Modeling Isotope Labeling Experiments - Symmetries in Atom Transition Networks

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Introduction

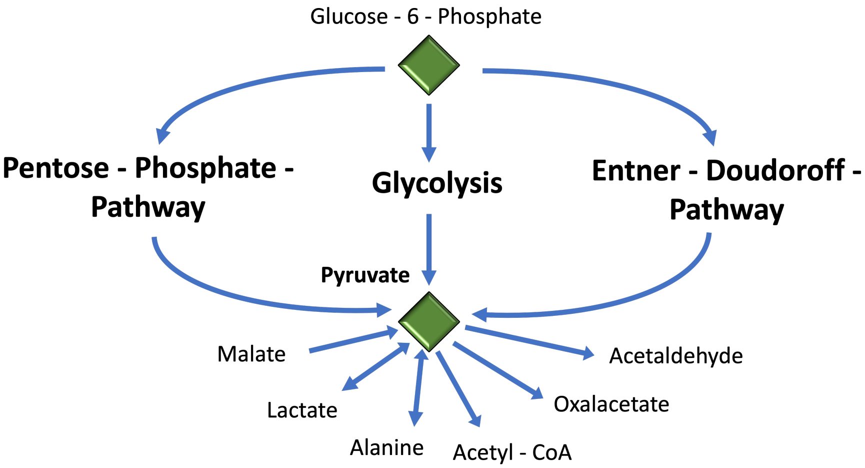


Figure: Metabolic interlacing of pyruvate production and degradation.

Isotope labeling experiments

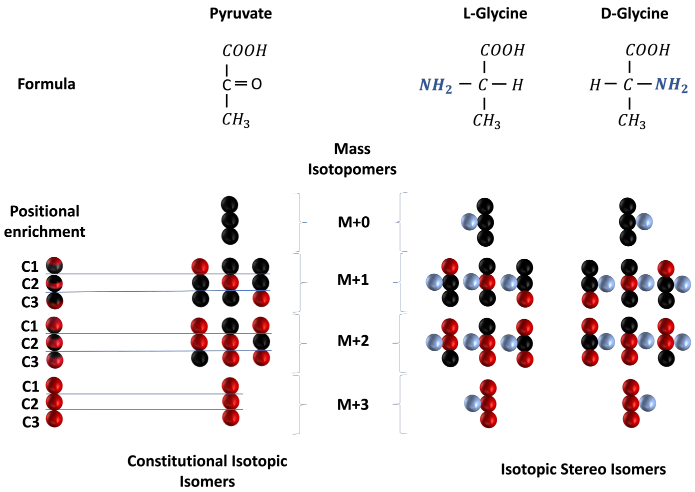


Figure: Schematic depiction of positional enrichment, isotopomers, and mass isotopomers

Isotope labeling experiments

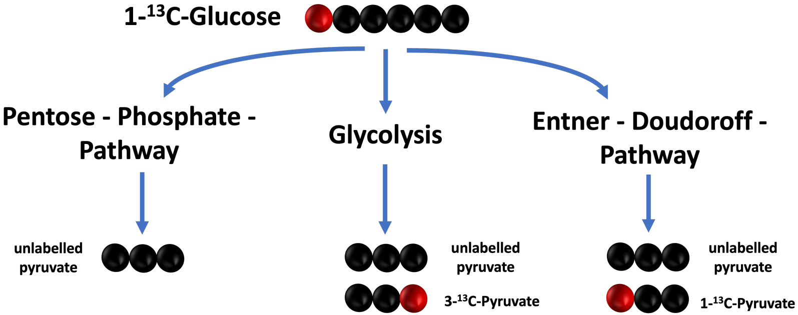


Figure: Metabolic development of 1-^{13}C-Glucose via different metabolic pathways.

