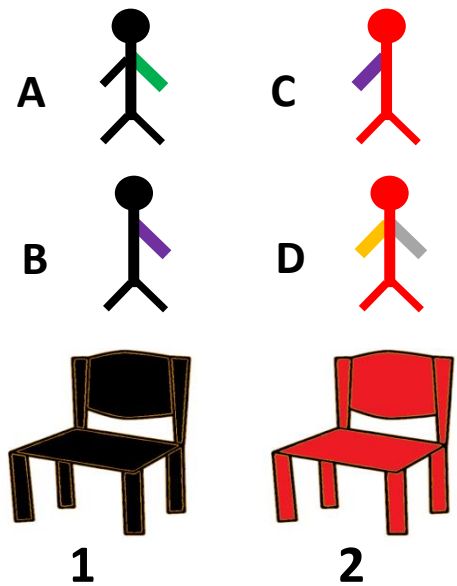


2



$$|\Omega| = (k + 1)^N = 9$$

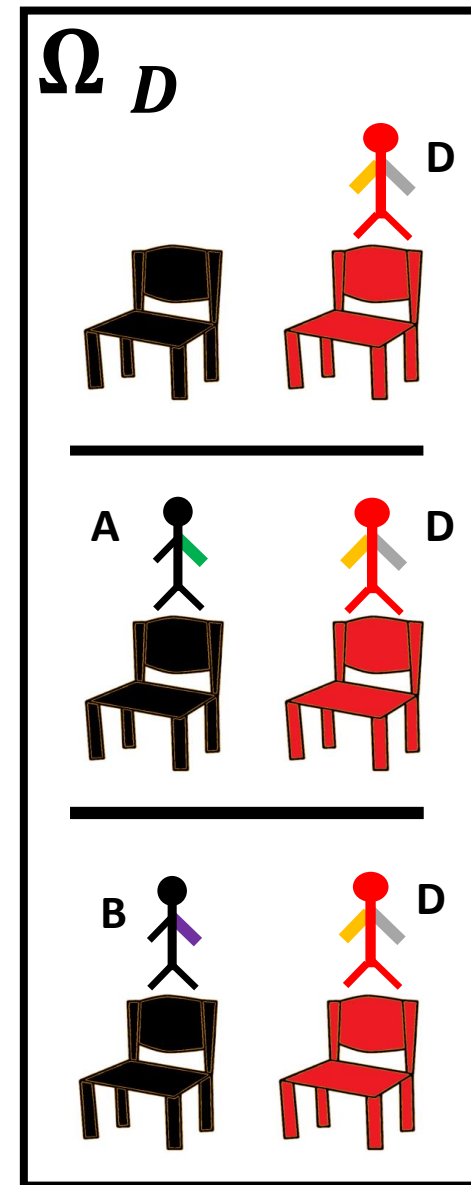
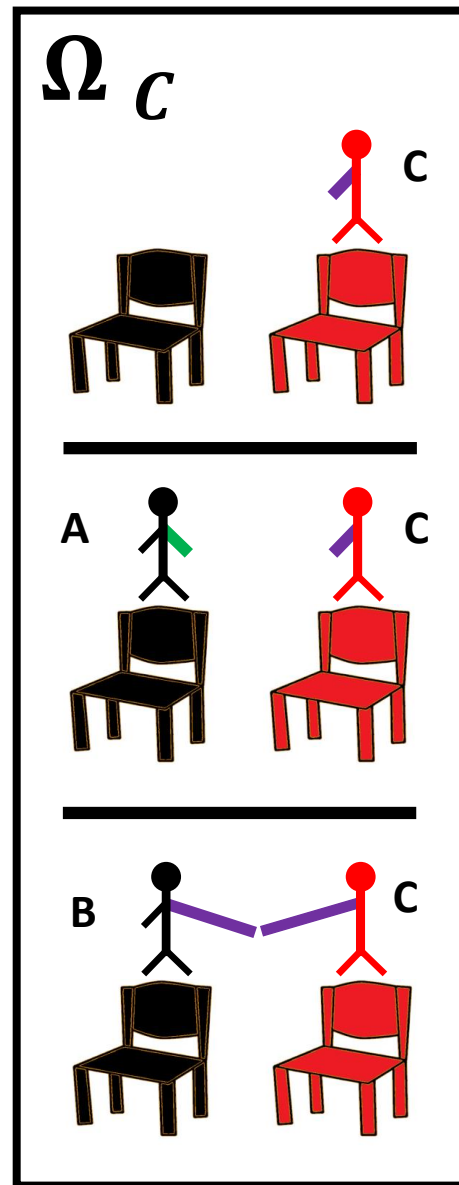
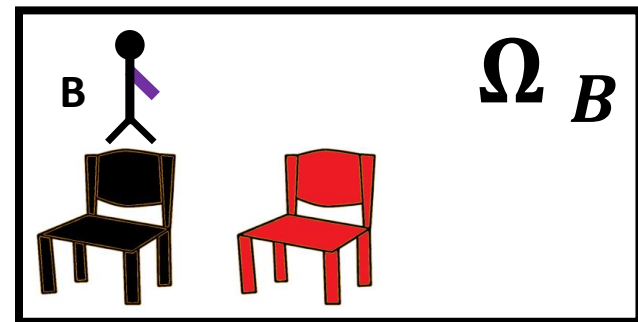
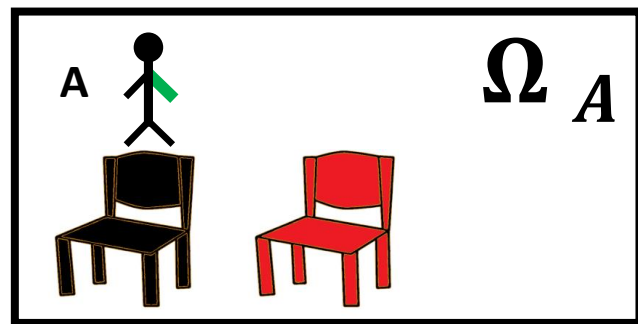
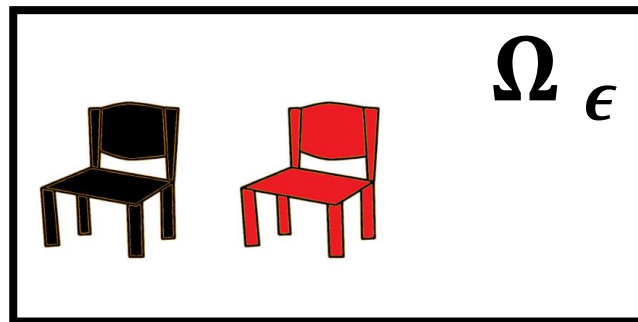
$$Q = \sum_{p \in \Omega} e^{-\Delta G(p)/k_B T}$$



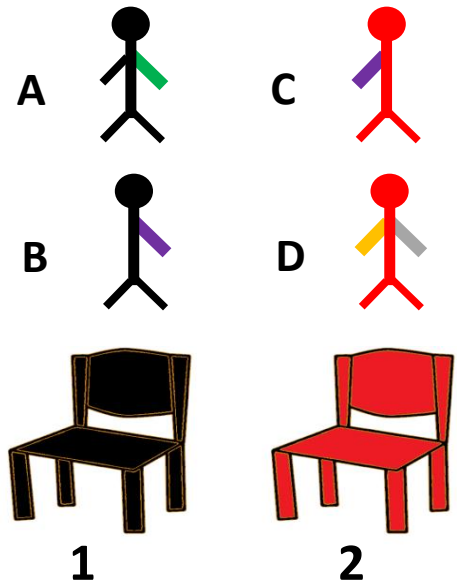
$$|\Omega| = (k + 1)^N = 9$$

$$Q = \sum_{p \in \Omega} e^{-\Delta G(p)/k_B T}$$

Ω



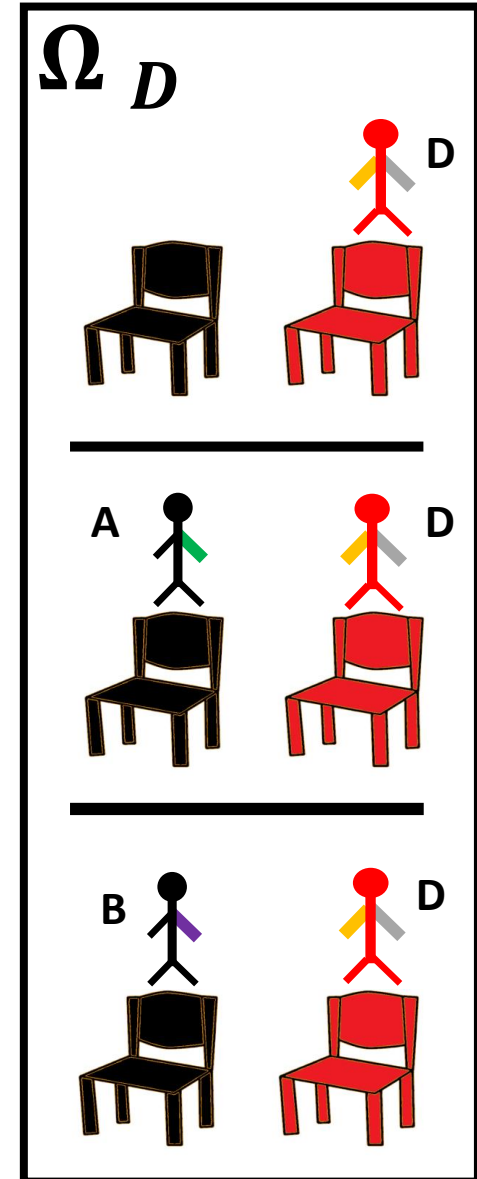
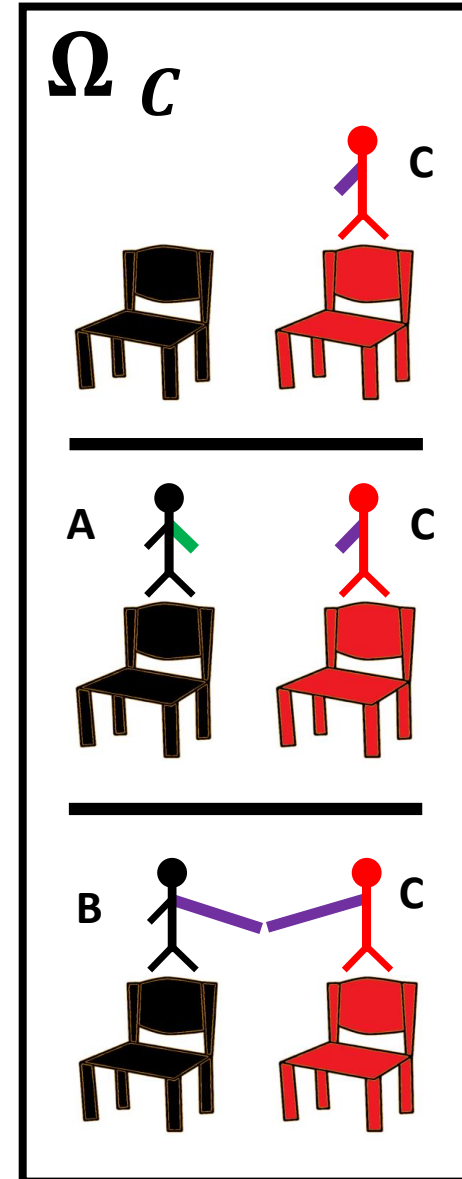
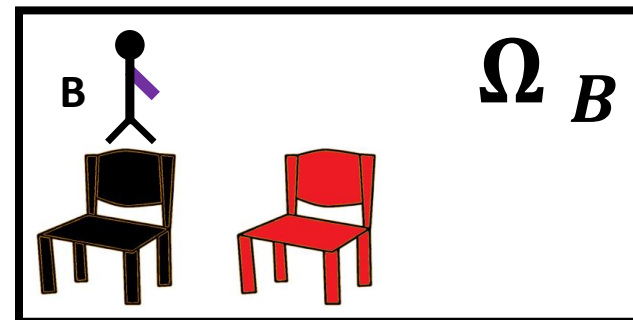
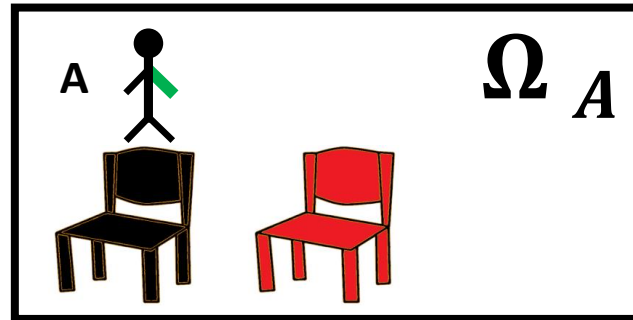
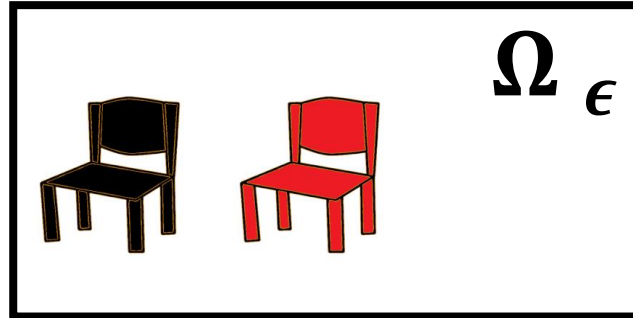
Is there recursive way to build these classes from themselves?



