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DRESDEN LEIPZIG

CENTER FOR SCALABLE DATA ANALYTICS AND ARTIFICIAL INTELLIGENCE

38th TBI Winterseminar in Bled
February 2023

Talk: **Comparison of Atom Maps**

Speaker: **PhD student - Marcos E. Gonzalez Laffitte**

Advisor: **Prof. Dr. Peter F. Stadler**

A work in collaboration with Nora Beier and Nico Domschke

Bioinformatik Uni Leipzig
ScaDS.AI Leipzig

GEFÖRDERT VOM

Bundesministerium für Bildung und Forschung

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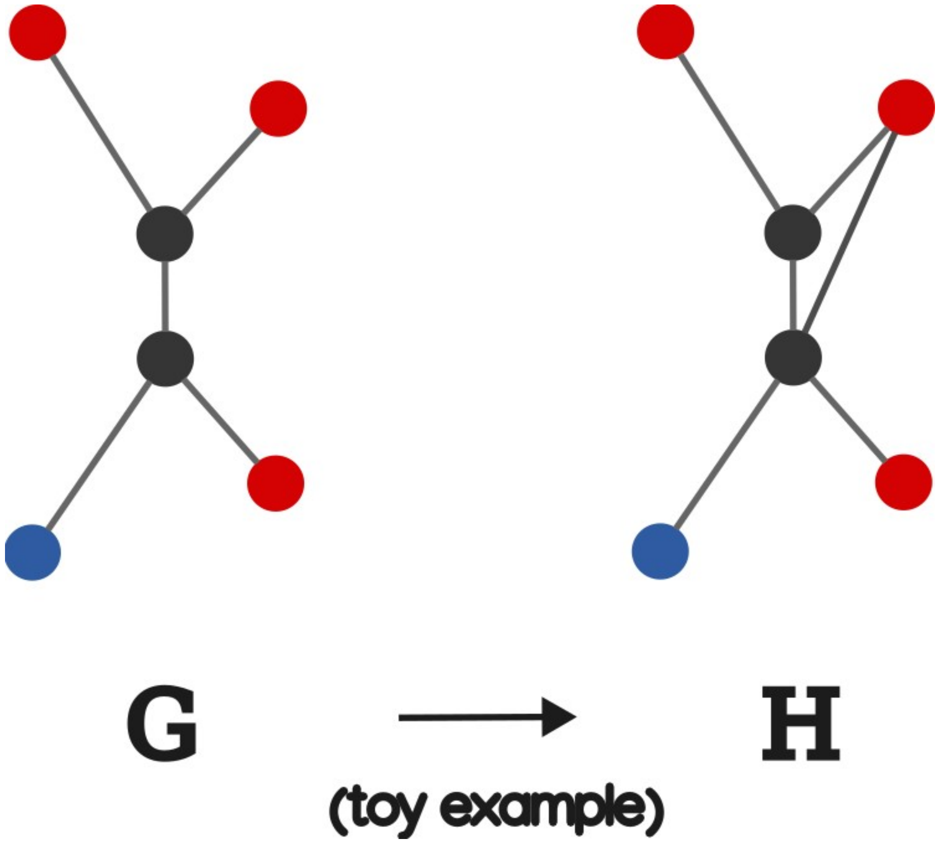
Introduction: Atom-to-Atom Maps

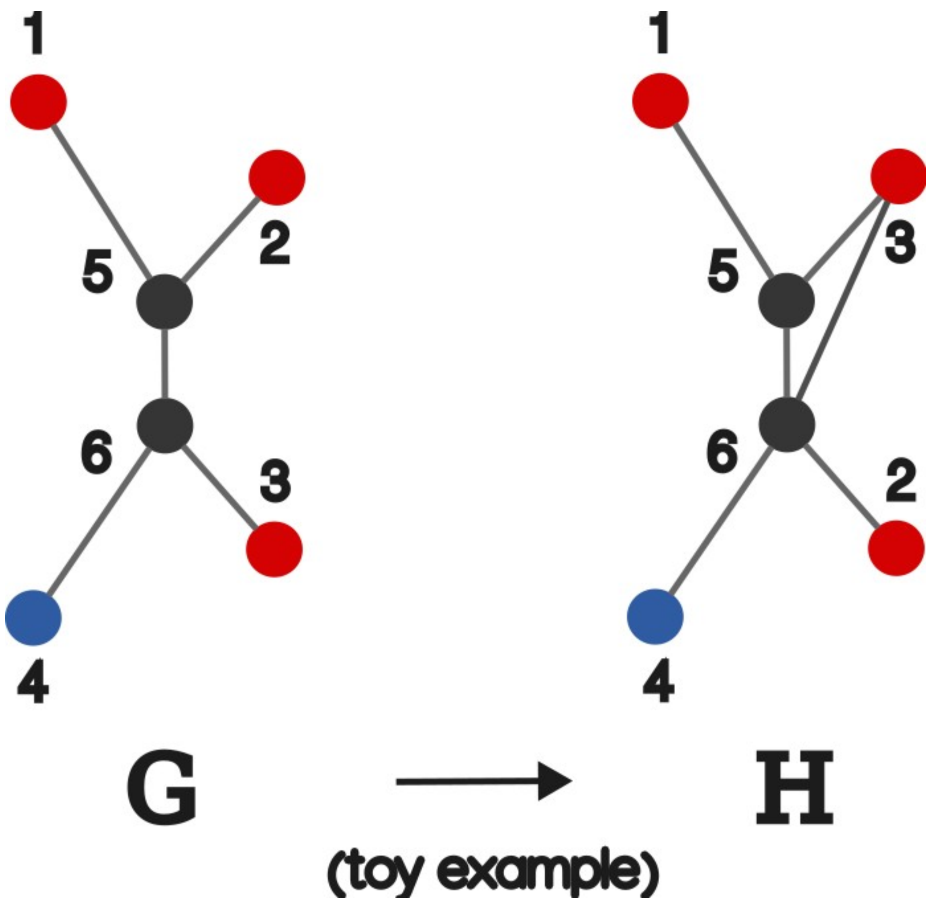


Intuitively speaking an **atom map** is a one-to-one correspondence describing how the atoms in the reactants have to be rearrange in order to obtain the products of a chemical reaction, thus *encoding* the mechanism of the reaction.

Definition

Let G and H be two simple graphs with associated vertex labelings $a_G : V(G) \to L_V$ and $a_H : V(H) \to L_V$. An **atom map** from G to H is a bijection $\alpha : V(G) \to V(H)$ which preserves vertex labels, i.e., $a_H(\alpha(x)) = a_G(x)$ for all $x \in V(G)$.