Overview

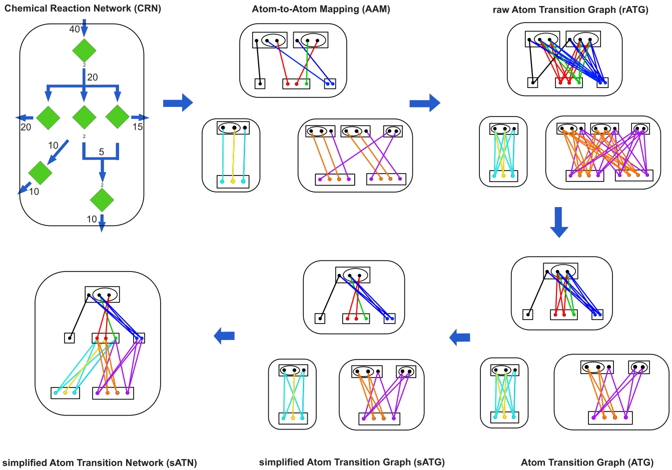


Figure: Overview of the construction process from a chemical reaction network (CRN) to a simplified atom transition network (sATN).

Complexes

- Molecules as molecule graphs [1]

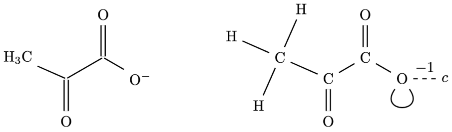


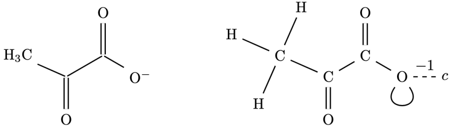
Figure: Example depiction for a molecular graph of pyruvate [1].

Complexes

- Molecules as molecule graphs [1]
- For $r \in R$:

$$Q := \sum_{c \in C} s^-_{cr} \cdot c, s^-_{cr} > 0$$
$$Q' := \sum_{c \in C} s^+_{cr} \cdot c, s^+_{cr} > 0 \quad (1)$$

are designated as *complexes*.



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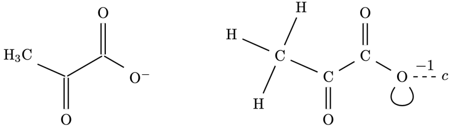
- For $r \in R$:

$$Q := \sum_{c \in C} s_{cr}^{-} \cdot c, s_{cr}^{-} > 0$$
$$Q' := \sum_{c \in C} s_{cr}^{+} \cdot c, s_{cr}^{+} > 0 \qquad (1)$$

  are designated as *complexes*.
- A reaction $r \in R$ can be considered as a transformation of complexes:

$$r = Q \to Q' \qquad (2)$$



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Atom-to-Atom mapping

Definition (Atom-to-atom mapping (AAM))

An atom-atom map (AAM) for a reaction $r = (Q \to Q')$ is a bijection of the vertex sets of the complexes $\varphi : V(Q) \to V(Q')$ that preserves atom labels and hence satisfies

$$\ell_{V(Q)}(x) = \ell_{V(Q')}(\varphi(x)) \tag{3}$$

for all $x \in V(Q)$.

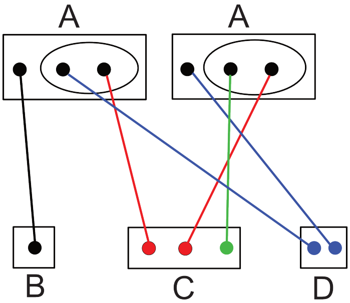

Figure: Depiction of an example reaction $2A \to B + C + D$.

Isomorphism

Definition (**Isomorphism**)

Let $G = (V, E)$ and $H = (W, F)$ be two undirected (directed) graphs with vertex labels $\ell_G : V \to L_V$ and $\ell_H : W \to L_H$. An isomorphism is a **bijection** $\mu : V \to W$ such that

$$\{x, y\} \in E \Leftrightarrow \{\mu(x), \mu(y)\} \in F \qquad ((x, y) \in E \Leftrightarrow (\mu(x), \mu(y) \in F)) \tag{4}$$

and $\ell_G(x) = \ell_H(\mu(x))$.