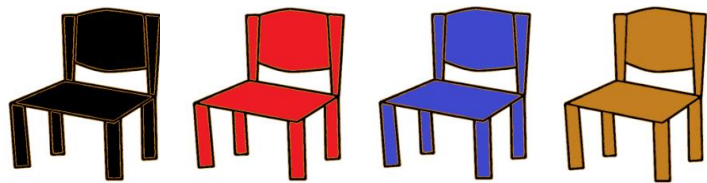
$$|\Omega| = (k + 1)^N = 9$$

$$Q = \sum_{p \in \Omega} e^{-\Delta G(p)/k_B T}$$

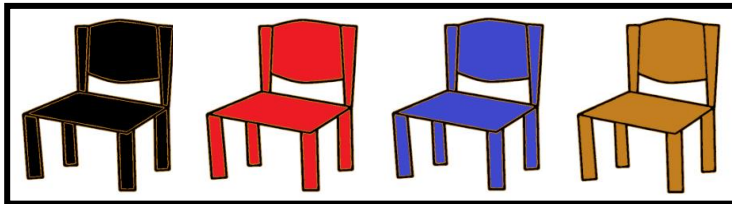
Ω



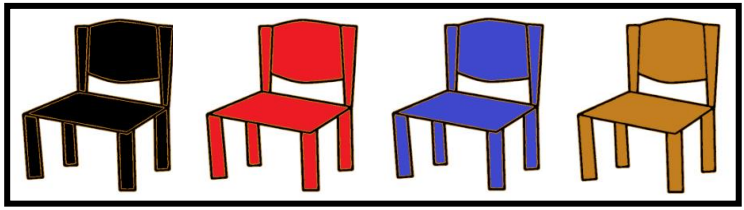
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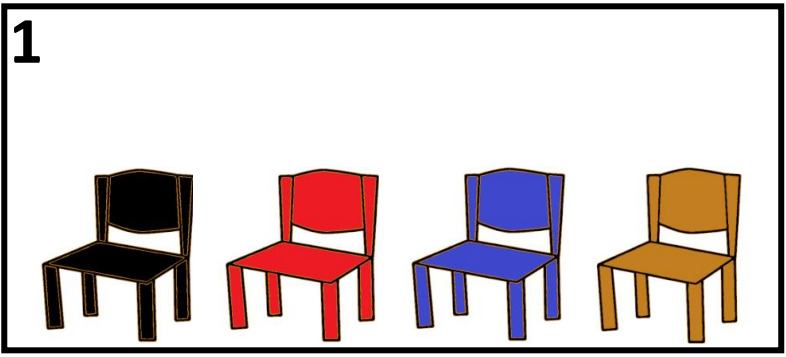
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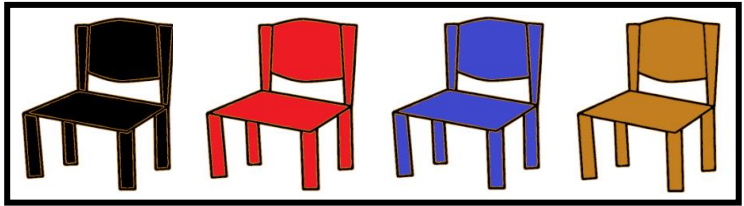


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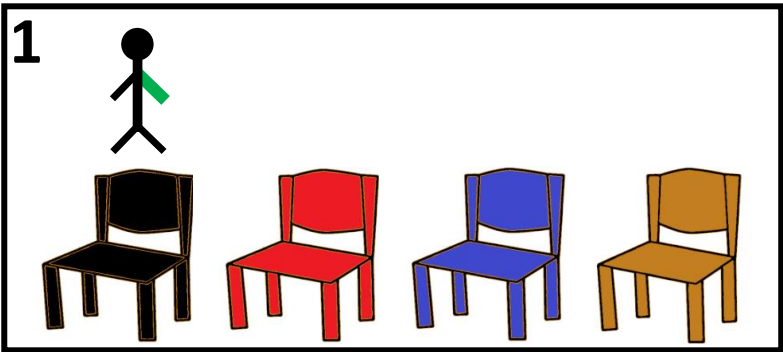


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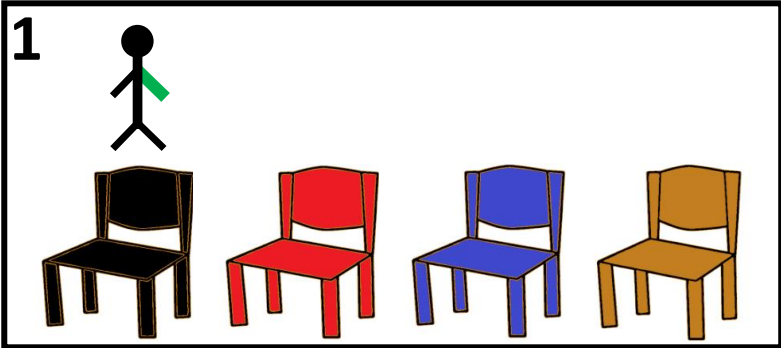
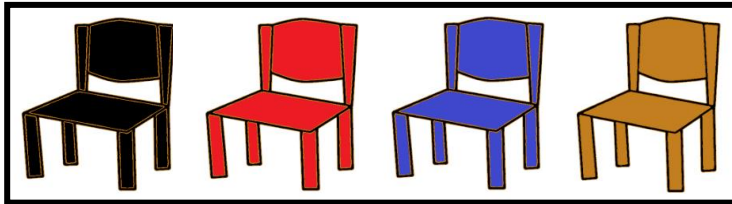
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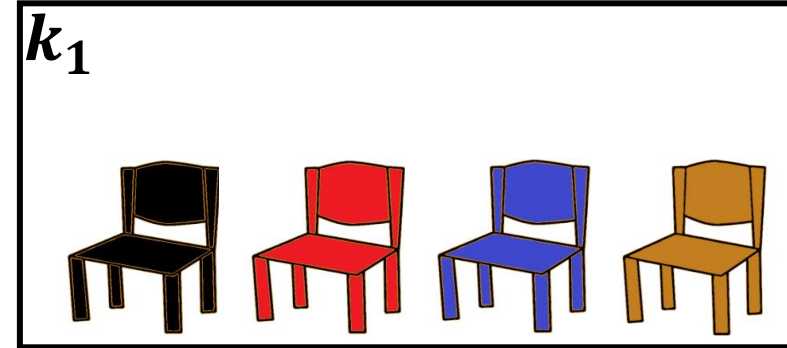
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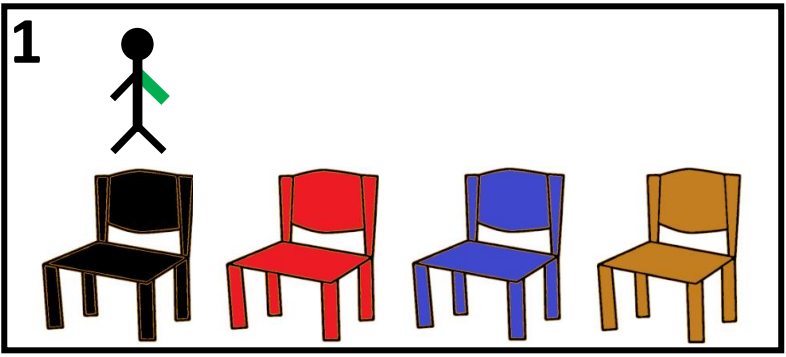
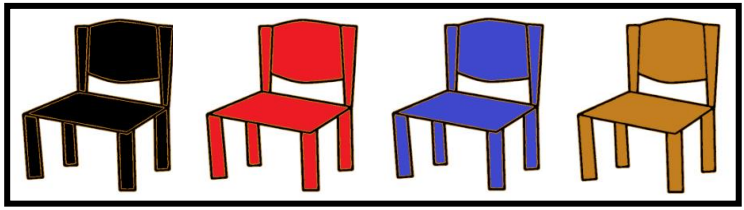


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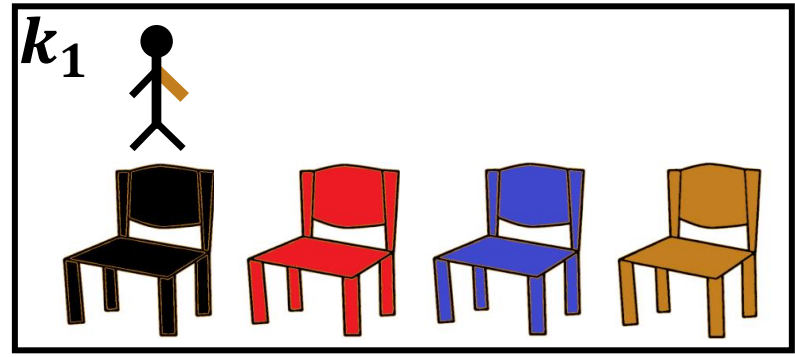


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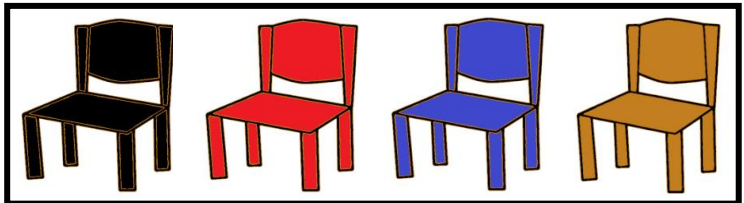


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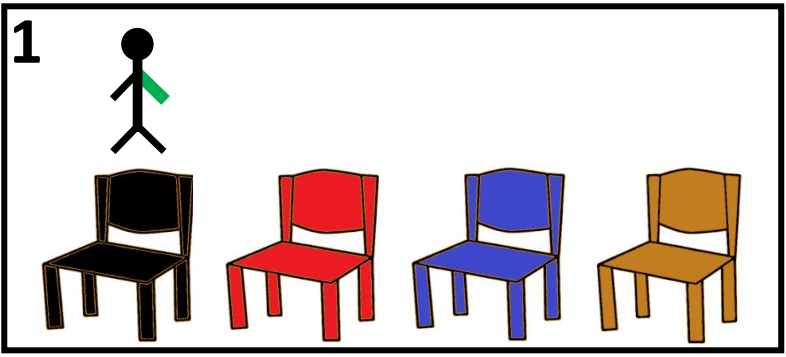