Introduction: Atom-to-Atom Maps



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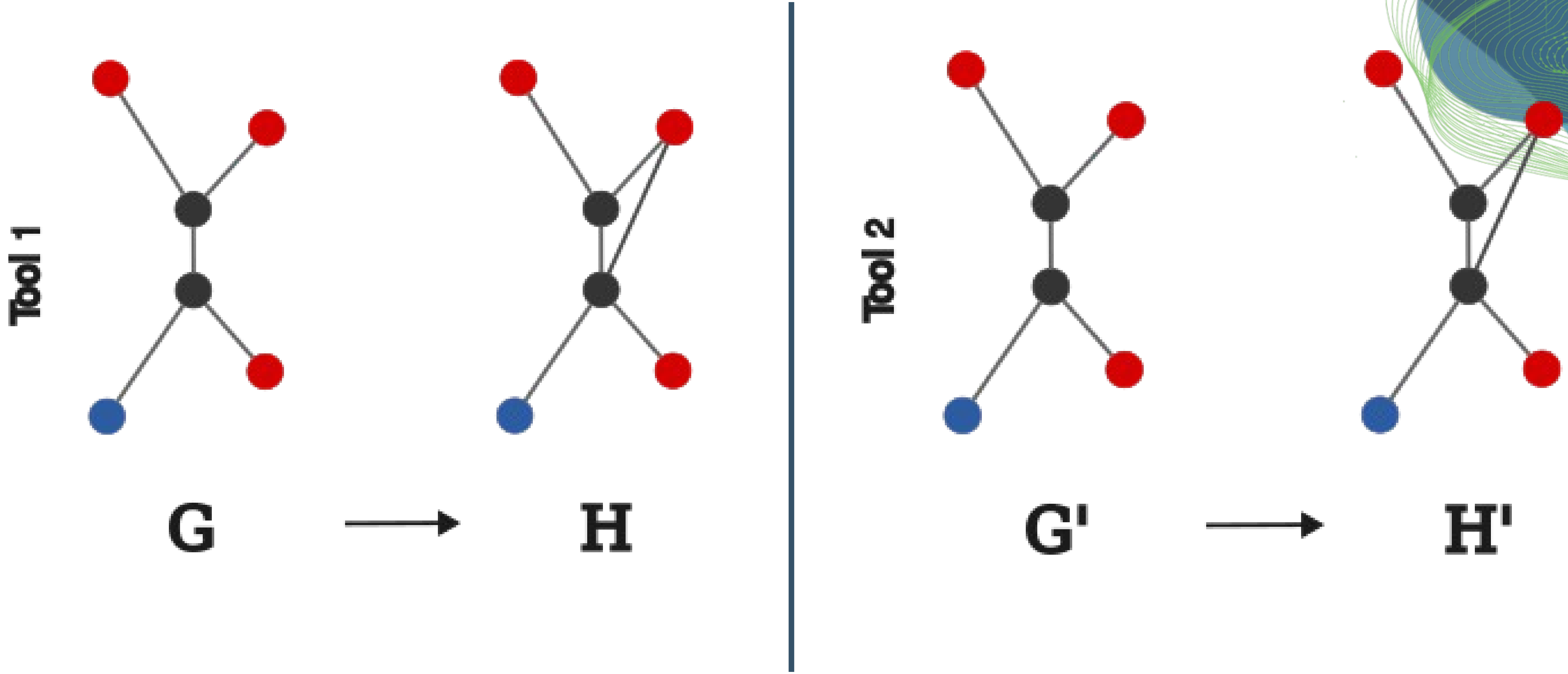
Problem: How do we know if two Atom Maps *encode* the same information or not?



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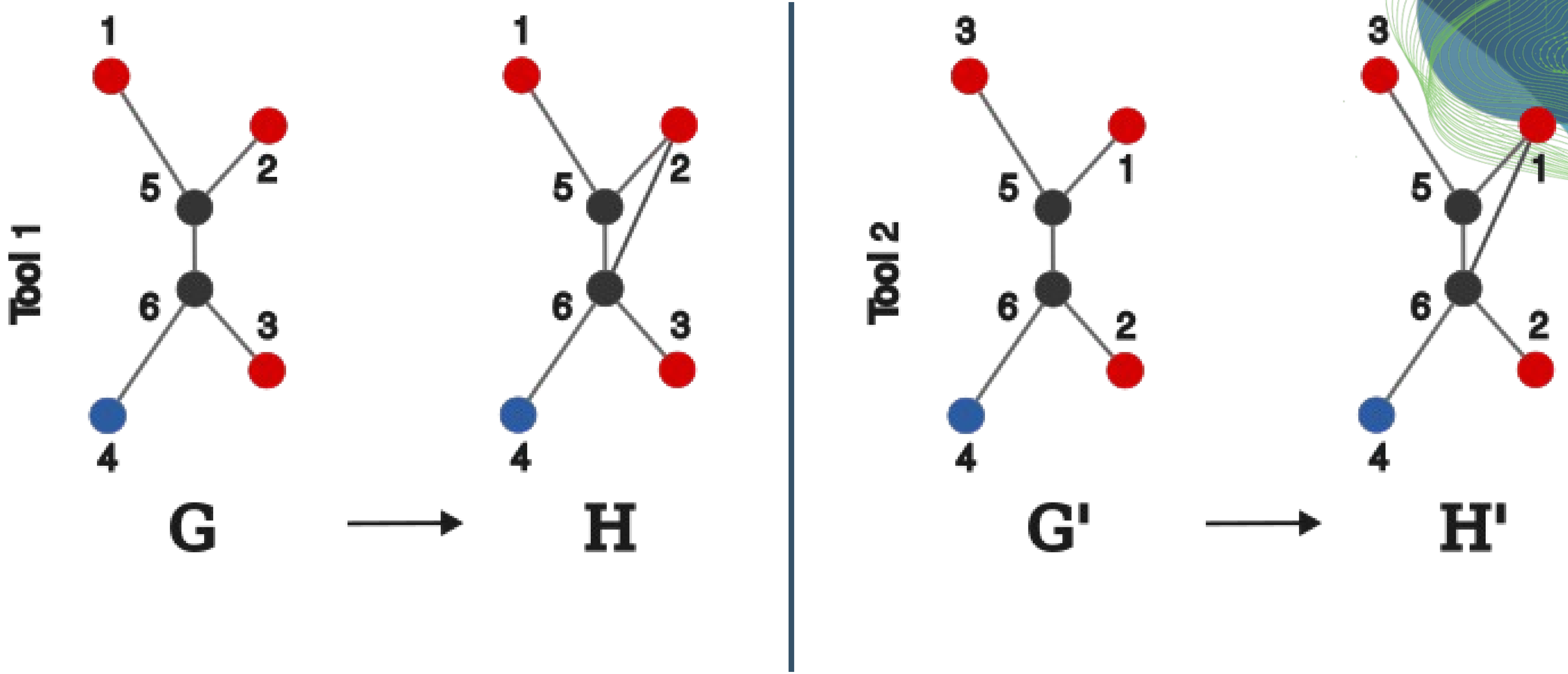

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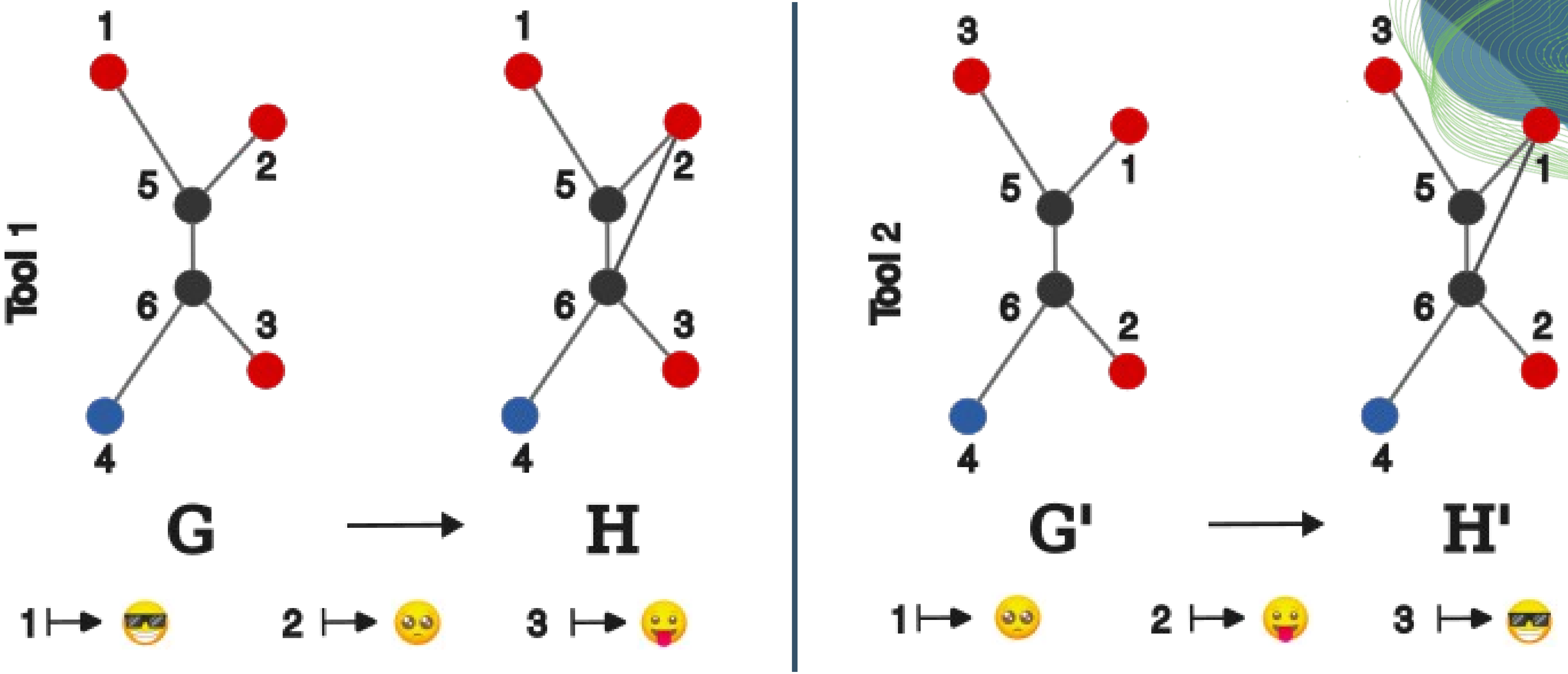

