Mixed-Integer Programming for Cycle Detection in Non-reversible Markov Processes

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Motivation

- Many chemical and biological processes can be interpreted as a **Markov State Models**

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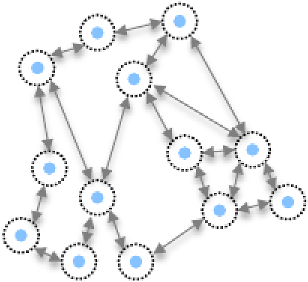
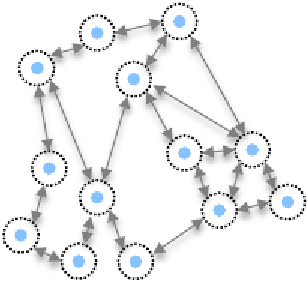
- After simulation (e.g. Monte-Carlo) a discrete set of states $\mathcal{S} = \{1, \ldots, n\}$ and a transition matrix P describe the underlying Markov process



Motivation

- Many chemical and biological processes can be interpreted as a **Markov State Models**
- After simulation (e.g. Monte-Carlo) a discrete set of states $\mathcal{S} = \{1, \dots, n\}$ and a transition matrix P describe the underlying Markov process
- A clustering of the states can be used to analyze the process



Problem Description

- Let $P \in \mathbb{R}^{n \times n}$ a transition matrix of a Markov process with stationary distribution $\pi \in \mathbb{R}^n$.
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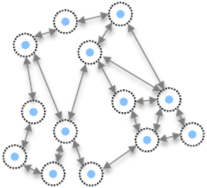

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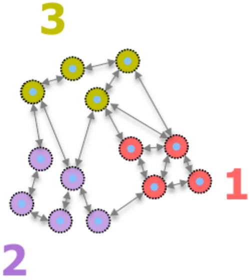

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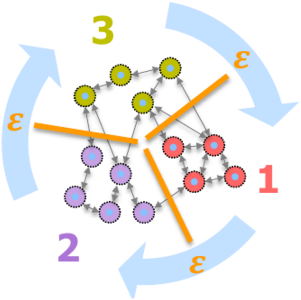

Why is this interesting in practice?

- If a process is **reversible** the leading eigenvalues can be used to find a meaningful clustering.

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State-of-the-art methods for non-reversible processes are, e.g.,

- Schur-decomposition[2]
- "Fuzzy" clustering (i.e. assign fractions of states to clusters) and apply a rounding heuristic

but none of them can prove optimality or has some guarantee for the solution quality.

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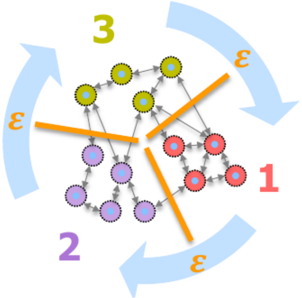
2. Maximize the **net-flow** between consecutive clusters and the **coherence** within each cluster.



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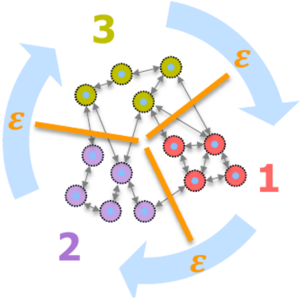

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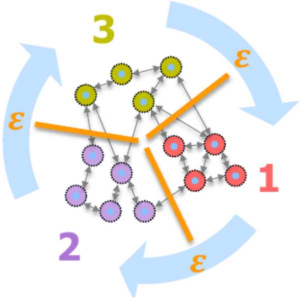
4. We want to be able to either **prove optimality** or to measure the **solution quality**.



Cycle-Clustering MINLP

$$\max \ \textbf{net-flow} + \alpha \cdot \sum_{t \in \mathcal{C}} \textbf{coherence of } C_t$$

$$\text{s.t.} \quad \sum_{t \in \mathcal{C}} x_{it} = 1 \qquad \forall i \in \mathcal{S} \qquad (1)$$

$$\sum_{i \in \mathcal{S}} x_{it} \geq 1 \qquad \forall t \in \mathcal{C} \qquad (2)$$

$$x_{it} \in \{0,1\} \qquad \forall i \in \mathcal{S}, \ \forall t \in \mathcal{C}$$