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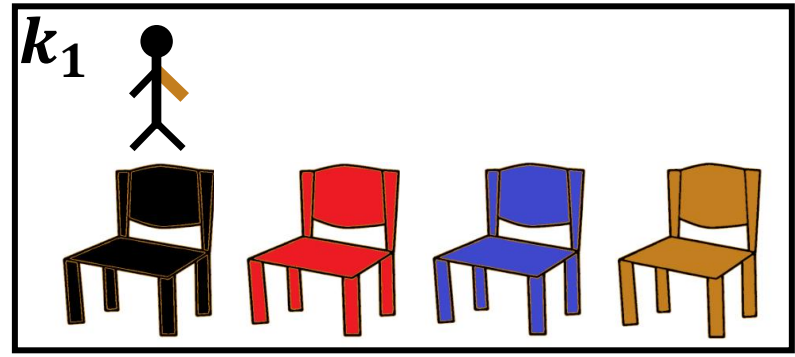
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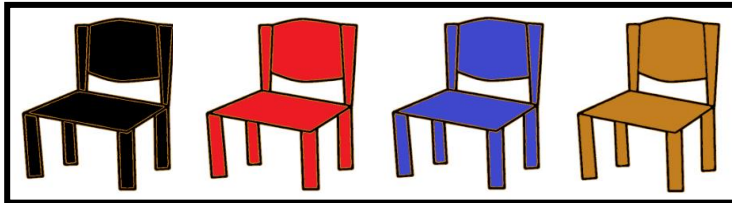
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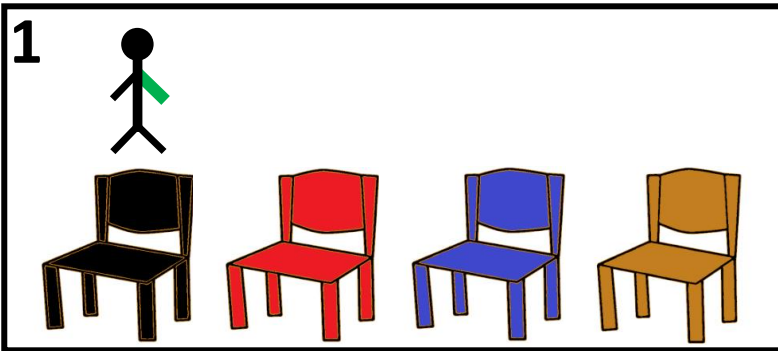
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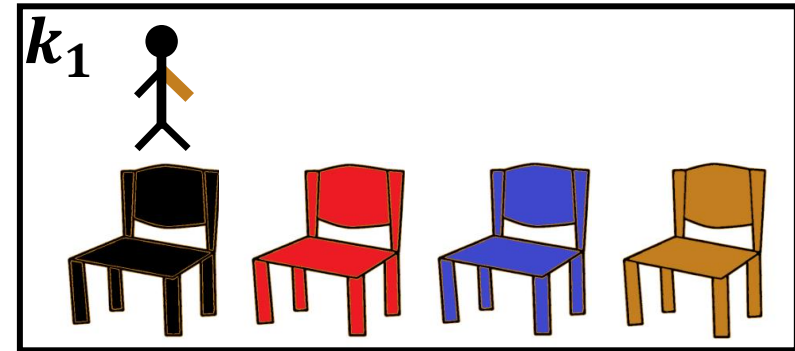
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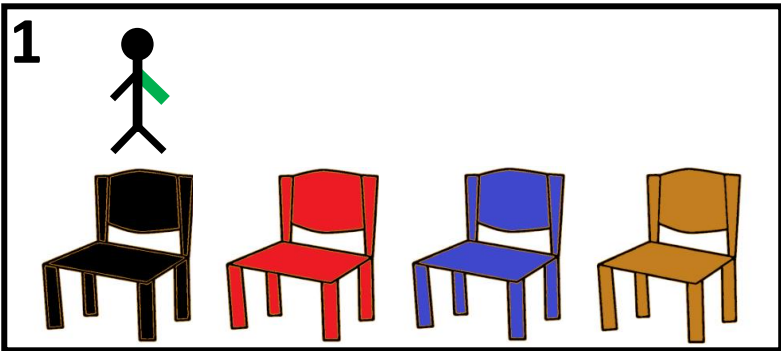
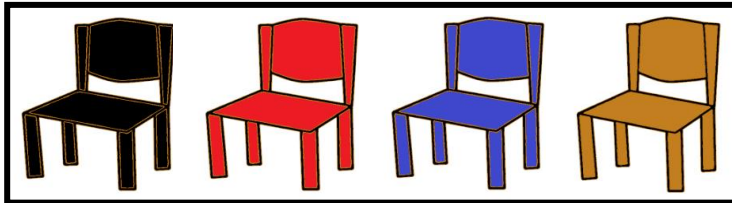


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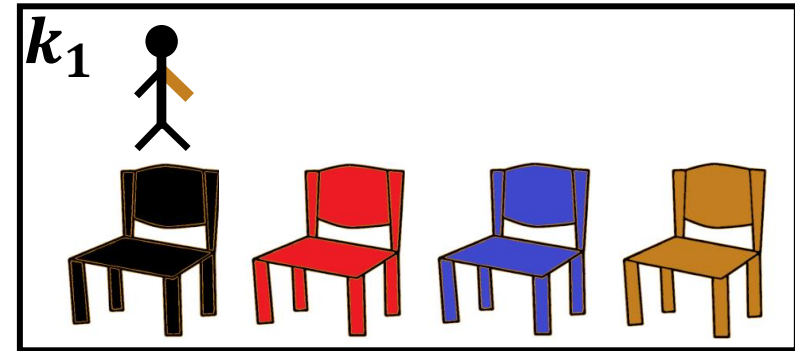


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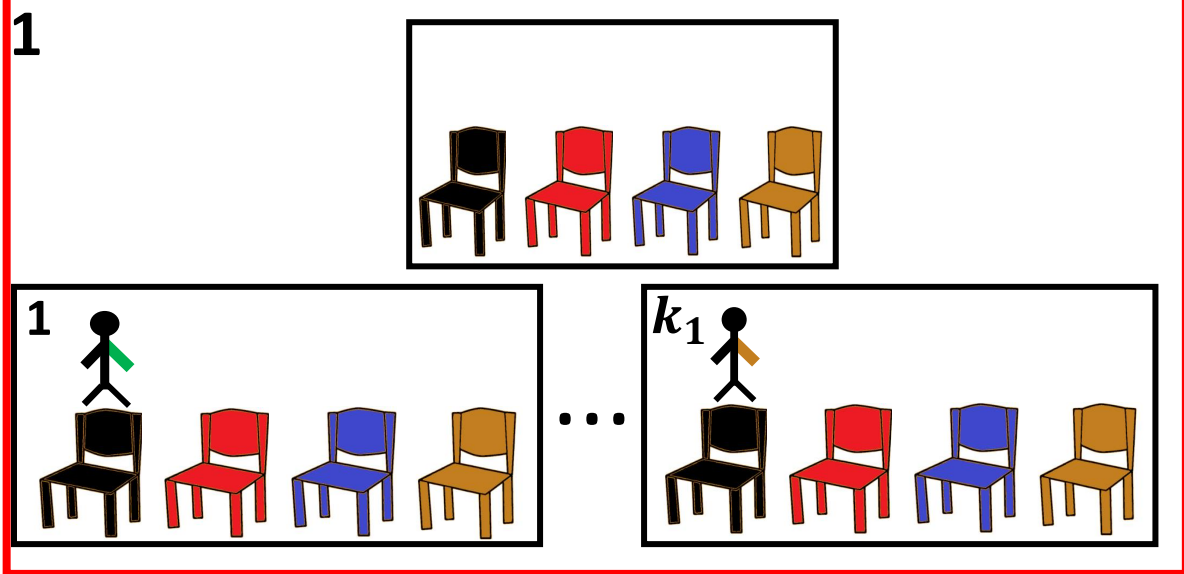
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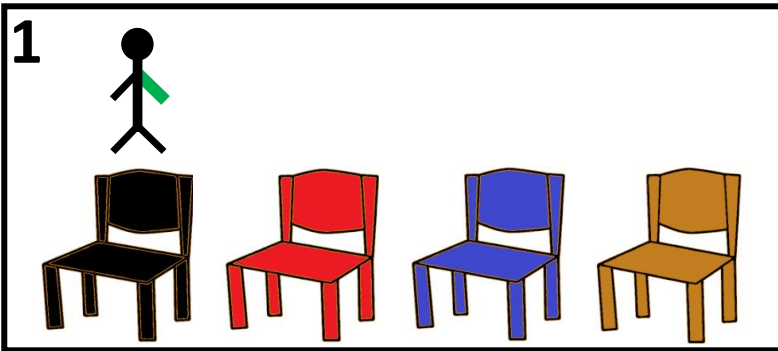
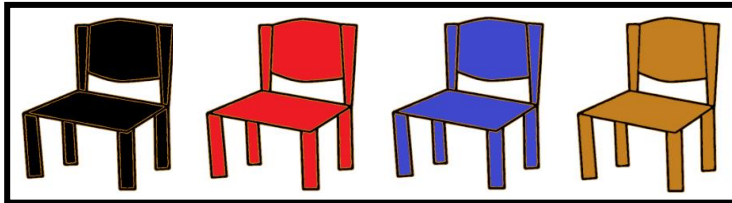


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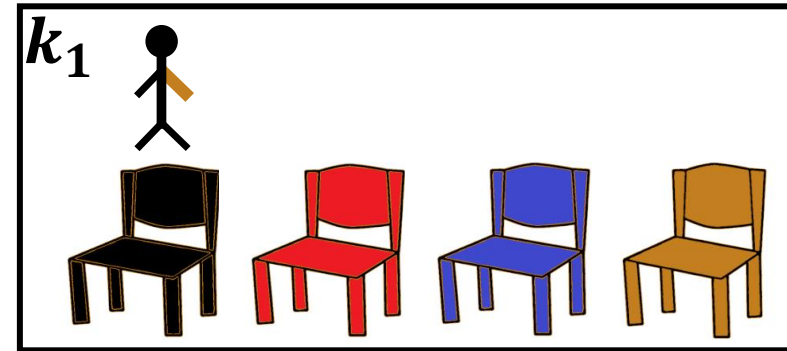


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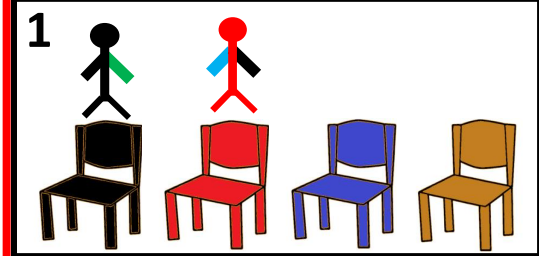
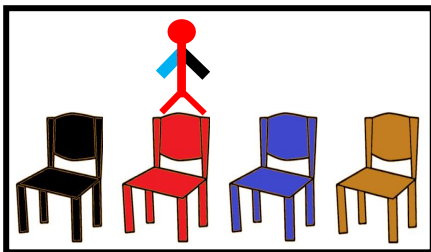


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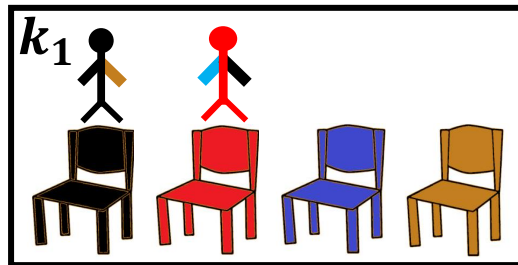


1

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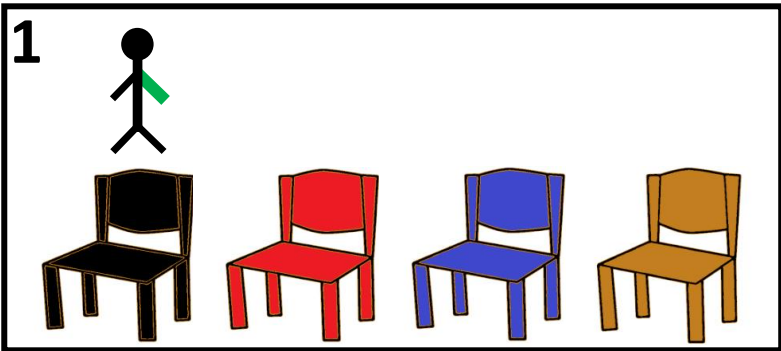
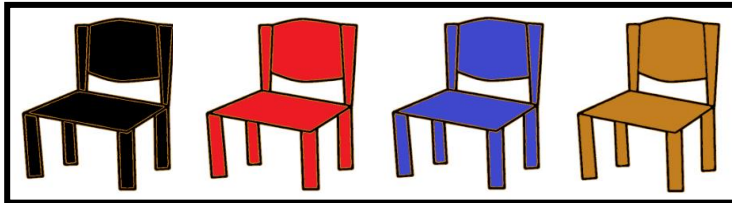