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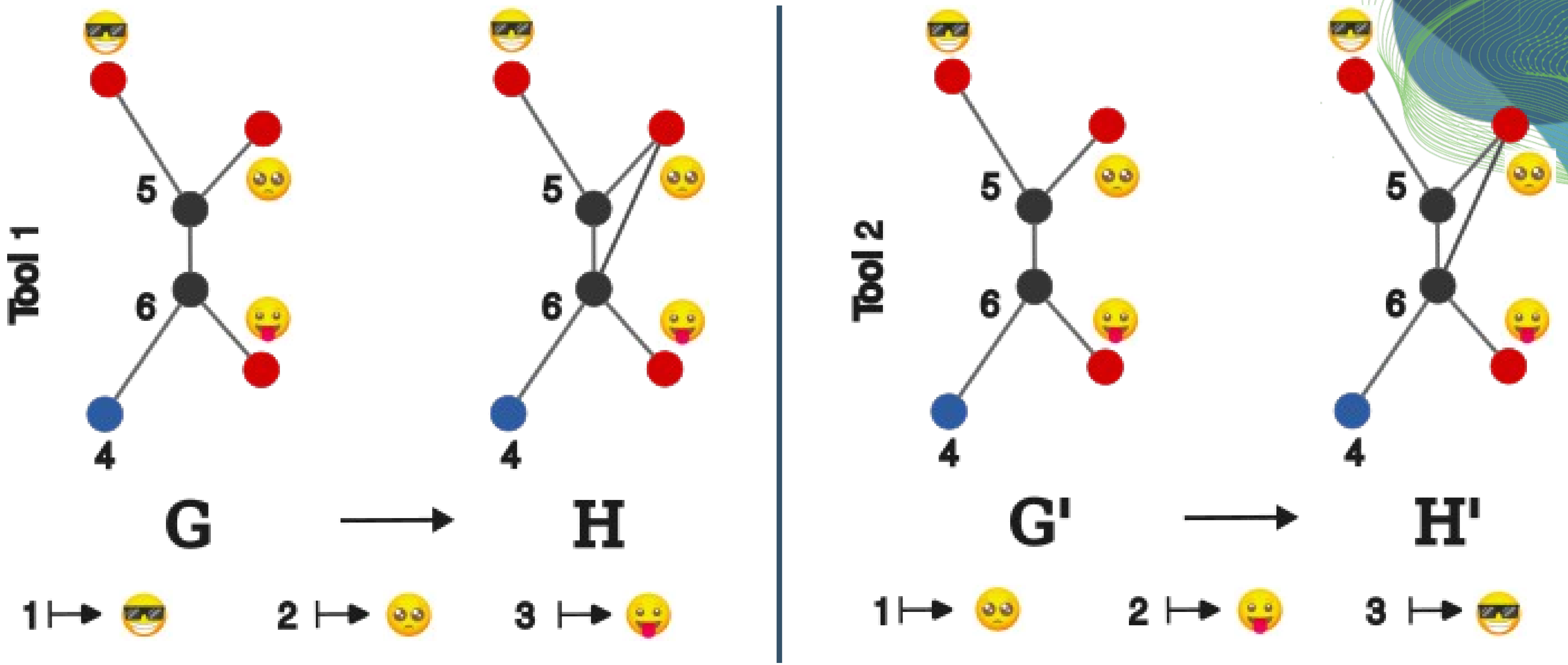
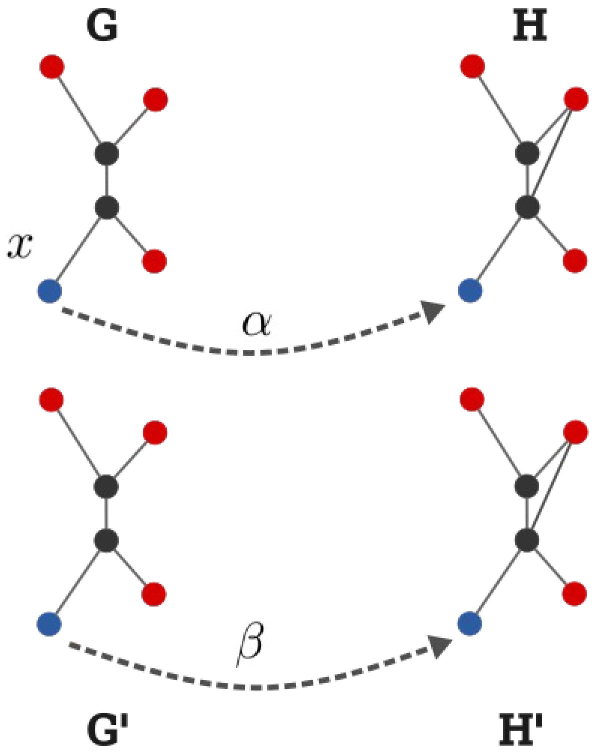


Defining Equivalent Atom Maps

(Motivation)



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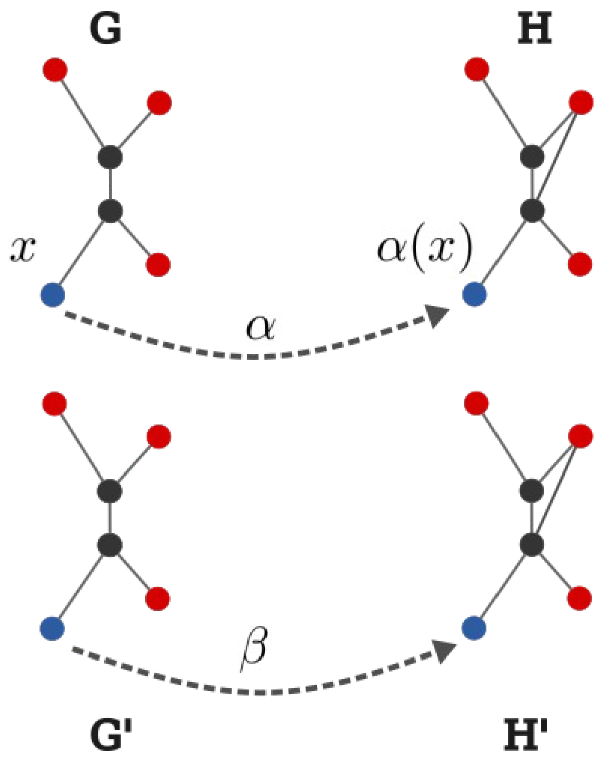

$\alpha(x) =$

Defining Equivalent Atom Maps

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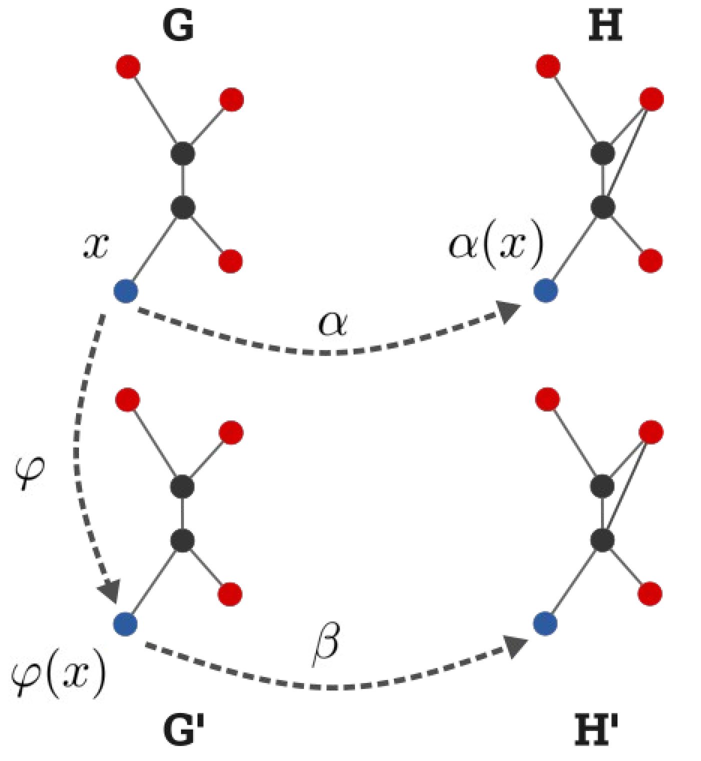