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s.t. \quad & \sum_{t\in\mathcal{C}} x_{it} = 1 && \forall i \in \mathcal{S} && (1)\\
& \sum_{i\in\mathcal{S}} x_{it} \geq 1 && \forall t \in \mathcal{C} && (2)\\
& \epsilon_t = \sum_{i\neq j\in\mathcal{S}} \pi_i p_{ij} \left(x_{it}x_{j\phi(t)} - x_{i\phi(t)}x_{jt}\right) && \forall t \in \mathcal{C} && (3)\\
& x_{it} \in \{0,1\} && \forall i \in \mathcal{S},\ \forall t \in \mathcal{C} &&\\
& \epsilon_t \in \mathbb{R}_{\geq 0} && \forall t \in \mathcal{C} &&
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- Cont. variable ϵ_t representing the net-flow between C_t and $C_{\phi(t)}$

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$$\max \sum_{t\in\mathcal{C}} \epsilon_t + \alpha \cdot \boxed{\sum_{t\in\mathcal{C}} \sum_{i,j\in\mathcal{S}} \pi_i p_{ij} x_{it} x_{jt}}$$

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Linearizing the MINLP-Formulation

- automatic linearization by SCIP / textbook linearization ✗

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- compact linearization for binary quadratic problems (L. Liberti, 2007) ✓/✗
- problem specific linearization which uses the cyclic structure ✓
  - Set of **relevant transitions**: $E := \{(i,j) \in \mathcal{S} \times \mathcal{S} : \; i \neq j, \; \pi_i p_{ij} + \pi_j p_{ji} > 0\}$
  - Binary variables $y_{ij} = 1 \Leftrightarrow$ states i and j are in the same cluster, $\forall i,j \in E\colon i < j$
  - Binary variables $z_{ij} = 1 \Leftrightarrow$ states $i \in C_t$ and $j \in C_{\phi(t)}$, $\forall i,j \in E$

MIP Model

$$\max \sum_{(i,j)\in E} z_{ij}(\pi_i p_{ij} - \pi_j p_{ji}) + \alpha \sum_{(i,j)\in E:\ i<j} y_{ij}(\pi_i p_{ij} + \pi_j p_{ji})$$

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Facets of the Linearization

Theorem

Let $(i, j) \in E$, $t \in \mathcal{C}$, and $m \geq 4$. Then the inequalities

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Proof idea

1. Let $\hat{a}x + \hat{b}y + \hat{c}z \leq \hat{\delta}$ facet-defining with

$$\{(x, y, z) \in CCP \mid ax + by + cz = \delta\} \subseteq \{(x, y, z) \in CCP \mid \hat{a}x + \hat{b}y + \hat{c}z = \hat{\delta}\}$$

2. Compare coefficients and show that $ax + by + cz \leq \delta$ is a multiple of $\hat{a}x + \hat{b}y + \hat{c}z \leq \hat{\delta}$

Follows the proof technique of Chopra and Rao (1993).

Valid Inequalities

1. various types of triangle inequalities
   - special case: $m = 3$
   - general case: $m \geq 4$ (motivated by S. Chopra and M. R. Rao. (1993); M. Grötschel and Y. Wakabayashi (1990))

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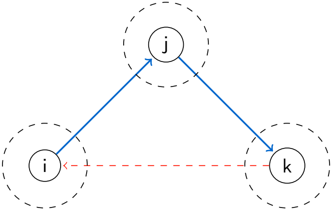
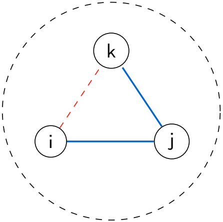
Simple Triangle Inequalities



special case $m = 3$:

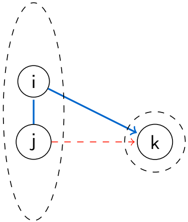
$$z_{ij} + z_{jk} - z_{ki} \leq 1 \quad \forall (i,j),(j,k),(k,i) \in E$$



holds in general:

$$y_{ij} + y_{jk} - y_{ik} \leq 1 \quad \forall (i,j),(j,k),(k,i) \in E$$

Triangle Inequalities Involving 2 Clusters



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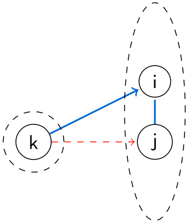

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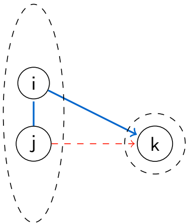

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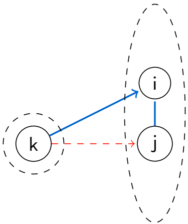

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$$y_{ij} + z_{ik} - z_{jk} \leq 1$$

$$y_{ij} + z_{ki} - z_{kj} \leq 1$$

Facet-Defining Triangle Inequalities

A combination of

- $y_{ij} + y_{jk} - y_{ik} \leq 1$
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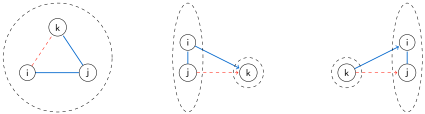
yield a facet-defining inequality.