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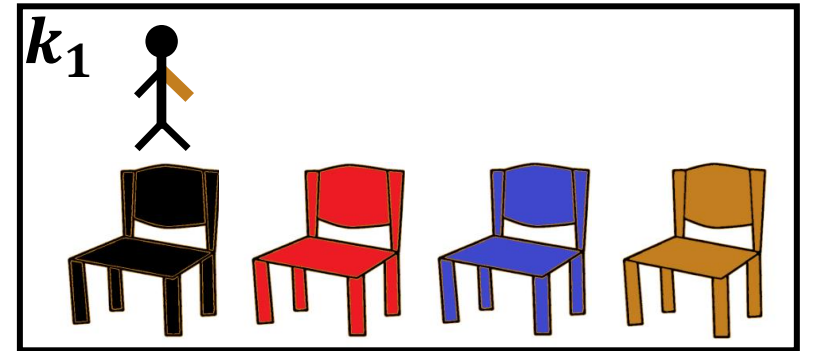


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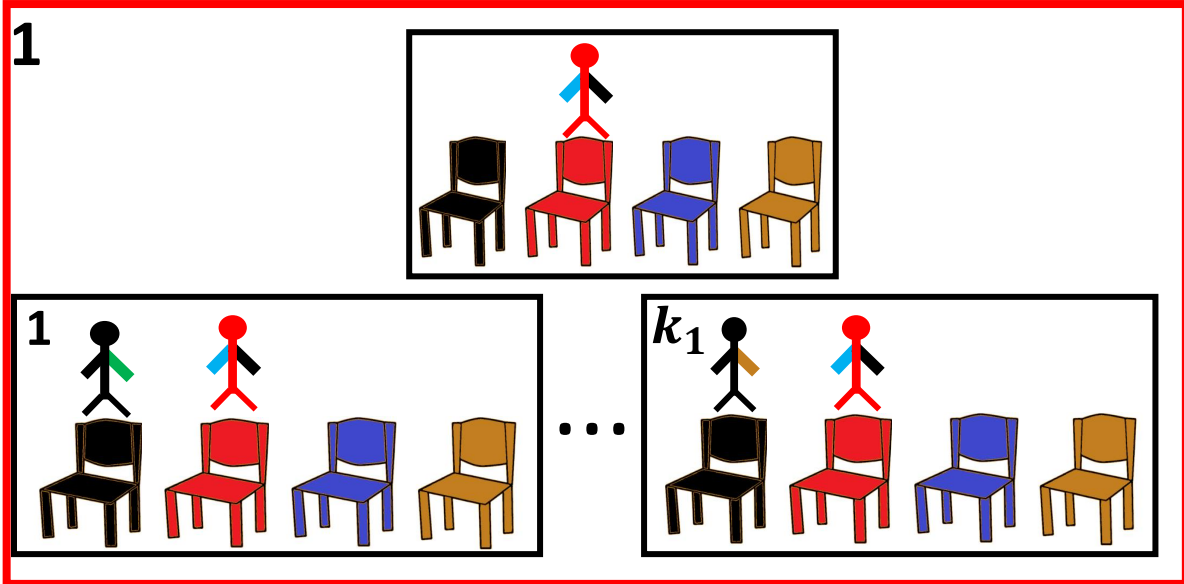
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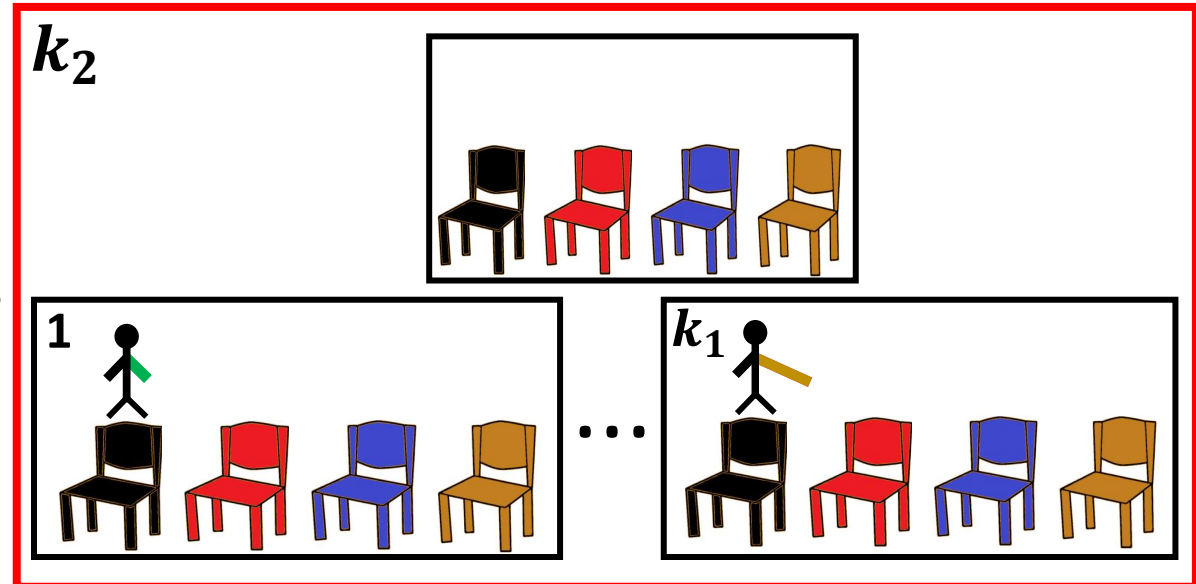
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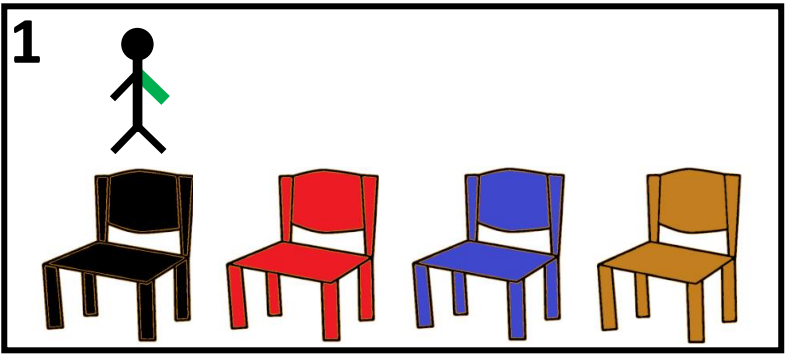
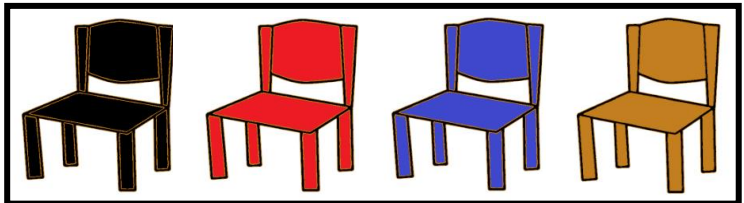
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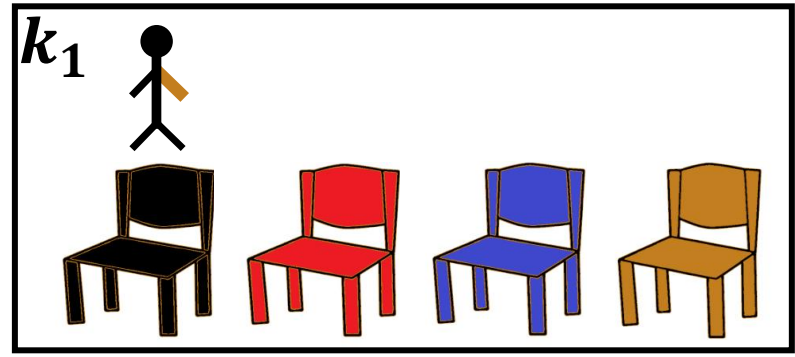
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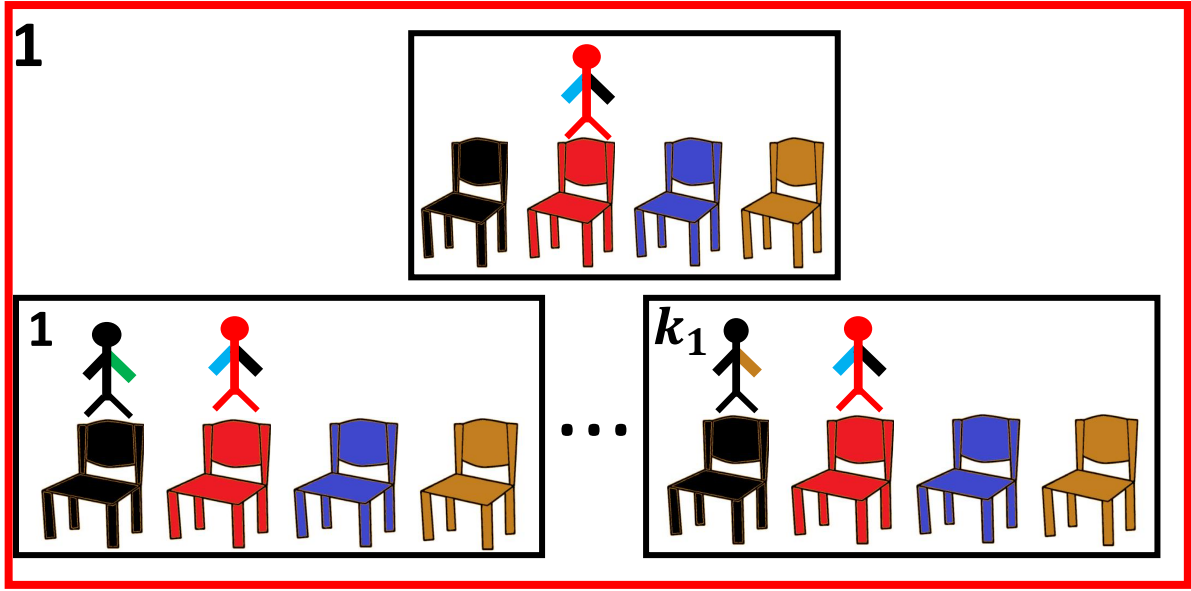
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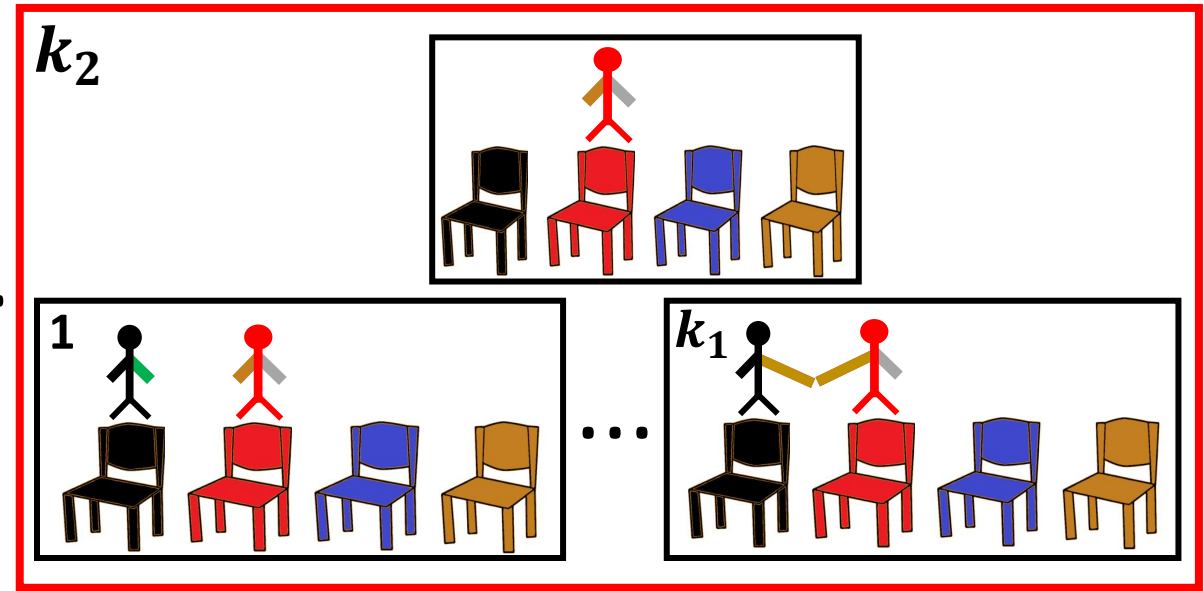
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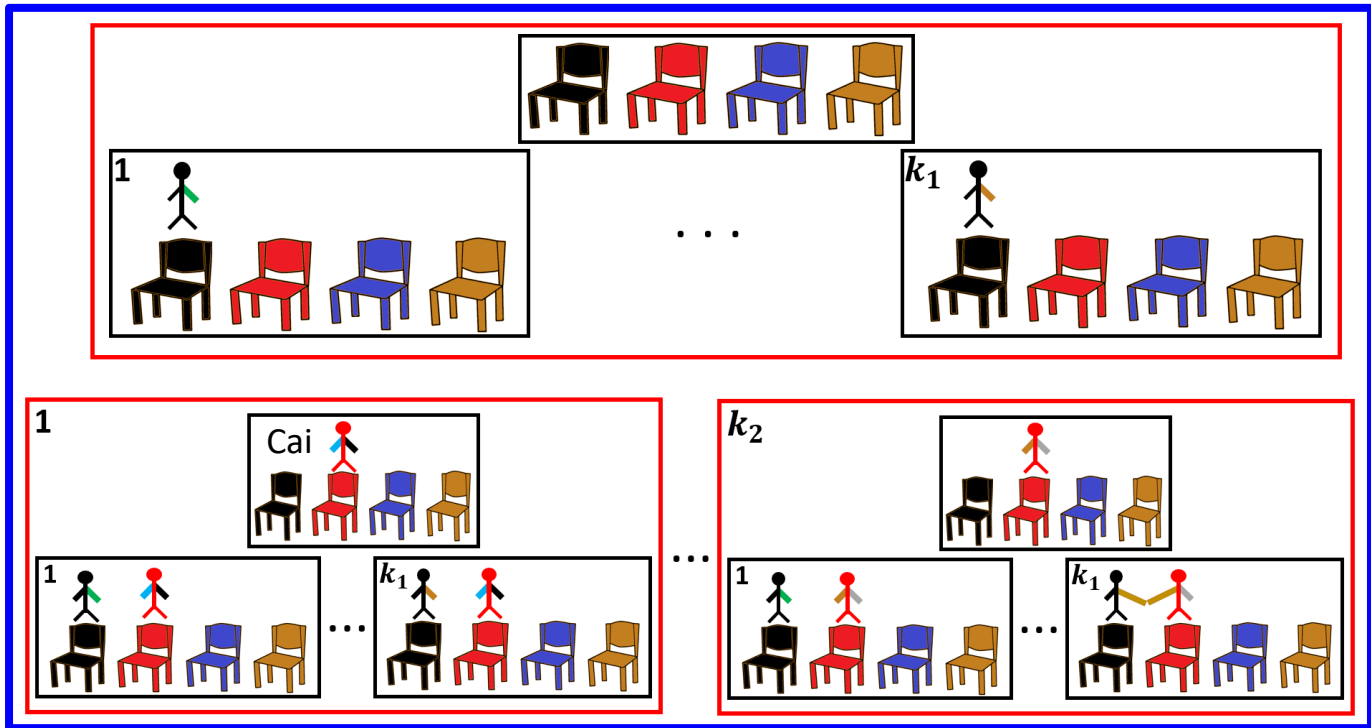