$\alpha(x) = \quad \varphi(x) \quad \text{for } \varphi \in Iso^L(G, G')$

Defining Equivalent Atom Maps

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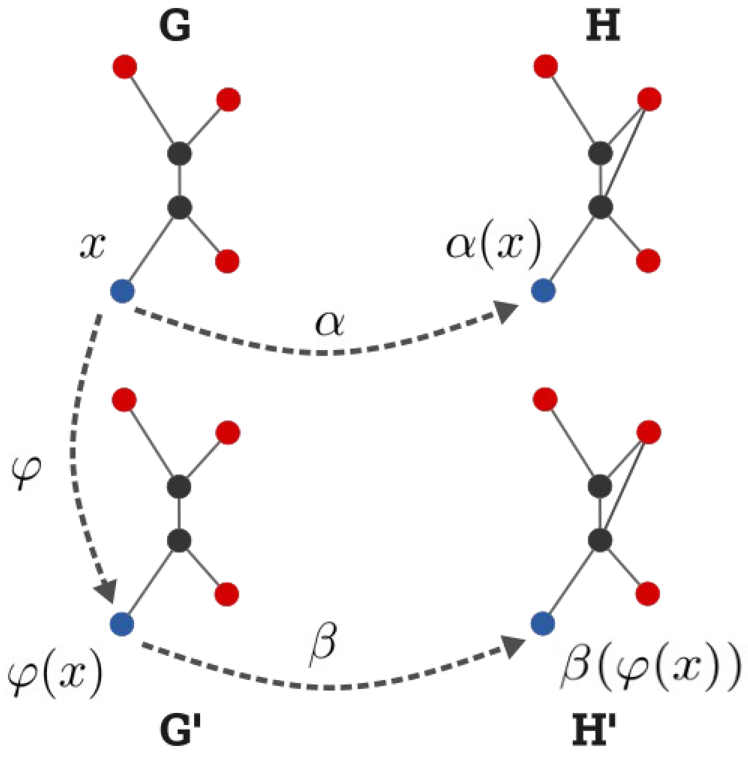
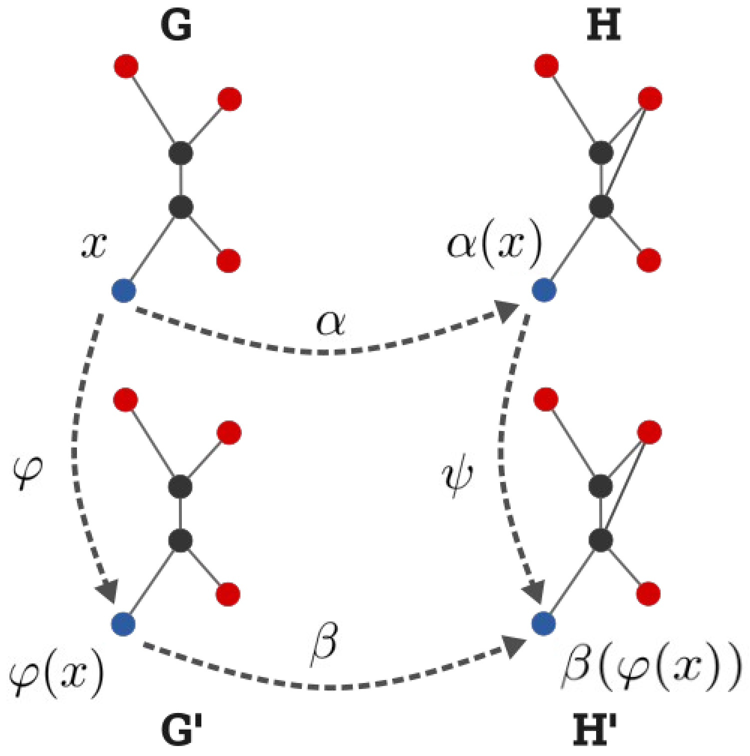


$$\alpha(x) = \quad \beta(\varphi(x)) \quad \text{for } \varphi \in Iso^L(G, G')$$

Defining Equivalent Atom Maps

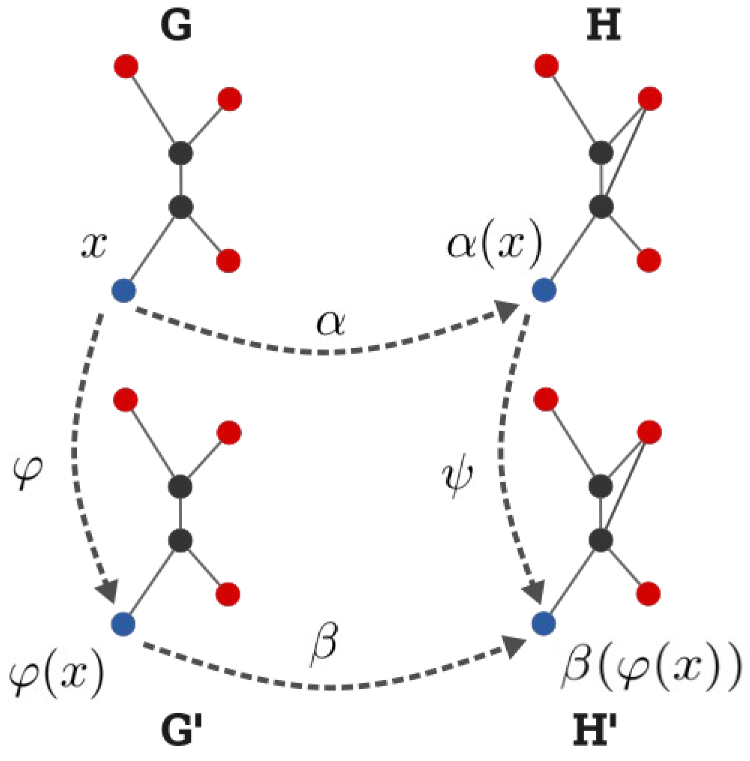
(Motivation)



$$\alpha(x) = \psi^{-1}(\beta(\varphi(x))), \text{ for } \varphi \in Iso^L(G, G'), \psi \in Iso^L(H, H')$$

Defining Equivalent Atom Maps

(Motivation)



$$\alpha(x) = \psi^{-1}(\beta(\varphi(x))), \text{ for } \varphi \in Iso^L(G, G'), \psi \in Iso^L(H, H')$$
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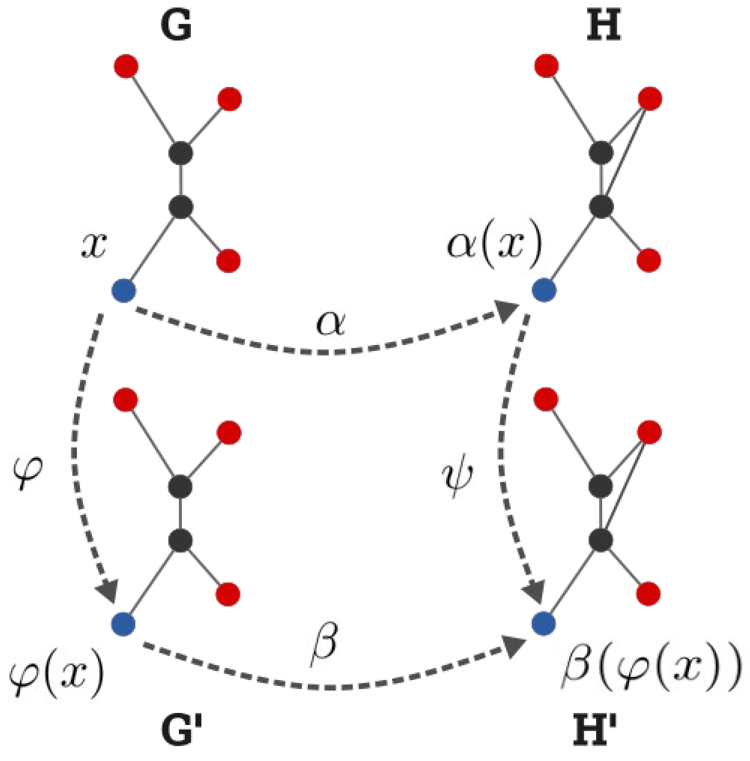