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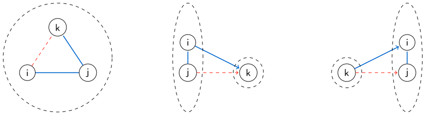


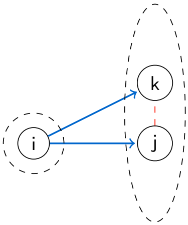
Theorem

Let $i, j, k \in \mathcal{S}$ with $(i,j), (j,k), (i,k) \in E$. Then the triangle inequality

$$y_{ij} + y_{jk} - y_{ik} + 0.5\,(z_{ij} + z_{ji} + z_{jk} + z_{kj} - z_{ik} - z_{ki}) \leq 1$$

is facet-defining for the cycle clustering polytope.

Triangle Inequalities Involving 2 Clusters (cont.)



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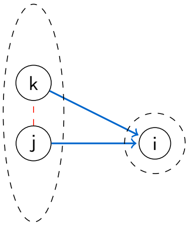

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Facet-Defining Triangle Inequalities (cont.)

Theorem

Let $i, j, k \in \mathcal{S}$ with $(i,j), (j,k), (i,k) \in E$.

- *If $m > 4$, then*

  $$z_{ij} + z_{ik} - y_{jk} \leq 1 \quad \textit{and} \quad z_{ji} + z_{ki} - y_{jk} \leq 1$$

  are facet-defining for the cycle clustering polytope.

- *If $m = 4$, then*

  $$z_{ij} + z_{ik} - 2y_{jk} - (z_{jk} + z_{kj} + z_{ji} + z_{ki}) \leq 0$$

  is facet-defining for the cycle clustering polytope.

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Let $i, j, k \in \mathcal{S}$ with $(i,j), (j,k), (i,k) \in E$.

- *If $m > 4$, then*

  $$z_{ij} + z_{ik} - y_{jk} \leq 1 \quad \text{and} \quad z_{ji} + z_{ki} - y_{jk} \leq 1$$

  are facet-defining for the cycle clustering polytope.

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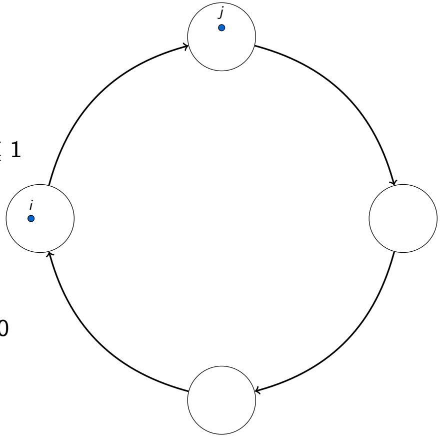

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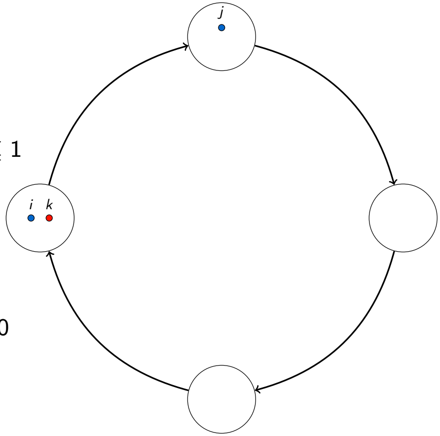

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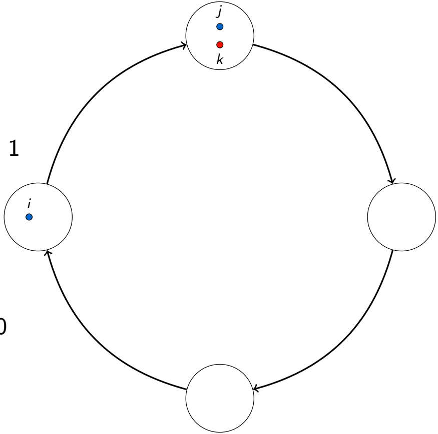