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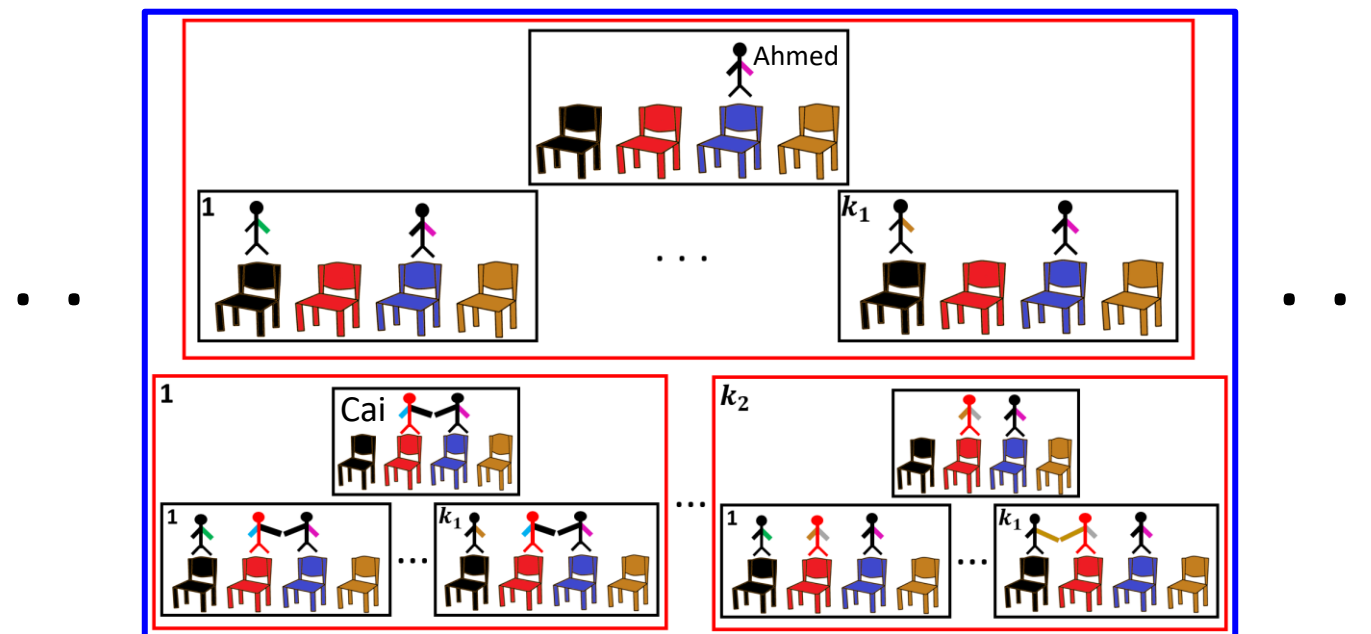
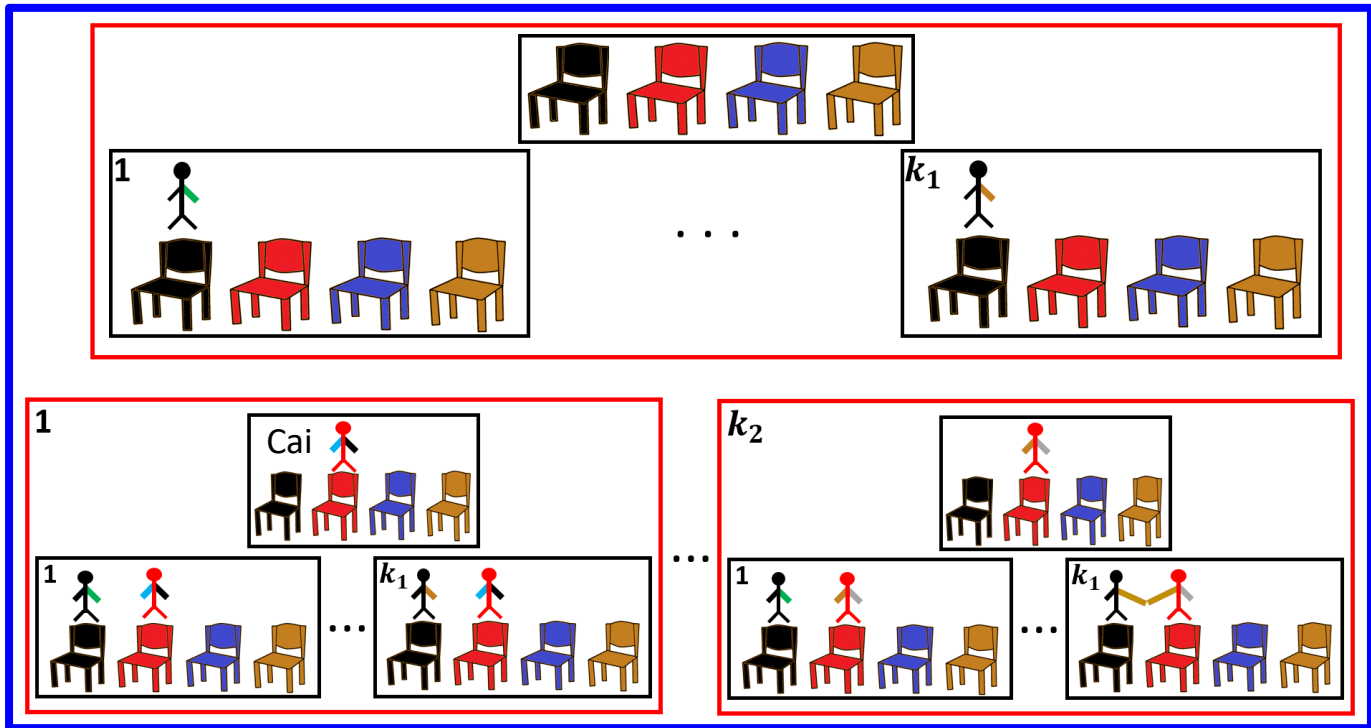
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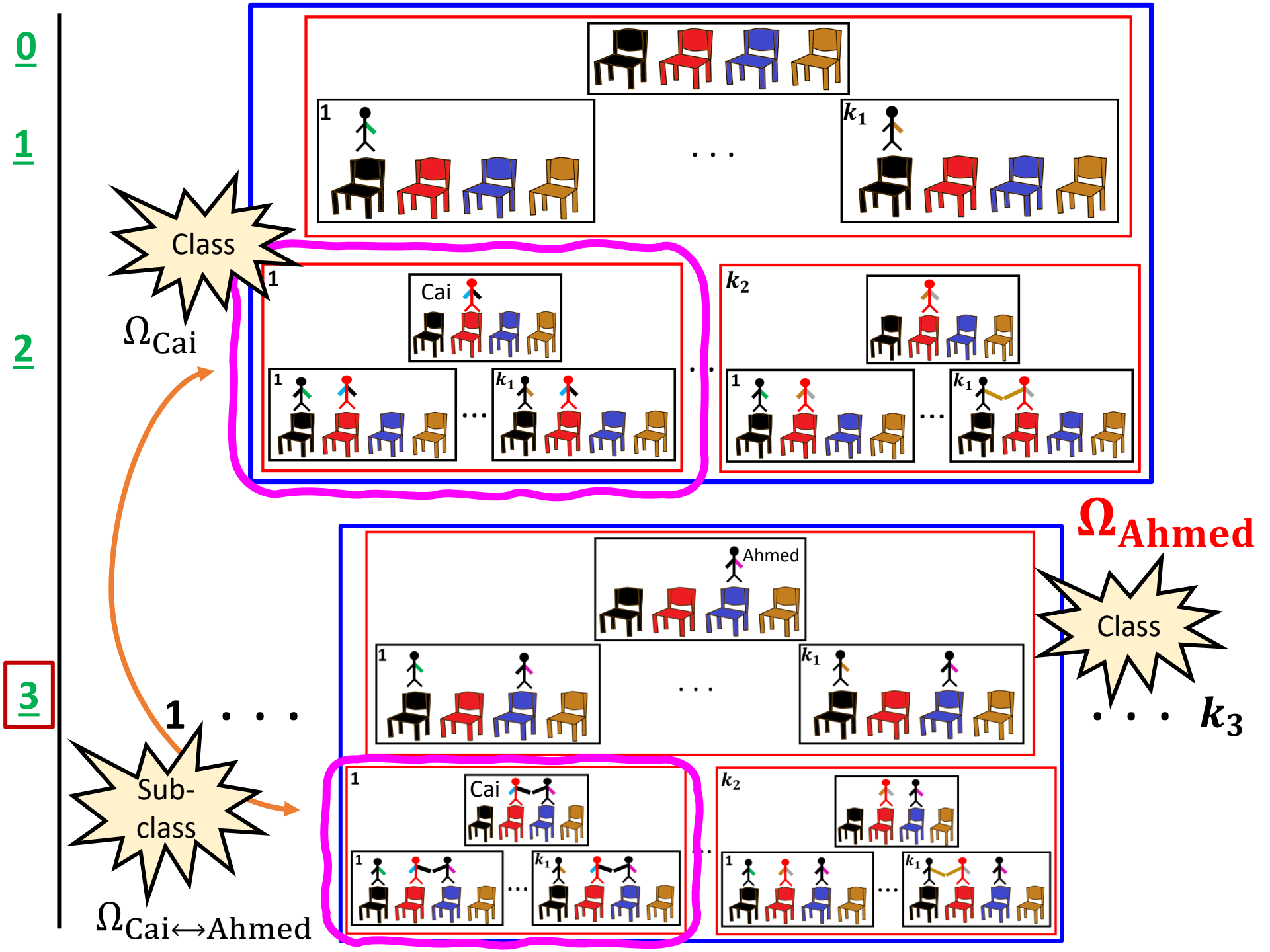
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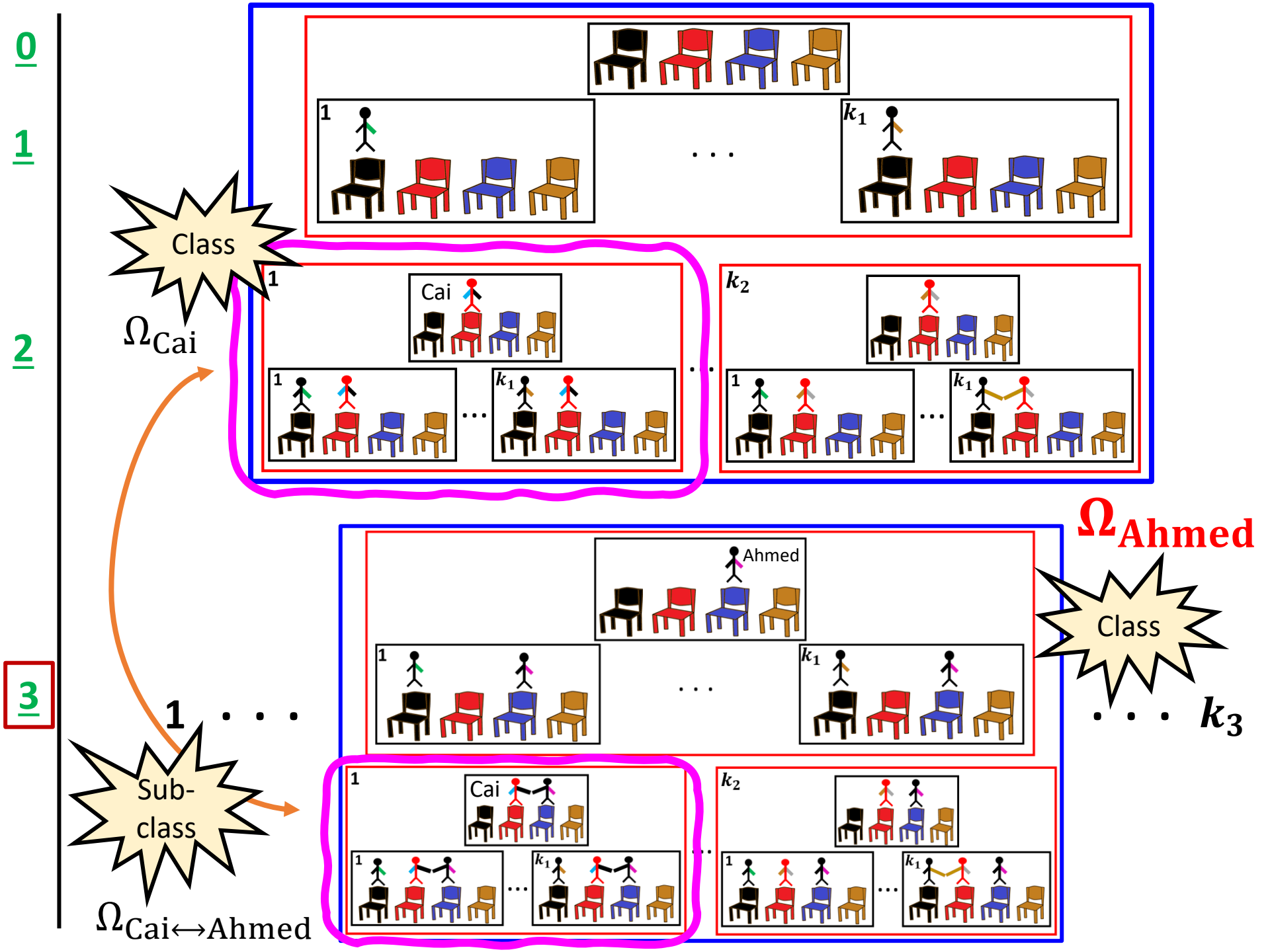