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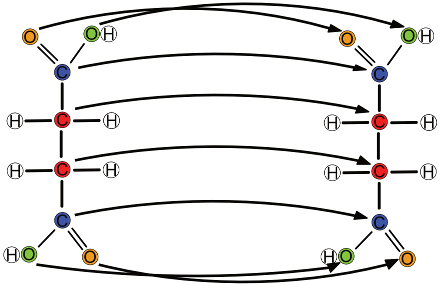
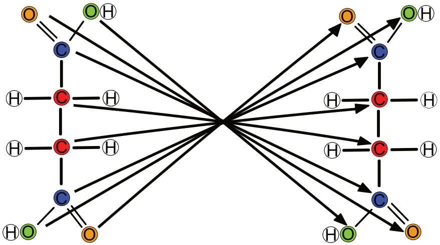
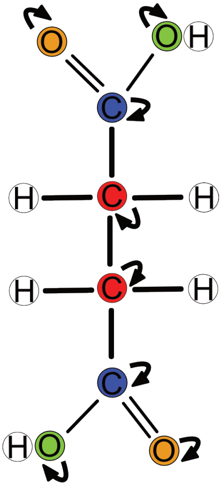
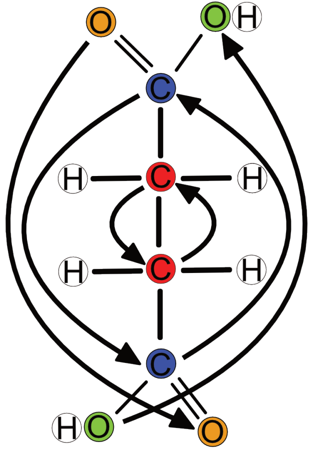




Automorphism





The set of automorphisms $\mathrm{Aut}(G)$ on a graph G forms a group under composition.

Orbit

Definition (Orbit)

Let G be a graph and $\varrho : V(G) \to V(G)$ an automorphism and $(\mathrm{Aut}(G), \circ)$ the group of automorphisms on G under composition. Then the orbit of a vertex $x \in V(G)$ is defined as:

$$\mathrm{orb}(x) := \{y \in V(G) \mid \exists \varrho \in \mathrm{Aut}(G) : \varrho(x) = y\} \tag{5}$$

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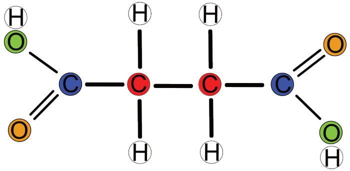

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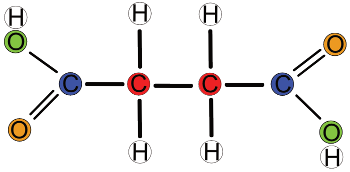

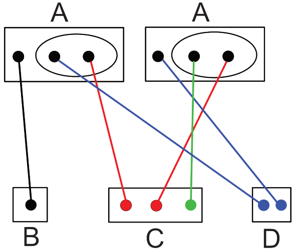

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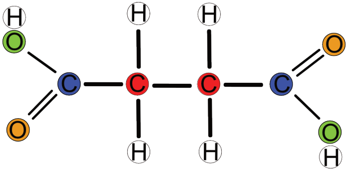

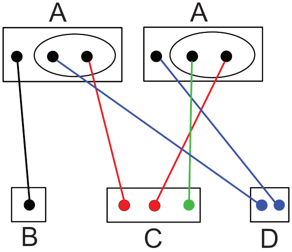

For $\rho \in \mathrm{Aut}(Q)$ and $\rho' \in \mathrm{Aut}(Q')$ and AAM $\varphi : V(Q) \to V(Q')$ the maps φ and $\rho' \circ \varphi \circ \rho^{-1}$ describe the same chemical reaction

Equivalent AAMs

Definition (Equivalent AAMs)

Let $\varphi : V(Q) \to V(Q')$ and $\psi : V(Q) \to V(Q')$ be two vertex label preserving bijections. Then φ and ψ are equivalent if there are automorphisms $\varrho \in \mathrm{Aut}(Q)$ and $\varrho' \in \mathrm{Aut}(Q')$ such that $\psi = \varrho' \circ \varphi \circ \varrho^{-1}$.