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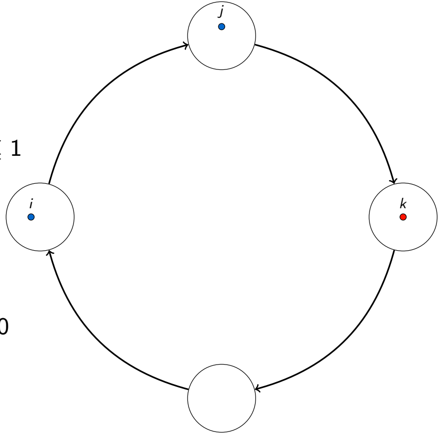

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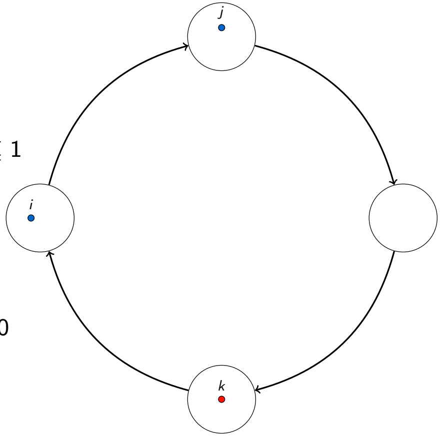

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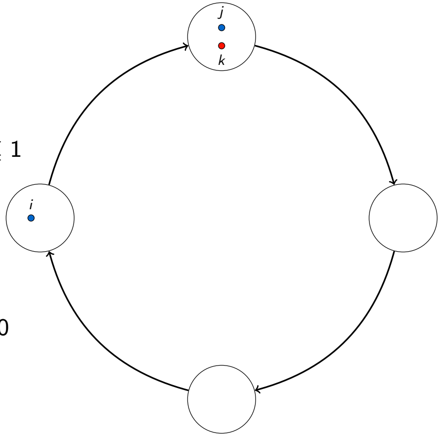

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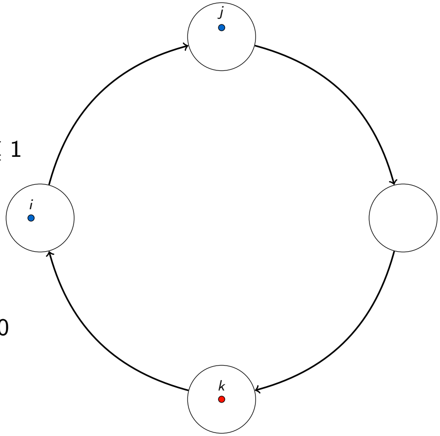
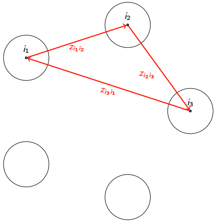


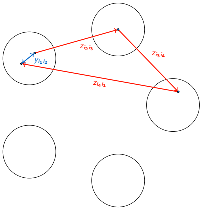
Valid Inequalities

1. various types of triangle inequalities
   - special case: $m = 3$
   - general case: $m \geq 4$ (motivated by S. Chopra and M. R. Rao. (1993); M. Grötschel and Y. Wakabayashi (1990))
2. **subtour and path inequalities**
   - motivated by TSP subtour elimination inequalities
3. partitioning inequalities
   - modification of M. Grötschel and Y. Wakabayashi (1990)

Subtour Elimination Inequalities

- Let $K = \{(i_1, i_2), (i_2, i_3), \ldots, (i_{s-1}, i_s), (i_s, i_1)\} \subset E$ with $1 < |K| < m$
- $U \subset K$, $|U| \leq |K| - 1$





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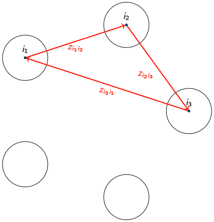

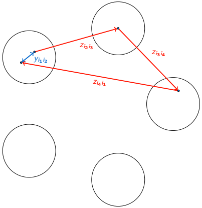

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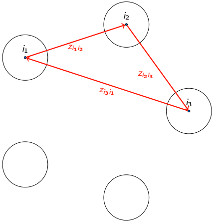

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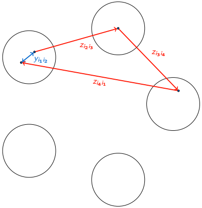

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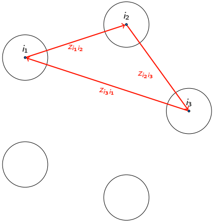

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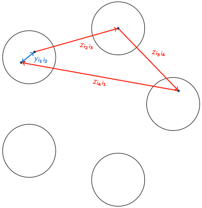

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- none of them is facet-defining
- but can be separated in polynomial time