3

1 . . .

. . . k_3





Layer = chair

There is a 1-1 correspondence between each **class** of higher layers and a **sub-class** of any class in the current layer.

Ω_{Cai}



$\Omega_{\text{Cai} \leftrightarrow \text{Ahmed}}$

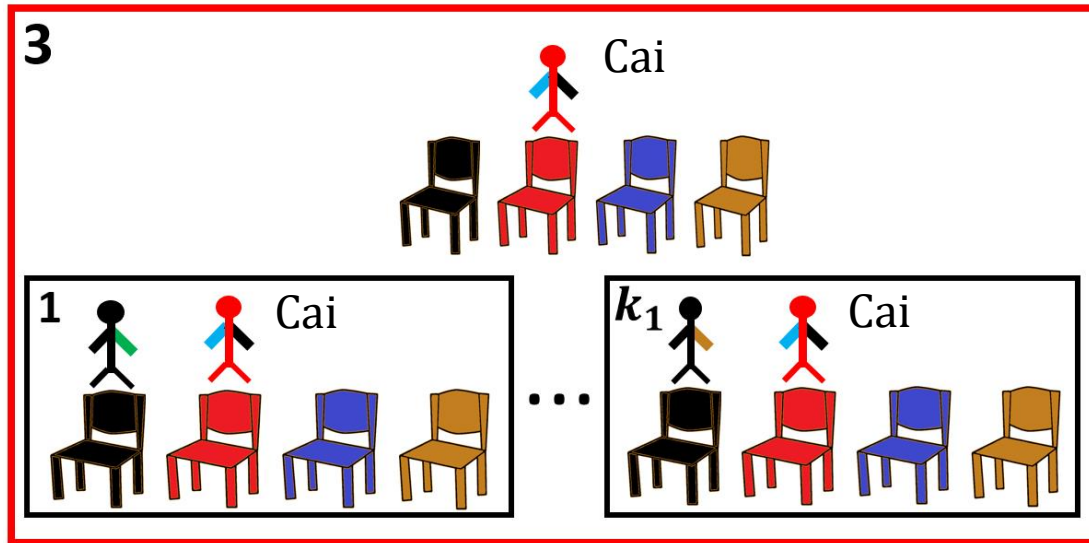
$\subset \Omega_{\text{Ahmed}}$

Can we use this inductive construction process to propagate information through this hierarchy ?

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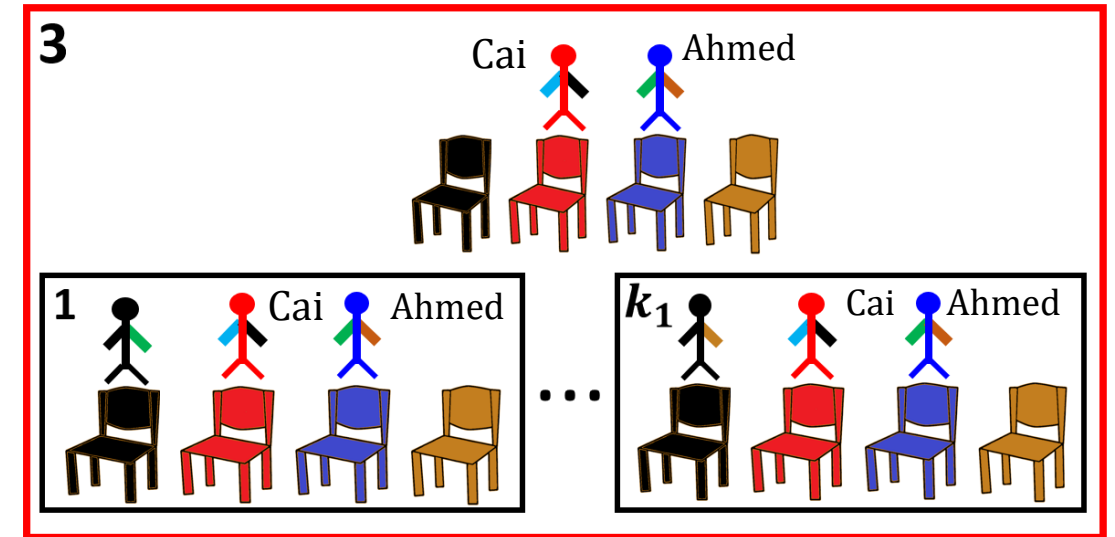
1 - Propagate information from exactly the previous layer (Direct neighbour handshaking possibility).

Ω_{Cai}



Information given: $Q(\Omega_{\text{Cai}})$

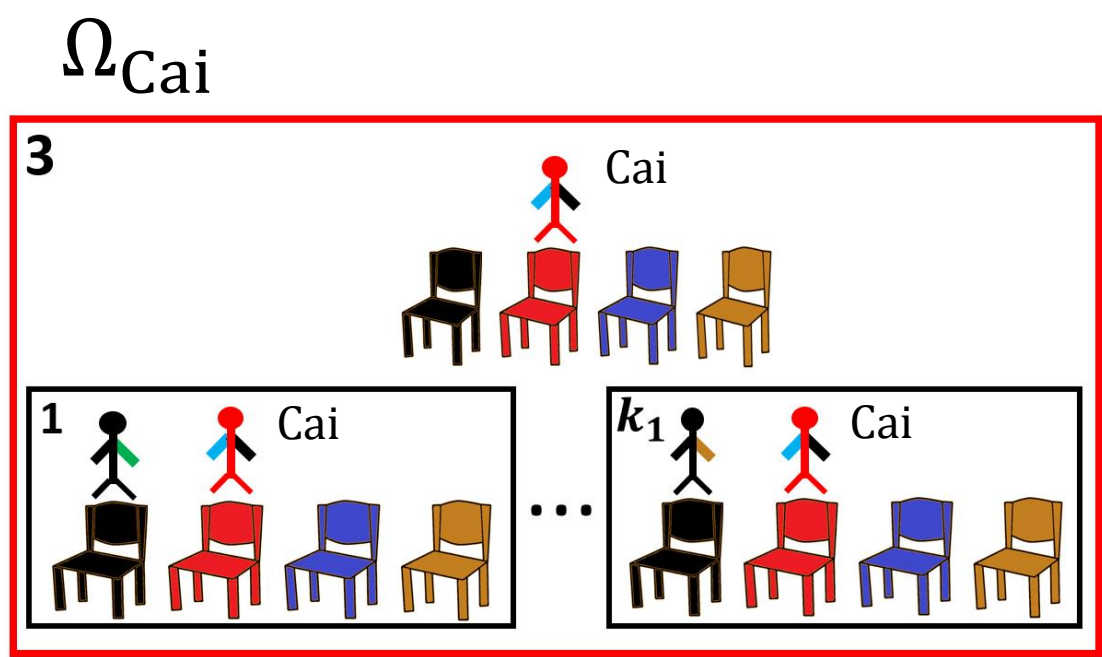
$\Omega_{\text{Cai} \rightarrow \text{Ahmed}}$