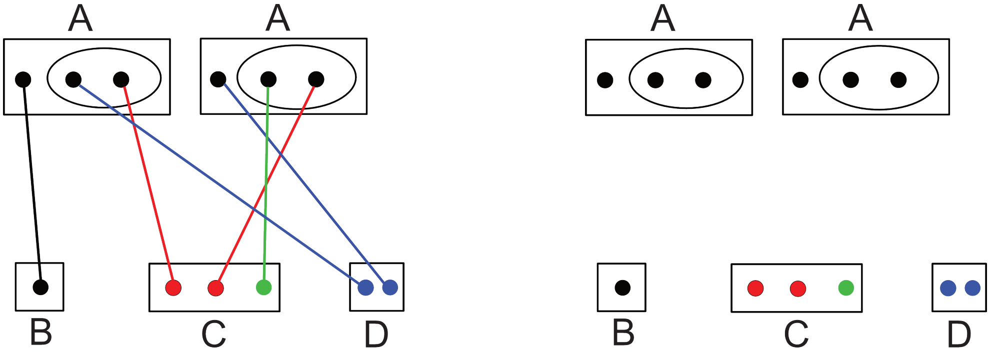

Figure: Example for two equivalent AAMs for example reaction $2A \to B + C + D$.

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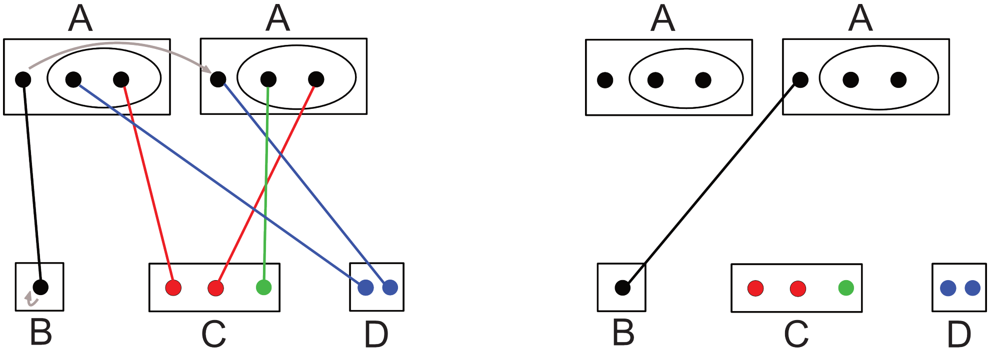

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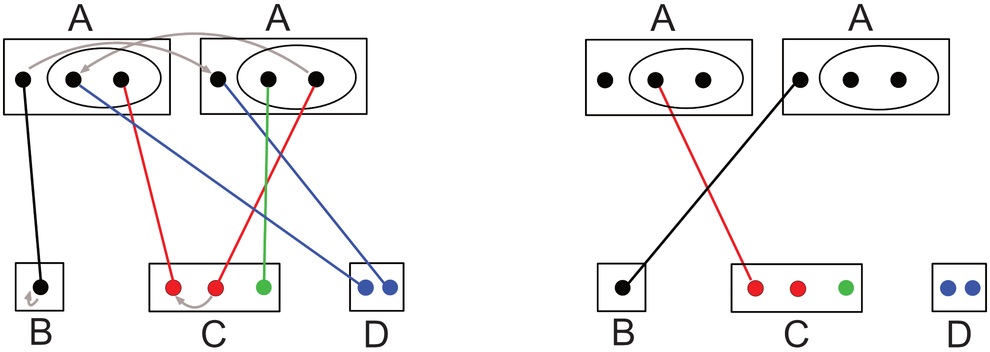