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$$\text{for all } x \in V(G)$$

Definition

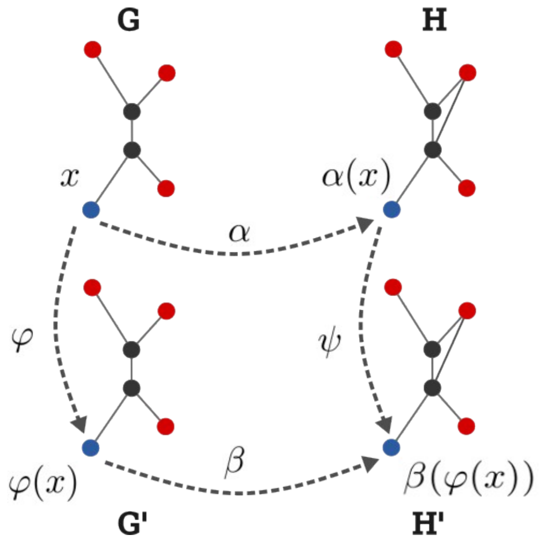
We say that two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are **equivalent**, in symbols $\alpha \equiv \beta$, if there are $\varphi \in Iso^L(G, G')$ and $\psi \in Iso^L(H, H')$ such that $\psi \circ \alpha = \beta \circ \varphi$.

Lemma

The equivalence of atom maps, $\equiv$, is an equivalence relation.

Idea of the proof. Follows since the identity, and the inverses and the compositions of isomorphisms, are all isomorphisms.

Comparing Atom Maps
Method 1: [ISO-$\equiv$] Exhaustive Enumeration of Isomorphisms

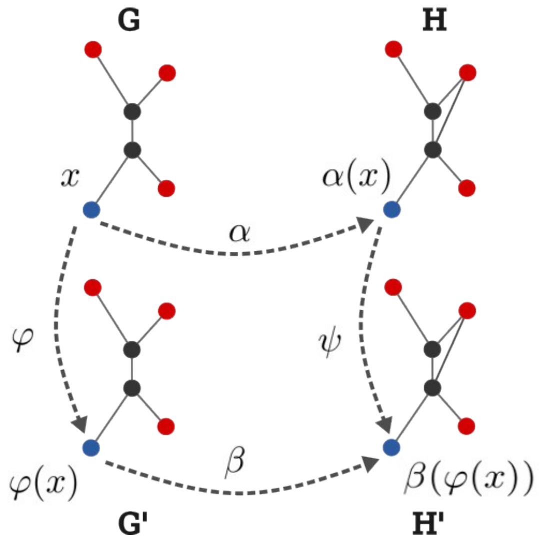


forall $\varphi \in Iso^L(G, G')$ **do**
  forall $\psi \in Iso^L(H, H')$ **do**
    if ($\psi = \beta \circ \varphi \circ \alpha^{-1}$) **then**
      return ($"\alpha \equiv \beta", \varphi, \psi$)
    end
  end
end

Definition

We say that two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are **equivalent**, in symbols $\alpha \equiv \beta$, if there are $\varphi \in Iso^L(G, G')$ and $\psi \in Iso^L(H, H')$ such that $\psi \circ \alpha = \beta \circ \varphi$.

Comparing Atom Maps
Method 1: [ISO-≡] Exhaustive Enumeration of Isomorphisms




```
forall φ ∈ Iso^L(G, G') do
    forall ψ ∈ Iso^L(H, H') do
        if ( ψ = β ∘ φ ∘ α^{-1} ) then
            return ( "α ≡ β", φ, ψ )
        end
    end
end
```

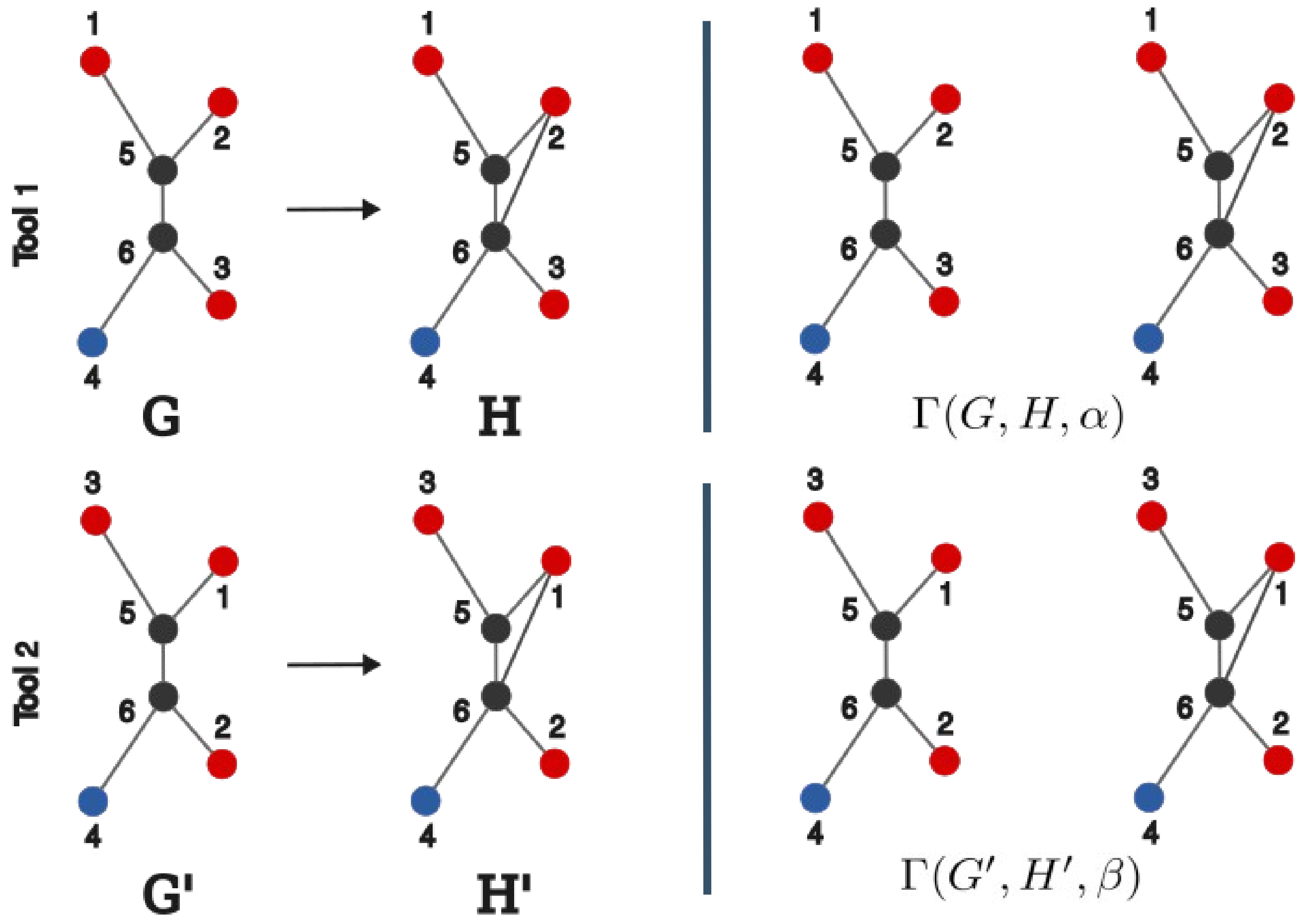
Definition

We say that two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are **equivalent**, in symbols $\alpha \equiv \beta$, if there are $\varphi \in Iso^L(G, G')$ and $\psi \in Iso^L(H, H')$ such that $\psi \circ \alpha = \beta \circ \varphi$.

