Flux Coupling Analysis, Part II

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(joint work with A. Larhlimi, CompLife’06)

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Flux coupling algorithms

- **Flux Coupling Finder (FCF)** [Burgard et al. 2004]:
  - Based on linear fractional optimization
  - Shortcomings:
    - FCF needs bounds on the fluxes through exchange reactions.
    - FCF requires a reconfiguration of the metabolic network.
    - A post-processing step is needed to deduce reaction couplings.
    - A large number of linear optimization problems has to be solved.

- Alternative approach?
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Reaction classification

- The steady state flux cone

\[ C = \{ v \in \mathbb{R}^{m \times n} \mid Sv = 0, v_i \geq 0 \text{ for all } i \in \text{Irr} \} \]

- **Lineality space**

\[ \text{lin.space}(C) = \{ v \in \mathbb{R}^{m \times n} \mid Sv = 0, v_i = 0 \text{ for all } i \in \text{Irr} \} \]
A reversible reaction $j \in \text{Rev}$ is called **pseudo-irreversible** if $v_j = 0$ for all $v \in \text{lin.space}(C)$.

A reversible reaction that is not pseudo-irreversible is called **fully reversible**.
Decomposition of the reaction set

- $F_{rev} = \{ i \mid i \text{ is fully reversible}\}$.
- $P_{rev} = \{ i \mid i \text{ is pseudo-irreversible and there exist } v^+, v^- \in C \text{ such that } v^+_i > 0, v^-_i < 0\}$.
- $I_{rev} = I_{irr} \cup \{ i \mid i \text{ is pseudo-irreversible and } v_i \geq 0, \text{ for all } v \in C \text{ or } v_i \leq 0, \text{ for all } v \in C\}$.

**Question**

How do flux coupling relations depend on the reversibility type of reactions?
Reversibility type and flux coupling

Definition

Let \(i, j\) be two unblocked reactions. The coupling relations \(\rightarrow^0, \leftrightarrow^0, \sim^\lambda\) are defined in the following way:

1. \(i \rightarrow^0 j\) if for all \(v \in C\), \(v_i = 0\) implies \(v_j = 0\).
2. \(i \leftrightarrow^0 j\) if for all \(v \in C\), \(v_i = 0\) is equivalent to \(v_j = 0\).
3. \(i \sim^\lambda j\) if there exists \(\lambda \in \mathbb{R}\) such that for all \(v \in C\), \(v_j = \lambda v_i\).

Theorem

Let \(i, j\) be two unblocked reactions such that at least one of the relations \(i \rightarrow^0 j\), \(i \leftrightarrow^0 j\) or \(i \sim^\lambda j\) is satisfied. Then either (a) or (b) holds:

(a) \(i\) and \(j\) are both (pseudo-)irreversible: \(i, j \in \text{Irev} \cup \text{Prev}\).
(b) \(i\) and \(j\) are both fully reversible: \(i, j \in \text{Frev}\).
Pseudo-irreversible reactions

Proposition

Suppose $i, j$ are unblocked, $i \in \text{Prev}$ and $j \in \text{Irev} \cup \text{Prev}$. Then the following are equivalent

1. $i \iff 0 \rightarrow j$
2. $i \iff 0 \leftrightarrow j$
3. $i \sim^\lambda j$
Reversibility type and flux coupling

<table>
<thead>
<tr>
<th>$i/j$</th>
<th>$I_{rev}$</th>
<th>$P_{rev}$</th>
<th>$F_{rev}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Rightarrow$</td>
<td>$\Rightarrow$</td>
<td>$\Rightarrow$</td>
</tr>
<tr>
<td>$I_{rev}$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>$P_{rev}$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>$F_{rev}$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
</tbody>
</table>

- Coupling relations do not occur for arbitrary pairs of reactions
- Many cases are not possible (only 10/27 possible cases of reaction couplings)
Fluxes through pseudo-irreversible (or fully reversible) reactions that are coupled are proportional to each other (enzyme subset)
Reversibility type and flux coupling

### Table: Reversibility Couplings

<table>
<thead>
<tr>
<th>i/j</th>
<th>$I_{rev}$</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Rightarrow$</td>
<td>$\Rightarrow$</td>
<td>$\Rightarrow$</td>
</tr>
<tr>
<td>$I_{rev}$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>$P_{rev}$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
<tr>
<td>$F_{rev}$</td>
<td></td>
<td>$\checkmark$</td>
<td>$\checkmark$</td>
</tr>
</tbody>
</table>

- Symmetric couplings can occur only between reactions with the same reversibility type.
- Reactions in an enzyme subset must have the same reversibility type.
Reversibility type and flux coupling

<table>
<thead>
<tr>
<th>$i/j$</th>
<th>$I_{rev}$</th>
<th>$P_{rev}$</th>
<th>$F_{rev}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{rev}$</td>
<td>$\Rightarrow$</td>
<td>$\Leftarrow$</td>
<td>$\Leftarrow$</td>
</tr>
<tr>
<td>$P_{rev}$</td>
<td>$\Rightarrow$</td>
<td>$\Leftarrow$</td>
<td>$\Leftarrow$</td>
</tr>
<tr>
<td>$F_{rev}$</td>
<td>$\Rightarrow$</td>
<td>$\Leftarrow$</td>
<td>$\Leftarrow$</td>
</tr>
</tbody>
</table>

- Only a zero flux through an irreversible reaction may imply a zero flux through another irreversible reaction.
Reversibility type and flux coupling

\[ F_{rev} \]
\[ P_{rev} \]
\[ I_{rev} \]
A new algorithm for flux coupling analysis

- Compute a set of generators of the flux cone $C$ using existing tools for polyhedral computations
- Classify the reactions according to their reversibility type
- Apply the mathematical results to identify blocked and coupled reactions
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## Computational results

<table>
<thead>
<tr>
<th>Metabolic network</th>
<th>Blk</th>
<th>Irev</th>
<th>Prev</th>
<th>Frev</th>
<th>MMB</th>
<th>FCMMB</th>
<th>TOTAL</th>
<th>FCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell</td>
<td>0</td>
<td>31</td>
<td>14</td>
<td>6</td>
<td>2.32</td>
<td>0.26</td>
<td>2.58</td>
<td>110.65</td>
</tr>
<tr>
<td>Central metabolism of <em>E. coli</em></td>
<td>0</td>
<td>92</td>
<td>18</td>
<td>0</td>
<td>214.49</td>
<td>2.55</td>
<td>217.04</td>
<td>477.14</td>
</tr>
<tr>
<td>Human cardiac mitochondria</td>
<td>121</td>
<td>83</td>
<td>3</td>
<td>9</td>
<td>1262.65</td>
<td>0.34</td>
<td>1262.99</td>
<td>13426.91</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>346</td>
<td>128</td>
<td>15</td>
<td>39</td>
<td>13551.44</td>
<td>0.43</td>
<td>13551.87</td>
<td>318374.15</td>
</tr>
<tr>
<td>E. coli K-12</td>
<td>435</td>
<td>480</td>
<td>49</td>
<td>110</td>
<td>261306.15</td>
<td>5.32</td>
<td>261311.47</td>
<td>≥ 1 week</td>
</tr>
</tbody>
</table>