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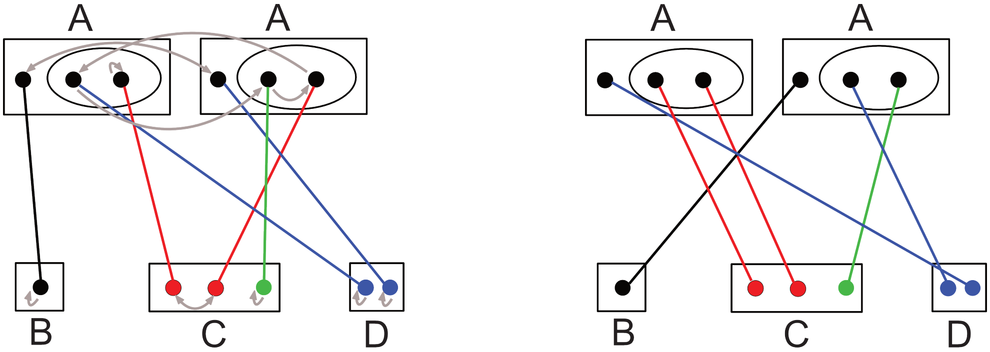

Figure: Example for two equivalent AAMs for example reaction $2A \to B + C + D$.

Raw atom transition graph

Definition (raw atom transition graph (rATG))

The *raw (reaction-wise) atom transition graph* (rATG) $\tilde{T}_{QQ'}$ of a single reaction $r = (Q \longrightarrow Q')$ with AAM φ is the bipartite graph with vertex set $V(T_{QQ'}) = V(Q) \cup V(Q')$ and a set of directed edges $E(\tilde{T}_{QQ'}) = \bigcup_{x \in V(Q)} E_{out}(x)$ where

$$E_{out}(x) \coloneqq \{(x, (\varrho' \circ \varphi \circ \varrho^{-1})(x) | \varrho \in \mathrm{Aut}(Q), \varrho' \in \mathrm{Aut}(Q')\} \tag{6}$$

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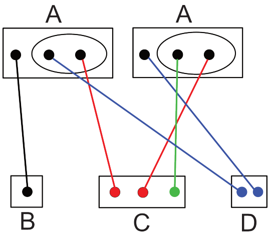

Figure: AAM

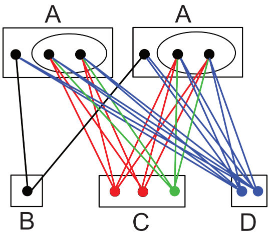

Figure: Edge-weights $w(x,y)$=???.

Edge-weights in rATGs

Definition

Let $r = (Q \to Q')$ be a reaction, $x \in V(Q)$ and $y \in V(Q')$. Then $\eta(x, y)$ is the number of pairs (x', y') such that $x' \in \mathrm{orb}_Q(x), y' \in \mathrm{orb}_{Q'}(y)$ and $y' = \varphi(x')$.

$$\eta(x, y) := |\{(x', y') \mid y' = \varphi(x'), x' \in \mathrm{orb}_Q(x), y' \in \mathrm{orb}_{Q'}(y)\}| \tag{7}$$

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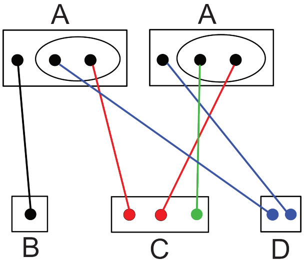

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- Set of edges from $\mathrm{orb}_Q(x)$ to $\mathrm{orb}_{Q'}(y)$ in the rATG:

$$E_{xy}^{\tilde{T}} := \{(x',y') \in E(\tilde{T}_{QQ'}) \mid x' \in \mathrm{orb}_Q(x), y' \in \mathrm{orb}_{Q'}(y)\} \tag{8}$$

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- Edge-weights in atom transition graphs:

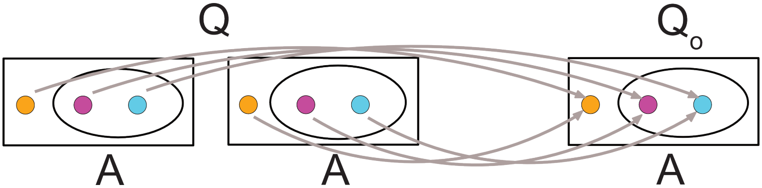
$$h_{\tilde{T}_{QQ'}}(x,y) = \frac{\eta(x,y)}{|E_{xy}^{\tilde{T}}|} = \frac{\eta(x,y)}{|\mathrm{orb}_Q(x)| \cdot |\mathrm{orb}_{Q'}(y)|} \tag{9}$$