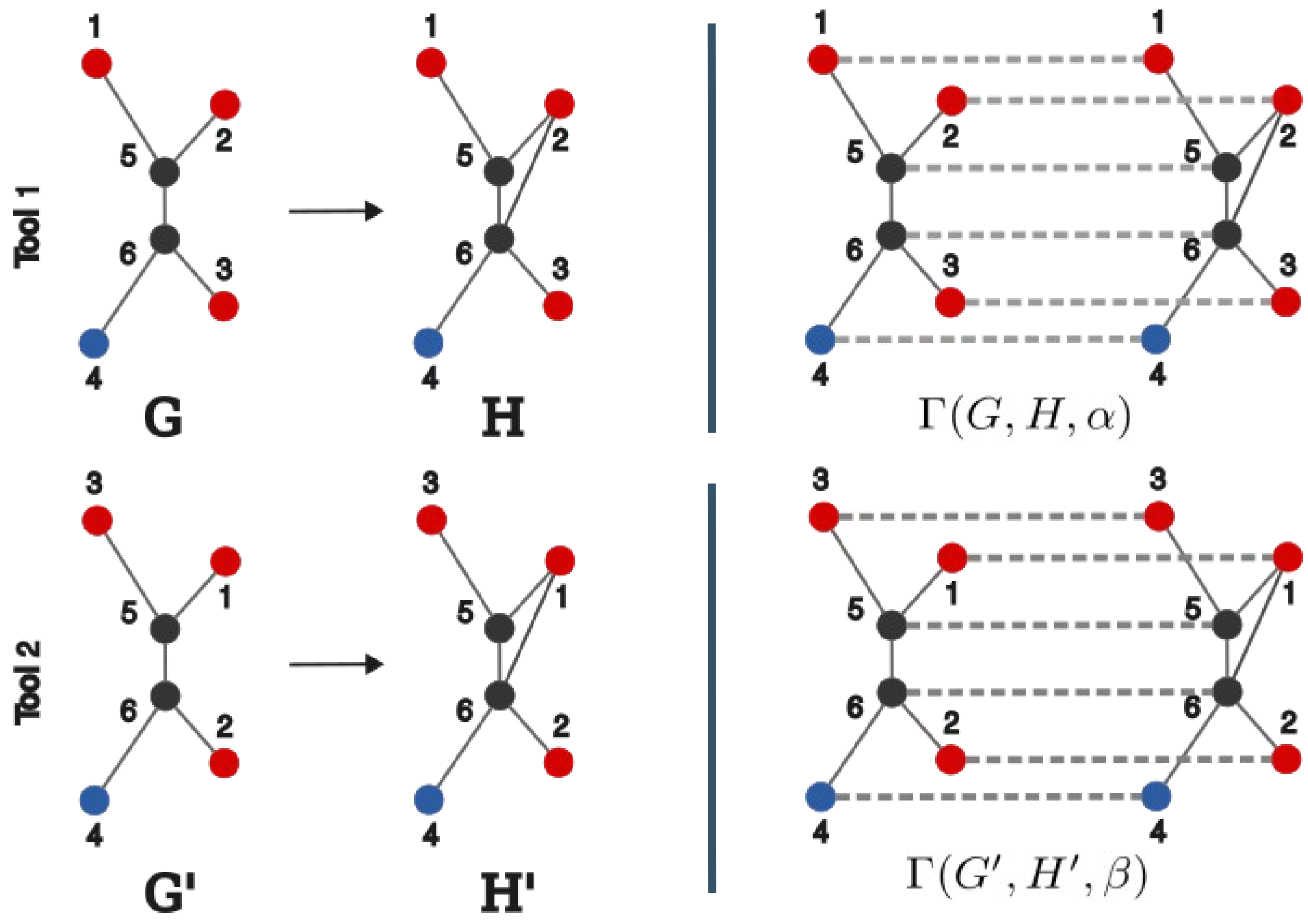
Lemma

Two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are equivalent iff there is $\varphi \in \mathrm{Iso}^L(G, G')$ such that $\beta \circ \varphi \circ \alpha^{-1} \in \mathrm{Iso}^L(H, H')$.

Comparing Atom Maps
Method 2: [AUX-Γ] Comparison of Auxiliary Graphs



Comparing Atom Maps
Method 2: [AUX-Γ] Comparison of Auxiliary Graphs



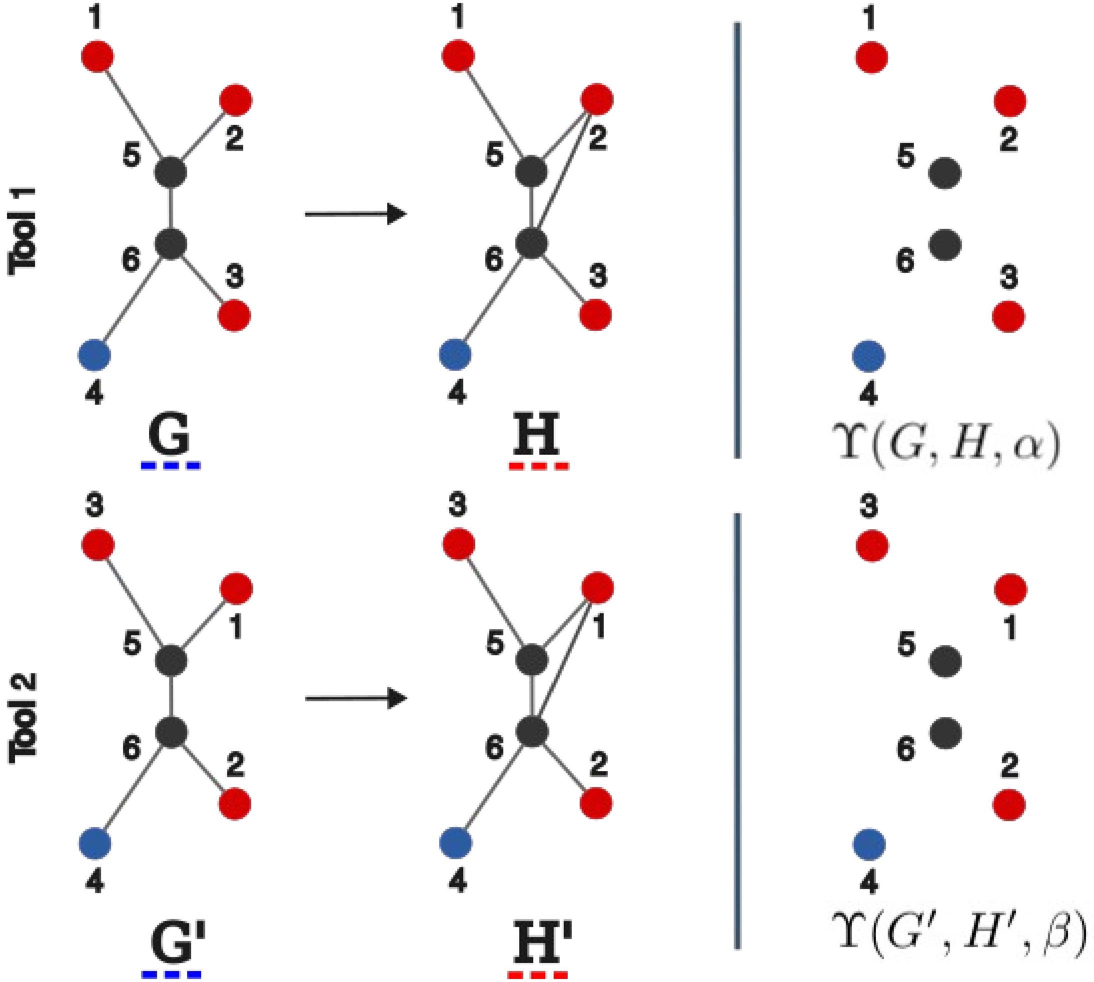
Theorem

Two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are equivalent **iff** their labeled auxiliary graphs are isomorphic, that is, $\Gamma(G, H, \alpha) \simeq \Gamma(G', H', \beta)$.