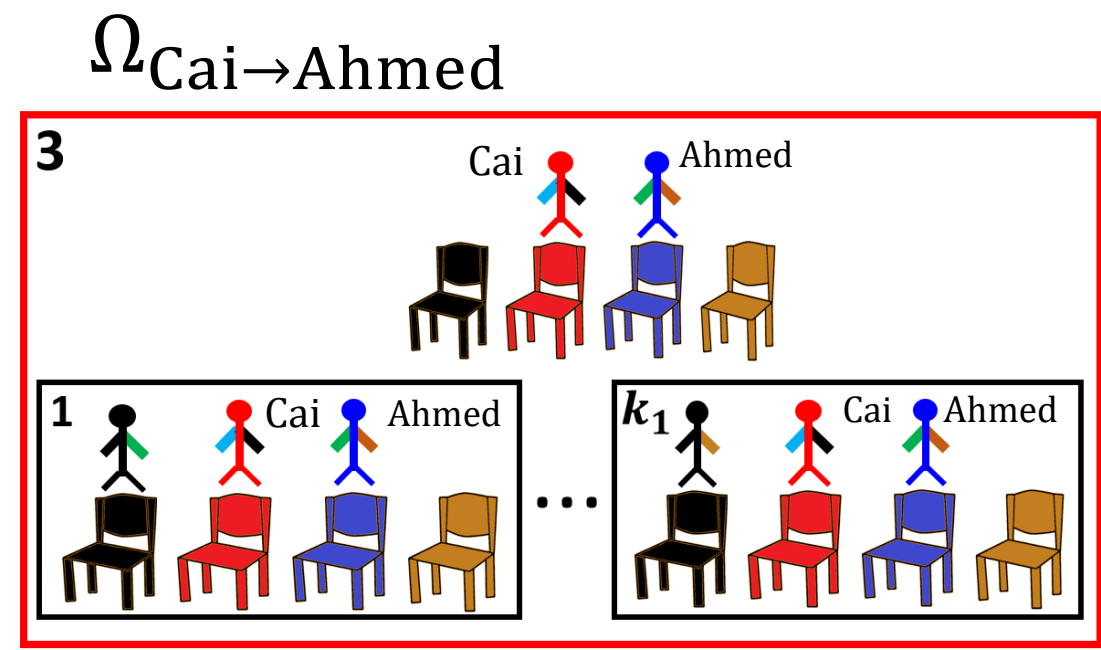
Information needed: $Q(\Omega_{\text{Cai} \leftrightarrow \text{Ahmed}})$

Can we use this inductive construction process to propagate information through this hierarchy ?

1 - Propagate information from exactly the previous layer (Direct neighbour handshaking possibility).



Information given: $Q(\Omega_{\text{Cai}})$

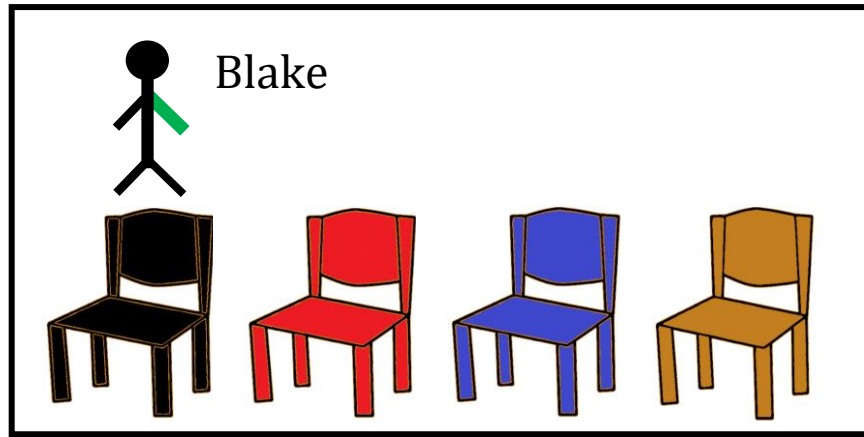


Information needed: $Q(\Omega_{\text{Cai} \leftrightarrow \text{Ahmed}})$

$$Q(\Omega_{\text{Cai} \leftrightarrow \text{Ahmed}}) = \dots = e^{\frac{\text{sit}(\text{Ahmed}) + \text{Sit_Cost}}{c}} * e^{\frac{\text{handshake}(\text{Cai}, \text{Ahmed})}{c}} * Q(\Omega_{\text{Cai}})$$

2 - Propagate information from the rest (No handshaking possibility).

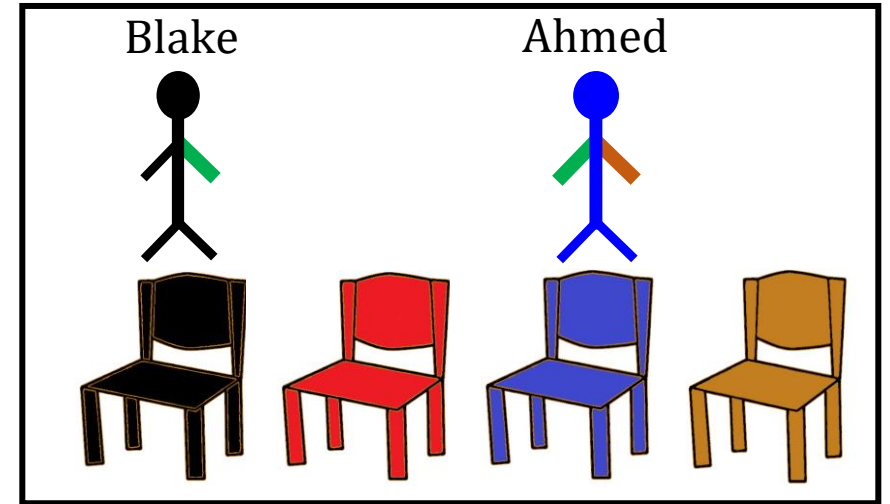
Ω_{Blake}



Information given: $Q(\Omega_{\text{Blake}})$

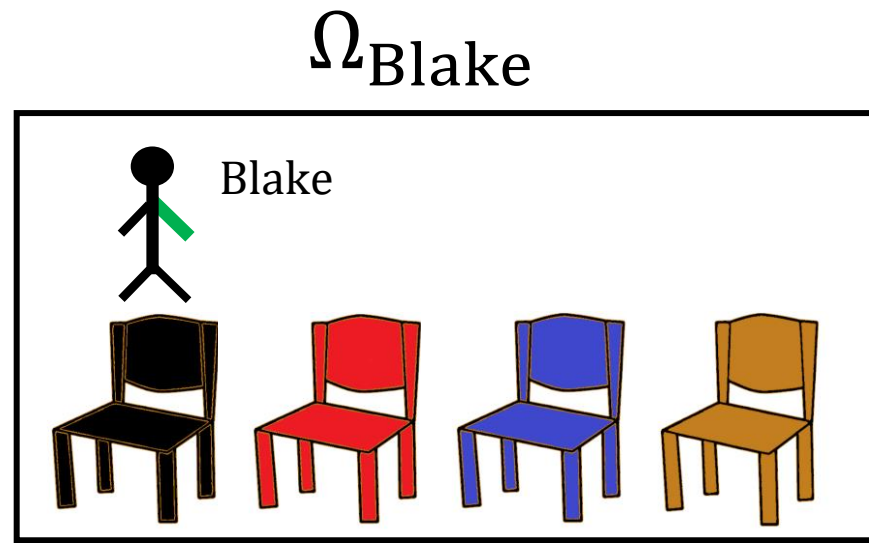


$\Omega_{\text{Blake} \leftrightarrow \text{Ahmed}}$

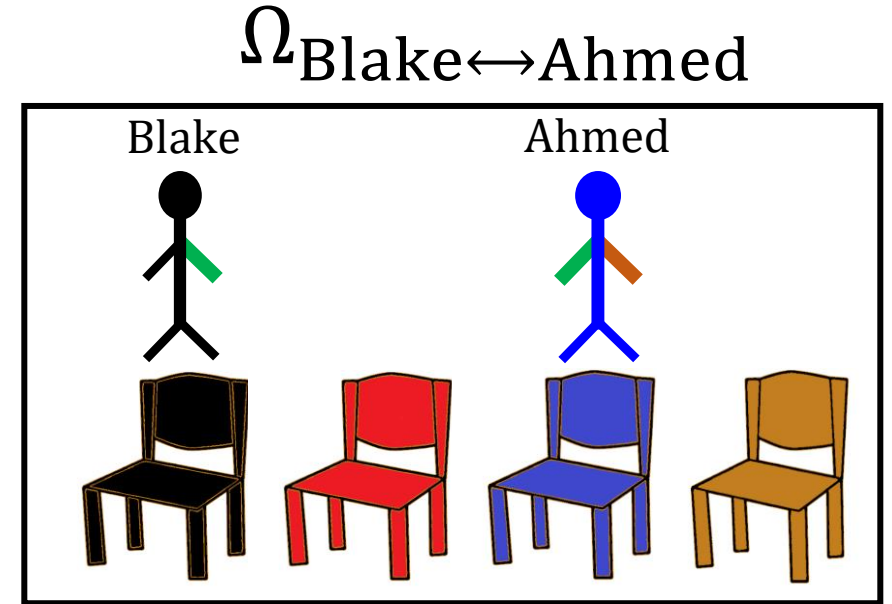


Information needed: $Q(\Omega_{\text{Blake} \rightarrow \text{Ahmed}})$

2 - Propagate information from the rest (No handshaking possibility).



Information given: $Q(\Omega_{\text{Blake}})$



Information needed: $Q(\Omega_{\text{Blake} \rightarrow \text{Ahmed}})$

$$Q(\Omega_{\text{Blake} \leftrightarrow \text{Ahmed}}) = \dots = e^{\frac{\text{sit}(\text{Ahmed}) + \text{sit_cost}}{c}} * Q(\Omega_{\text{Blake}})$$

$$Q(\Omega_p) = e^{\frac{sit(p)+sit_cost}{c}} * \left[\left(\sum_{\substack{p' \text{ is} \\ \text{direct neighbour}}} e^{\frac{handshake(p',p)}{c}} * Q(\Omega_{p'}) \right) + 1 + \sum_{\substack{p' \text{ is not} \\ \text{direct neighbour}}} Q(\Omega_{p'}) \right]$$

$$Q = 1 + \sum_p Q(\Omega_p)$$

$$Q(\Omega_p) = e^{\frac{sit(p)+sit_cost}{c}} * \left[\left(\sum_{\substack{p' \text{ is} \\ \text{direct neighbour}}} e^{\frac{handshake(p',p)}{c}} * Q(\Omega_{p'}) \right) + 1 + \sum_{\substack{p' \text{ is not} \\ \text{direct neighbour}}} Q(\Omega_{p'}) \right]$$

► **Theorem 2.** There is an $O(k^2N)$ time algorithm for the domain-level partition function for a 1D SDC of length N with $\leq k$ computation strands competing at each scaffold domain.

$$Q(\Omega_s) = e^{\frac{-\Delta G(M(s)) + \Delta G^{\text{assoc}}}{k_B T}} * \left[\sum_{s' \in LD_s} \left(e^{\frac{-\Delta G(R(s'), L(s))}{k_B T}} * Q(\Omega_{s'}) \right) + 1 + \sum_{\substack{s' < s \\ s' \notin LD_s}} Q(\Omega_{p'}) \right]$$

$$Q = 1 + \sum_{s \in T} Q(\Omega_s)$$

■ **Algorithm 2** 1D SDC partition function algorithm. The proof of Theorem 2 argues that this algorithm returns Z^S as defined in Equation (6). Note that arrays are indexed from 1, and recall that k_1, \dots, k_N are the counts of competing strands at scaffold domains d_1, \dots, d_N , and we let s_i^j be the j^{th} strand competing at domain d_i . See Figure 9.

```

1:  $Z_{\text{curr}} = [0, 0, \dots, 0]$       ▷ size  $k = \max(k_1, \dots, k_N)$ , current (partial) partition function
2:  $Z_{\text{prev}} = [0, 0, \dots, 0]$     ▷ size  $k = \max(k_1, \dots, k_N)$ , previous (partial) partition function
3:  $Z^S \leftarrow 1$ ;  $\text{sum}_a \leftarrow 0$ 
4: for  $i \leftarrow 1 \dots N$  do
5:    $\text{sum}_a \leftarrow \text{sum}_a + \sum_{i \in \{1, \dots, k\}} Z_{\text{prev}}[i]$       ▷  $\text{sum}_a$ : rightmost summation Equation (7)
6:    $Z_{\text{prev}} \leftarrow Z_{\text{curr}}$ 
7:    $Z_{\text{curr}} = [0, 0, \dots, 0]$ 
8:   for  $j \leftarrow 1 \dots k_i$  do                                ▷ each iteration computes Equation (7) for a strand
9:      $t_1 = e^{-(\Delta G(d^M(s_i^j)) + \Delta G^{\text{assoc}})/k_B T}$ 
10:    if  $i = 1$  then                                          ▷ first domain where is no neighbors at all
11:       $Z_{\text{curr}}[j] = t_1$ 
12:    else
13:       $t_2 \leftarrow 0$ 
14:      for  $m \leftarrow 1 \dots k_{i-1}$  do
15:         $t_2 \leftarrow t_2 + \left( e^{-(\Delta G(d^R(s_{i-1}^m), d^L(s_i^j)))/k_B T} \right) \cdot Z_{\text{prev}}[m]$ 
16:      end for
17:       $Z_{\text{curr}}[j] \leftarrow t_1 + t_2 + \text{sum}_a$ 
18:    end if
19:     $Z^S \leftarrow Z^S + Z_{\text{curr}}[j]$                                 ▷ computing Equation (6)
20:  end for
21: end for
22: return  $Z^S$ 