Atom equivalence classes

Definition (Atom equivalence relationships)

Let $r = (Q \to Q')$ be a reaction and $Q_\circ$ and $Q'_\circ$ the disjoint union of the pairwisely non-isomorphic connected components Q and Q', respectively. Then $\zeta : Q \uplus Q' \to Q_\circ \uplus Q'_\circ$ is a map such that

- $\zeta(Q) = Q_\circ$ and $\zeta(Q') = Q'_\circ$
- $\zeta(c)$ is a connected component of $Q_\circ$ or $Q'_\circ$ if and only if c is a connected component of Q or Q'
- ζ is an isomorphisms between connected components



Atom transition graph

Definition (Atom transition graph (ATG))

The atom transition graph (ATG) $T_r = T_{QQ'}$ of a reaction $r = (Q \to Q')$ is obtained as the quotient of the raw atom transition graph $\tilde{T}_{QQ'}$ w.r.t. the equivalence classes $\zeta^{-1}(\cdot)$ defined by the isomorphic connected components of Q and Q', respectively.

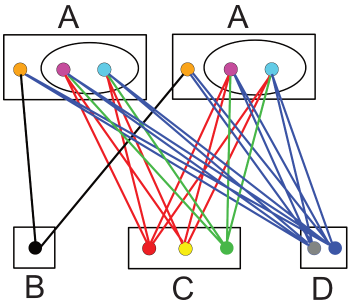


Figure: raw ATG

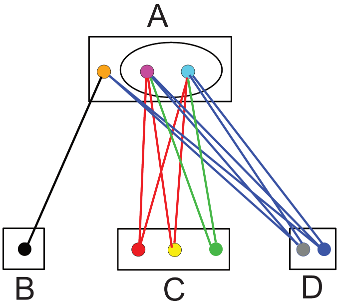
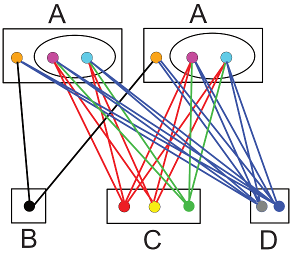


Figure: ATG

Edge-weights for ATGs

- The number of edges between $\mathrm{orb}_c(u), \mathrm{orb}_{c'}(v)$:

$$\left|E^T_{uv}\right| = \left|\mathrm{orb}_c(u)\right| \cdot \left|\mathrm{orb}_{c'}(v)\right| \tag{10}$$



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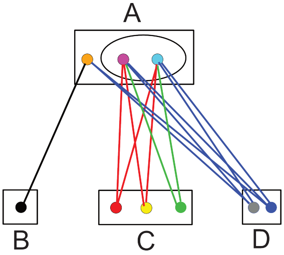

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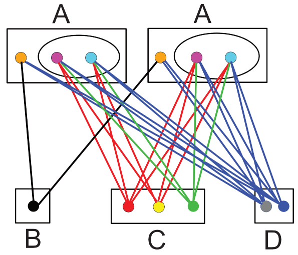
- Edge-weights in ATGs:

$$h_{T_{QQ'}}(u,v) = \frac{\eta(u,v)}{\left|E_{uv}^{T}\right|} = \frac{\eta(u,v)}{\left|\mathrm{orb}_c(u)\right| \cdot \left|\mathrm{orb}_{c'}(v)\right|} \tag{11}$$



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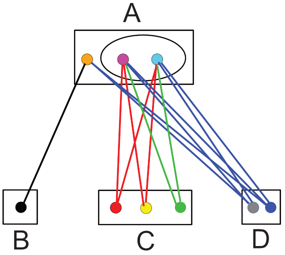