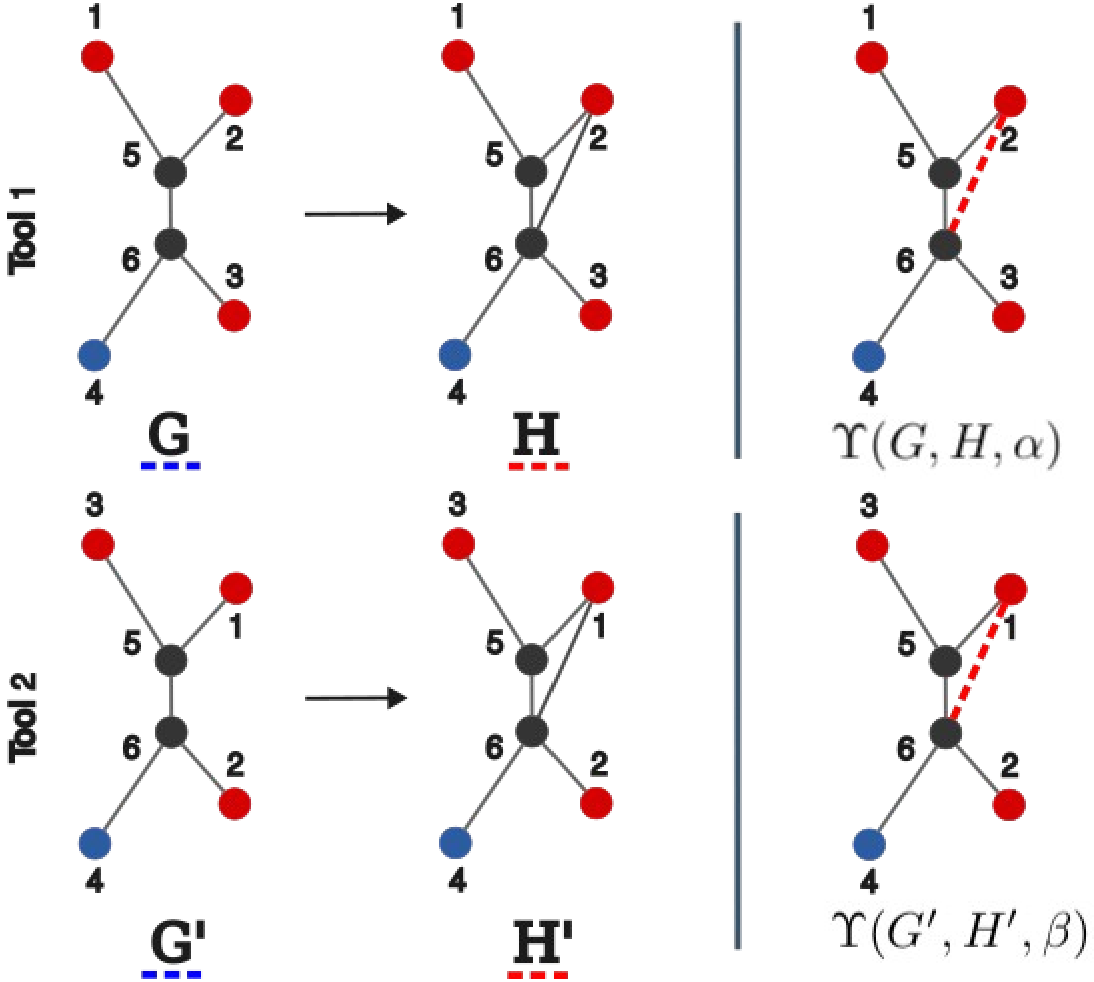
Idea of the proof.

If $\alpha \equiv \beta$ there are $\varphi \in \mathrm{Iso}^L(G, G')$ and $\psi \in \mathrm{Iso}^L(H, H')$ such that $\psi \circ \alpha = \beta \circ \varphi$ and so $\zeta := \varphi \dot\cup \psi$ can be proven to be an isomorphism from $\Gamma(G, H, \alpha)$ to $\Gamma(G', H', \beta)$. On the other hand, given an isomorphism ζ from $\Gamma(G, H, \alpha)$ to $\Gamma(G', H', \beta)$ one can prove that the restrictions ζ_G and ζ_H of ζ to, respectively, $V(G)$ and $V(H)$, are isomorphisms $\zeta_G \in \mathrm{Iso}^L(G, G')$ and $\zeta_H \in \mathrm{Iso}^L(H, H')$, satisfying $\zeta_H \circ \alpha = \beta \circ \zeta_G$, provided that the vertices in $\Gamma(G, H, \alpha)$ have labels of the form $(a_G(x), 1)$ if $x \in V(G)$ and $(a_H(x), 2)$ if $x \in V(H)$, and similarly for $\Gamma(G', H', \beta)$.

Comparing Atom Maps
Method 3: [ITS-ϒ] Comparison of Imaginary Transition Structures



Comparing Atom Maps
Method 3: [ITS-Υ] Comparison of Imaginary Transition Structures



Corollary

Two atom maps $\alpha : V(G) \to V(H)$ and $\beta : V(G') \to V(H')$ are equivalent **iff** their ITS graphs are isomorphic, that is, $\Upsilon(G, H, \alpha) \simeq \Upsilon(G', H', \beta)$.

Idea behind the main theorem.

The main theorem makes use of (a version of) the labeled auxiliary graphs $\Gamma(G, H, \alpha)$ and $\Gamma(G', H', \beta)$. Intuitively speaking the restriction to $V(G)$ of an isomorphism ζ from $\Gamma(G, H, \alpha)$ to $\Gamma(G', H', \beta)$ is an isomorphism from $\Upsilon(G, H, \alpha)$ to $\Upsilon(G', H', \beta)$. On the other hand, an isomorphism ξ from $\Upsilon(G, H, \alpha)$ to $\Upsilon(G', H', \beta)$ can be *extended* into an isomorphism θ from $\Gamma(G, H, \alpha)$ to $\Gamma(G', H', \beta)$ by setting $\theta(x) = \xi(x)$ for $x \in V(G)$ and $\theta(x) = \beta(\xi(\alpha^{-1}(x)))$ if $x \in V(H)$.

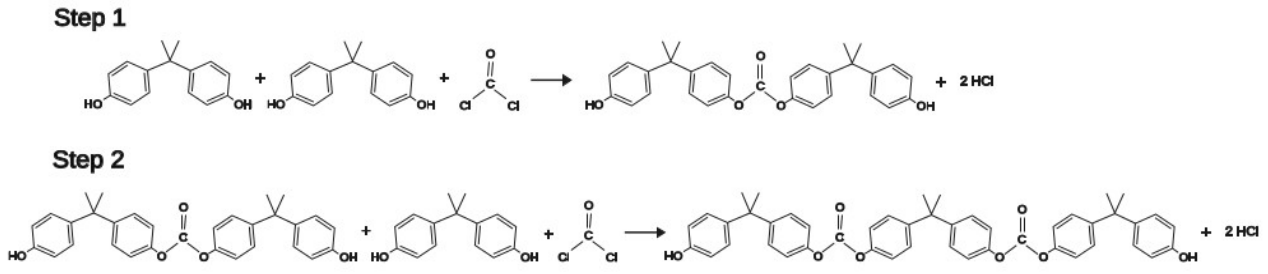
The ITS graphs were first introduced by Shinsaku Fujita in **Description of organic reactions based on imaginary transition structures. 1. introduction of new concepts**, J. Chem. Inf. Comput. Sci. 26 **(1986)** 205–212.

Later another version of them was introduced as *Condensed Graph of a Reaction* (or CGR) by Hoonakker et.al., in **A representation to apply usual data mining techniques to chemical reactions – illustration on the rate constant of SN2 reactions in water**, Int. J. Artif. Intelligence Tools 20 **(2011)** 253–270.

Computational Implementation and Running Time Comparison of the three Methods

We implemented the three methods mentioned before and analyzed the output of three existing Atom-Mapping Tools: RXNMapper, RDT and GraphormerMapper.