```

► **Theorem 1.** There is an $O(k^2N)$ time algorithm to determine the domain-level MFE for a 1D SDC of length N with $\leq k$ computation strands competing at each scaffold domain.

$$M^{\mathcal{S}} = \min_{s \in C_{d_N}} \{M_s^{\mathcal{S}}\}$$

$$M_s^{\mathcal{S}} = \Delta G(d^{\text{M}}(s)) + \Delta G^{\text{assoc}} + \min_{s' \in L_s} \{M_{s'}^{\mathcal{S}} + \Delta G(d^{\text{R}}(s'), d^{\text{L}}(s))\}$$

■ **Algorithm 1** 1D SDC MFE algorithm. The proof of Theorem 1 proof shows that this algorithm returns the value $M^{\mathcal{S}}$ defined in Equation (4). Note that arrays are indexed from 1. Notation: k_1, \dots, k_N are the counts of competing strands at scaffold domains d_1, \dots, d_N . Let s_i^j be the j^{th} strand competing at domain d_i .


```

1:  $M_{\text{curr}} = [0, 0, \dots, 0]$                                 ▷ size  $k = \max(k_1, \dots, k_N)$  for current MFES
2:  $M_{\text{prev}} = [0, 0, \dots, 0]$                                 ▷ size  $k = \max(k_1, \dots, k_N)$  for previous MFES
3: for  $i \leftarrow 1 \dots N$  do                                  ▷ index scaffold domains
4:    $M_{\text{prev}} \leftarrow M_{\text{curr}}$ 
5:   for  $j \leftarrow 1 \dots k_i$  do                            ▷ index computational strands at scaffold domain  $d_i$ 
6:     if  $i = 1$  then                                        ▷ first scaffold domain, has no left neighbour
7:        $M_{\text{curr}}[j] \leftarrow \Delta G(d^{\text{M}}(s_i^j))$ 
8:     else
9:       ▷  $O(k)$  steps to choose min and bind scaffold + entropic penalty
10:       $M_{\text{curr}}[j] \leftarrow [\min_{m \in \{1, 2, \dots, k_{i-1}\}} (M_{\text{prev}}[m] + \Delta G(d^{\text{R}}(s_{i-1}^m), d^{\text{L}}(s_i^j)))$ 
           $+ \Delta G(d^{\text{M}}(s_i^j)) + \Delta G^{\text{assoc}}]$ 
11:    end if
12:  end for
13: end for
14:  $M^{\mathcal{S}} \leftarrow \min_{k' \in \{1, 2, \dots, k_N\}} M_{\text{curr}}[k']$     ▷  $O(k)$  steps implement Equation (4) giving  $M^{\mathcal{S}}$ 
15: return  $M^{\mathcal{S}}$ 

```

GOAL

At equilibrium

$$\Pr\left[\leftarrow \begin{array}{cccc} \text{||} & \text{||} & \text{||} & \text{||} \\ \text{---} & \text{---} & \text{---} & \text{---} \\ \text{---} & \text{---} & \text{---} & \text{---} \\ \text{---} & \text{---} & \text{---} & \text{---} \end{array} \right] \gg \sum_c \Pr[c : \textit{is another configuration}]$$


Efficiently

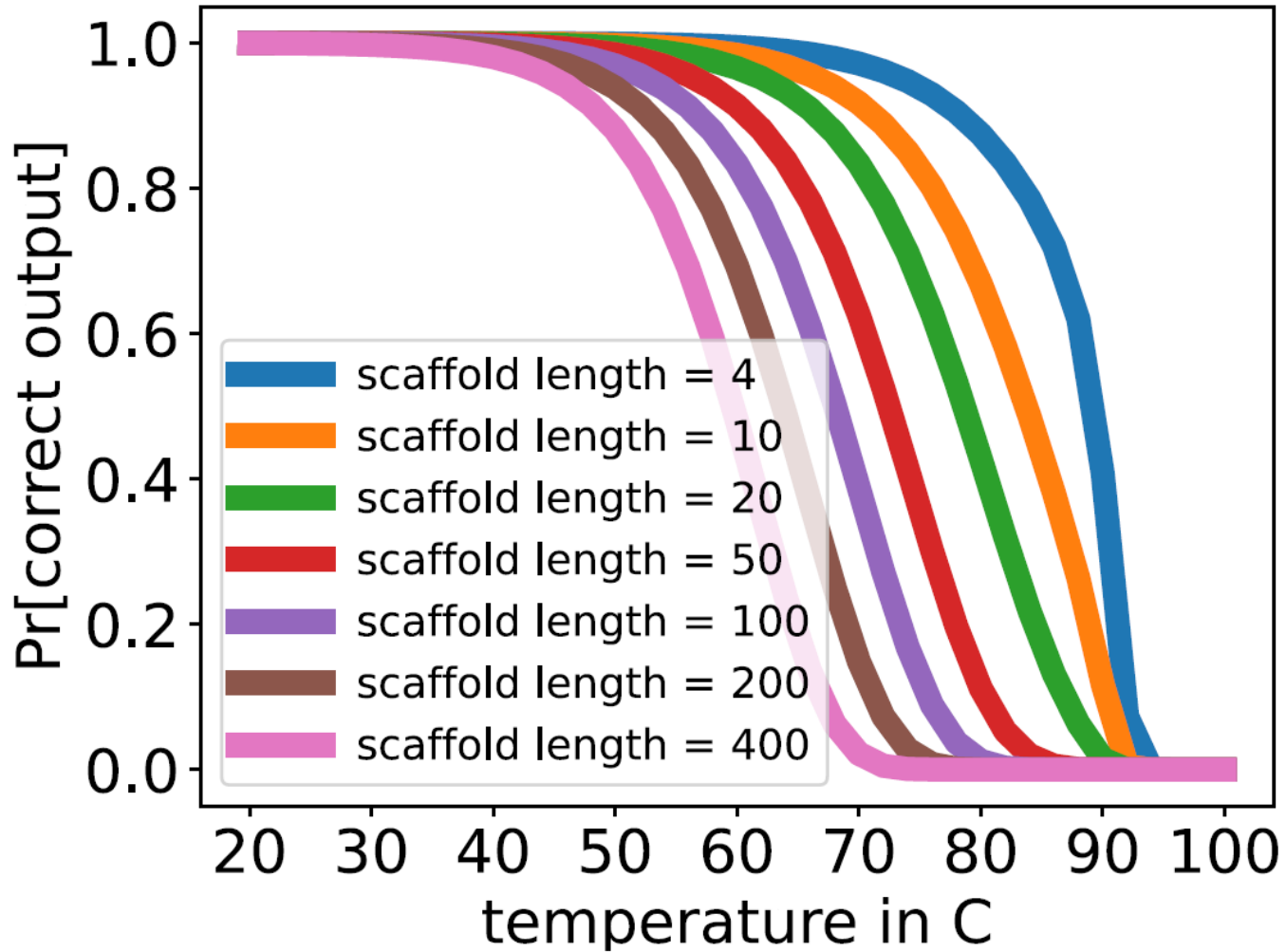


GOAL

At equilibrium

$$\Pr[\text{← scaffold with 4 red segments}] \gg \sum_c \Pr[c : \text{is another configuration}]$$


Efficiently



Benefits of Domain Based models !!

Previous: 1 simulation of length 13
Now: 280 simulations in 20 min [800 strands]

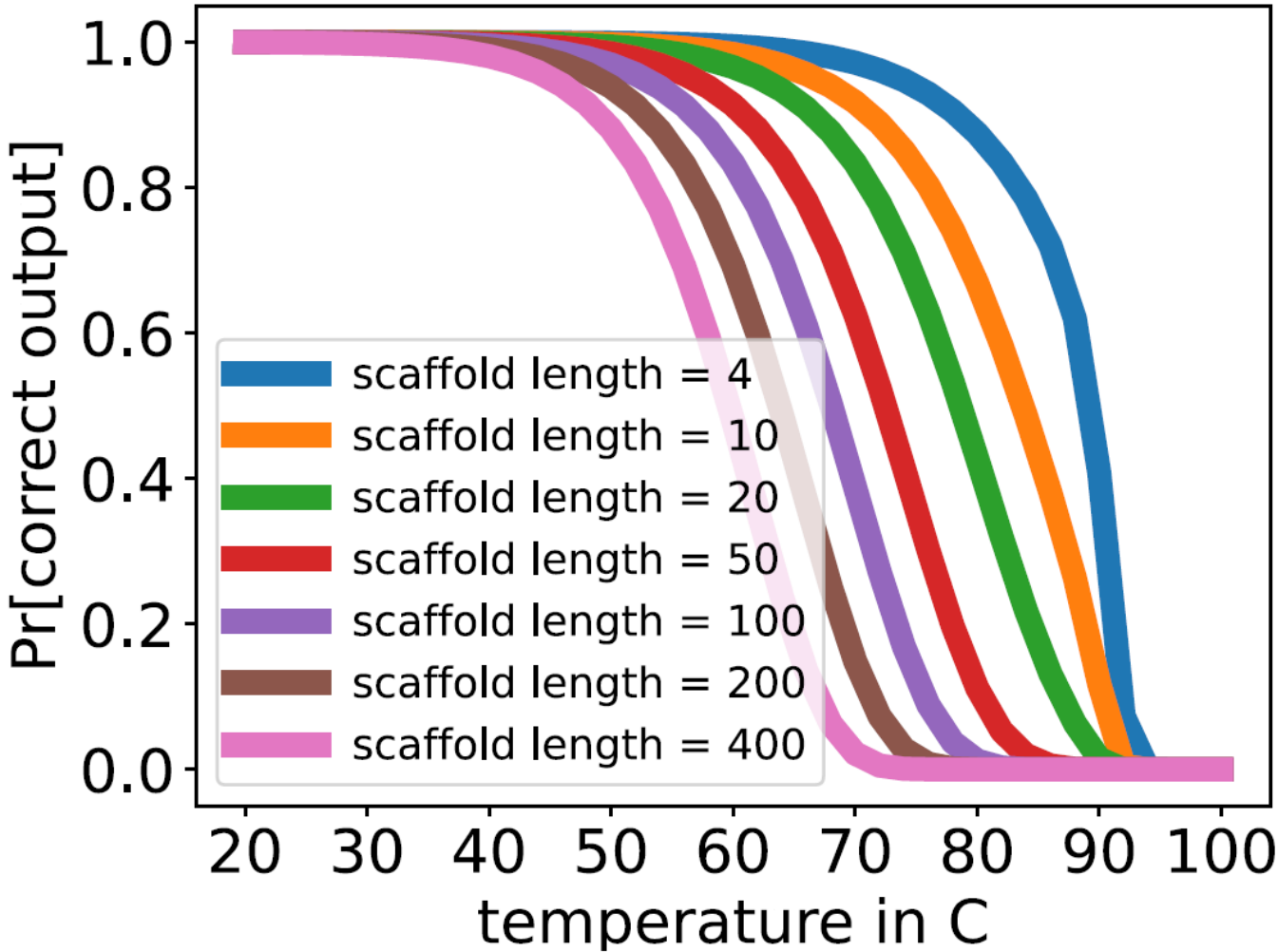
GOAL

At equilibrium



$$\Pr[\text{← scaffold with 4 binding sites}] \gg \sum_c \Pr[c : \text{is another configuration}]$$

Efficiently



Benefits of Domain Based models !!

Previous: 1 simulation of length 13
Now: 280 simulations in 20 min [800 strands]

Thanks



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