Figure: ATG

Simplified Atom Transition Graphs

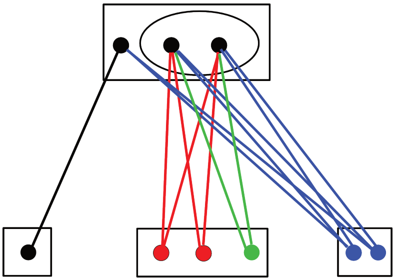


Figure: ATG

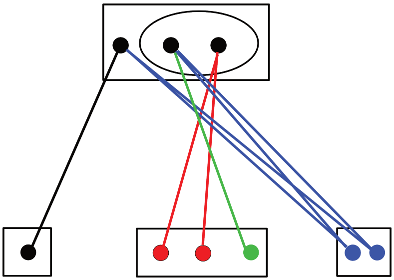


Figure: simplified ATG

Overview of atom transition graphs

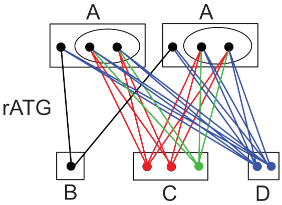


Figure: $h_{\tilde{T}_{QQ'}}(x,y) = \frac{\eta(x,y)}{|\mathrm{orb}_Q\, x|\cdot|\mathrm{orb}_{Q'}(y)|}$

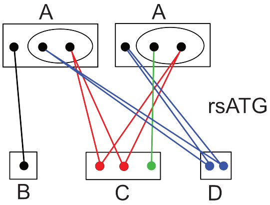
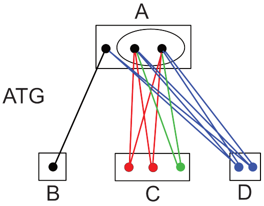


Figure: $h_{\tilde{S}_{QQ'}}(x,y) = |\mathrm{orb}_{Q'}(y)|^{-1}$



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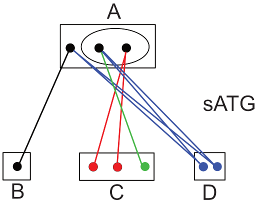

Figure: $h_{S_{QQ'}}(u,v) = \frac{\eta(u,v)}{|Z_v|\cdot|\mathrm{orb}_{c'}(v)|}$

Simplified Atom Transition Networks (sATN)

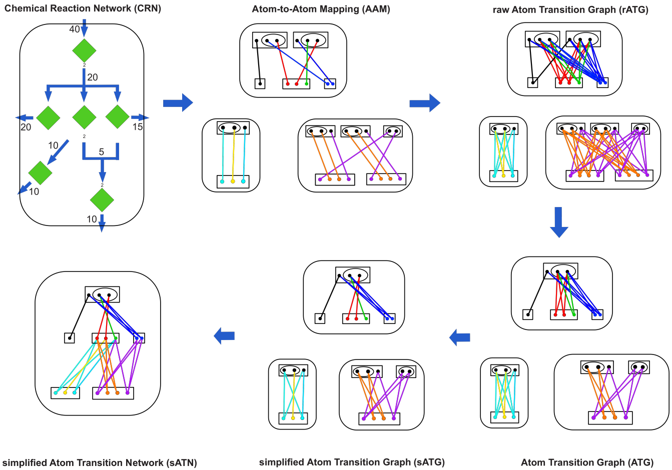

Figure: Overview over the construction from chemical reaction networks (CRN) to simplified atom transition networks (ATN)

Summary

- ✓ Non-trivial stoichiometries and symmetries
- ✓ Conserve valuations on the orbits of atoms.
- ✓ Linear inhomogenous system of differential equations
- ✓ Stationary and non-stationary ILEs
- ✓ Multi-labeling experiments.

Conclusion & Outlook

✓ Positional enrichment

Conclusion & Outlook

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- × MIDs

Conclusion & Outlook

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- ✓ Preprint on Research Square: https://doi.org/10.21203/rs.3.rs-5888287/v1
- ▸ Generalisation to elementary metabolite units and cumomers.

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