Polycondensation of bisphenol A (BPA) and phosgene

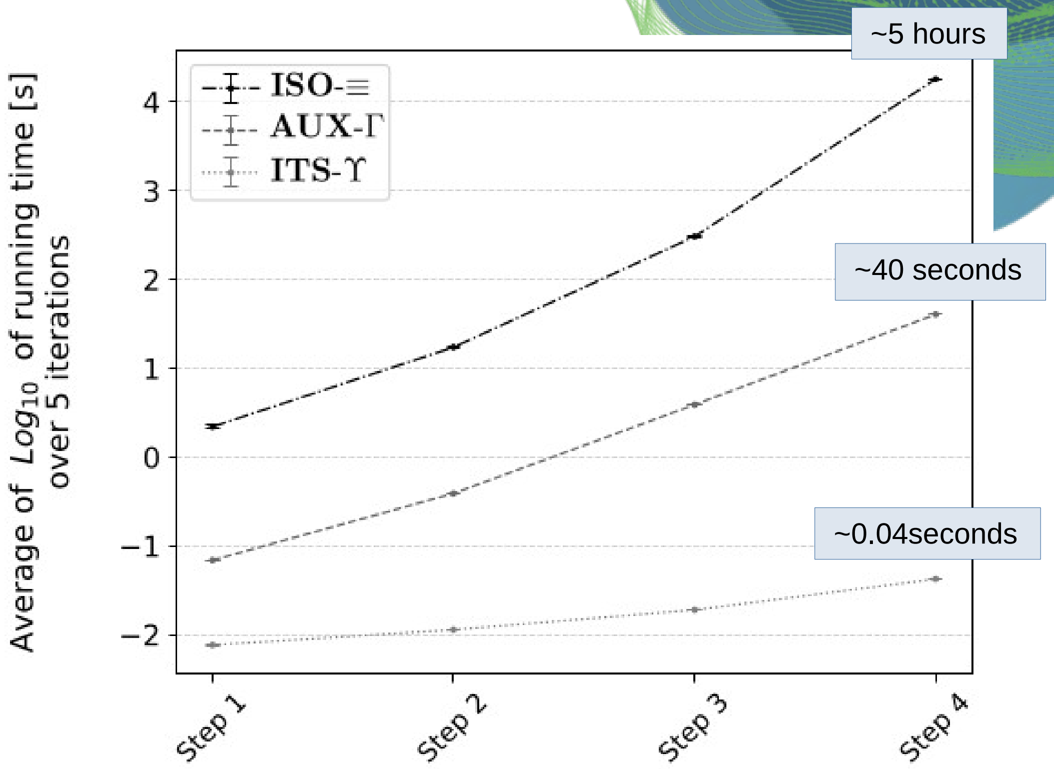


Step 1 $|\mathrm{Aut}(G)| = 1024$ $|\mathrm{Aut}(H)| = 256$

Step 2 $|\mathrm{Aut}(G)| = 4096$ $|\mathrm{Aut}(H)| = 2048$

Step 3 $|\mathrm{Aut}(G)| = 32,768$ $|\mathrm{Aut}(H)| = 16,384$

Step 4 $|\mathrm{Aut}(G)| = 262,144$ $|\mathrm{Aut}(H)| = 131,072$



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Comparison of Atom Maps

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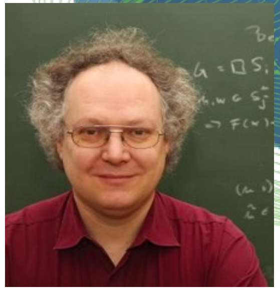

Peter F. Stadler

EEquAAM - Github Repository
Evaluation of the Equivalence of Atom-to-Atom Maps

- A. Lin et.al., **Atom-to-atom mapping: A benchmarking study of popular mapping algorithms and consensus strategies**, Molecular Inf. 41 **(2021)** 2100138.

- R. Nugmanov et.al, **Bidirectional graphormer for reactivity understanding: Neural network trained to reaction atom-to-atom mapping task**, Journal of Chemical Information and Modeling 62 **(2022)** 3307–3315.

Thank you for your attention

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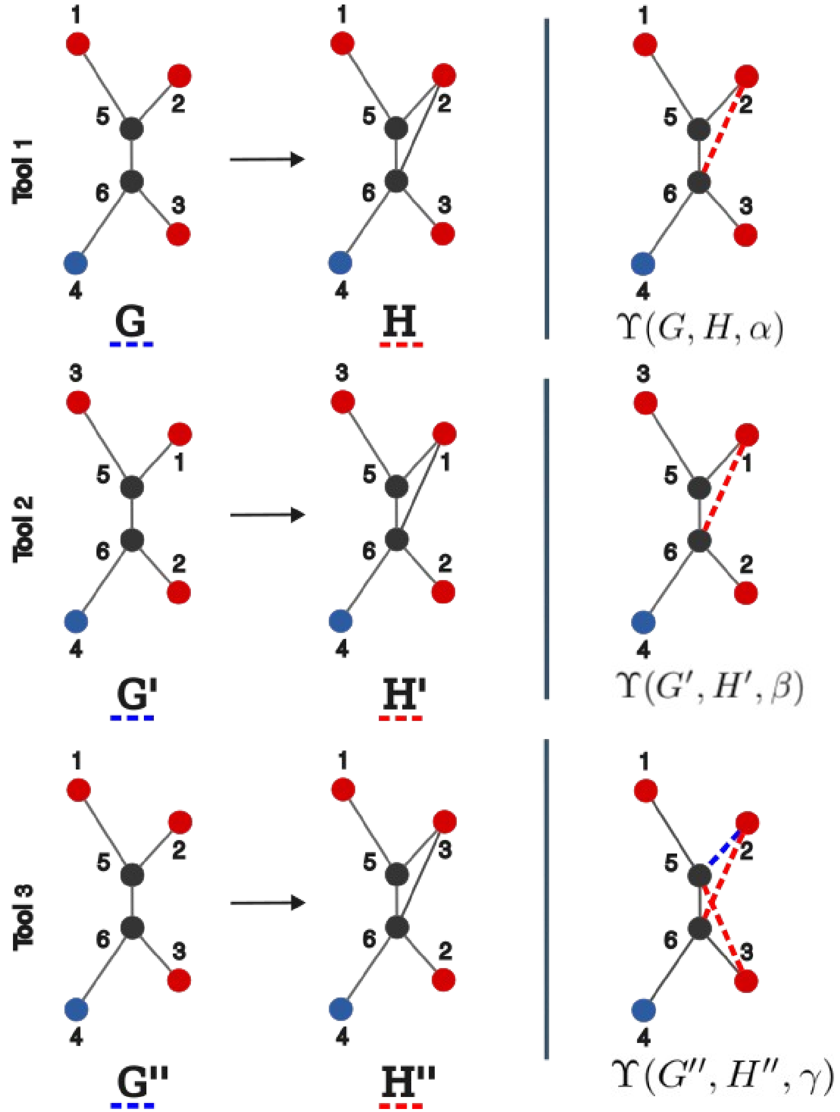
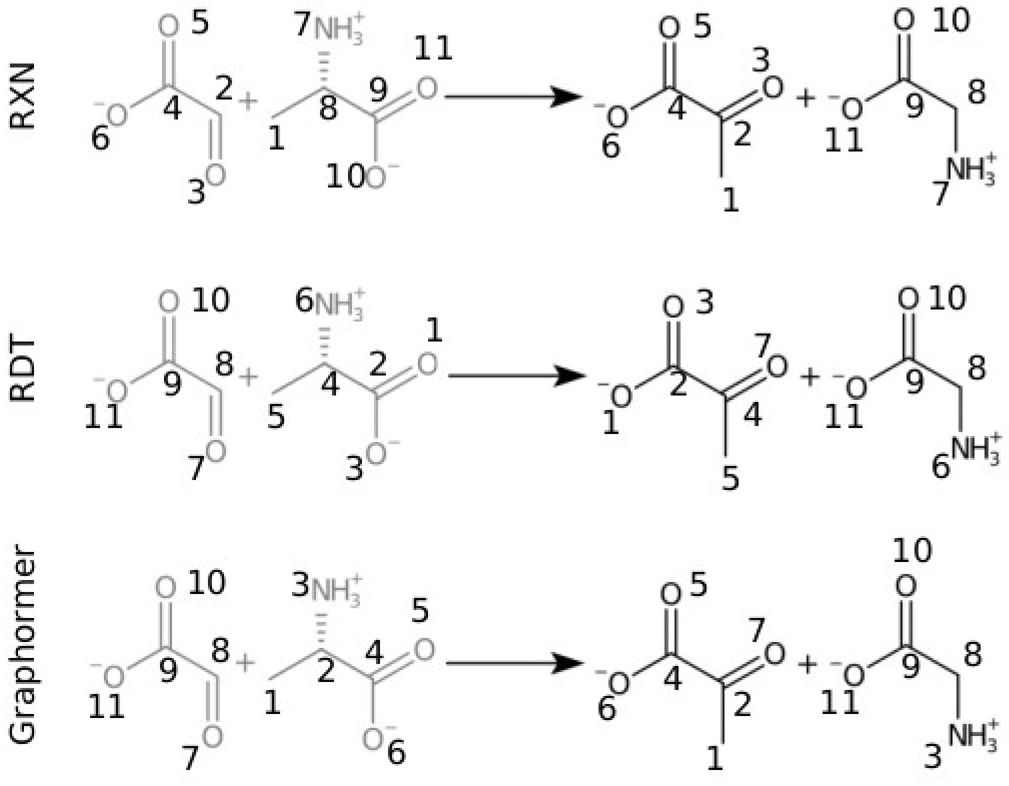
(Toy-) Example of not-equivalent atom maps...



(Real) Example of not-equivalent atom maps...



Non-equivalent atom maps for the reaction of L-alanine + glyoxylate to pyruvate + glycine.