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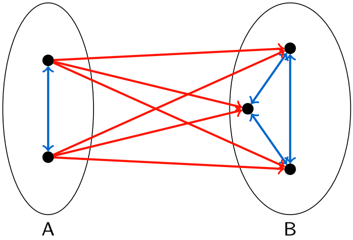
Partition Inequalities

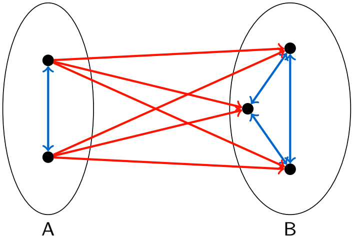


Partition Inequalities

Let $A, B \subset \mathcal{S}$, $A \cap B = \emptyset$. The partitioning inequality

$$\sum_{i \in A,\ j \in B} z_{ij} - \sum_{i<j \in A} y_{ij} - \sum_{i<j \in B} y_{ij} \leq \min\{|A|, |B|\} \tag{4}$$

is valid for the cycle clustering polytope.



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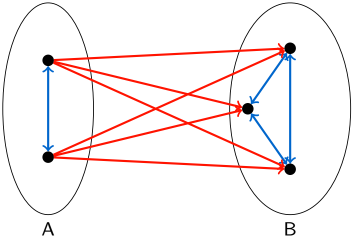


Theorem

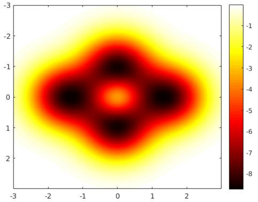
The partitioning inequalities of type (4) are facet-defining if $m > 4$ and $||A| - |B|| = 1$.

How do the inequalities perform in practice?

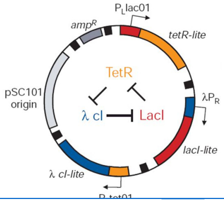
Our test instances:

1. Artificial potentials with 3, 4 or 6 minima
2. Repressilator (synthetic genetic regulatory network)
3. Hindmarsh-Rose (simulate membrane potential of cells in a human heart)

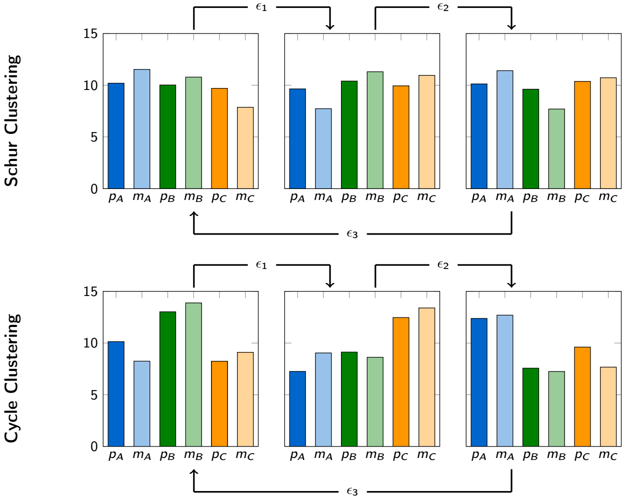
potential with 4 minima



Repressilator (Elowitz and Leibler, 2000)



Only one slide left before you see some numbers. . .



(solutions of a repressilator instance)

Computational Results: Impact of Inequalities

Inequ.	time [s]		nodes		dual integral	
default	130.6	-	256.6	-	1213.3	-
triangle	77.6	**0.59**	28.8	**0.11**	474.1	**0.39**
subtour	122.6	0.94	174.3	**0.68**	1036.4	**0.85**
partition	122.6	0.94	121.6	**0.47**	933.1	**0.77**
all	68.3	**0.52**	15.4	**0.06**	396.6	**0.33**

Test set of 176 instances with 50 – 250 states. Time limit 1h.

Mixed Integer Programming is more than cutting planes. . .

Beside of three different type of cutting planes we designed primal heuristics to improve the primal side as well:

- greedy heuristic assigning states to clusters
- exchange heuristic that swaps states between clusters
  (even if it gets worse in between)
- problem-tailored LP rounding heuristic

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Beside of three different type of cutting planes we designed primal heuristics to improve the primal side as well:

- greedy heuristic assigning states to clusters — −32% primal integral
- exchange heuristic that swaps states between clusters (even if it gets worse in between) — −53% primal integral
- problem-tailored LP rounding heuristic — −32% primal integral

Now, put it all together

Solver	solved	time [s]	primal int	dual int
SCIP	113	182.4	3274.8	1794.0
CC-SCIP	130	64.7	82.9	327.1
(out of competition)				
Gurobi	118	153.1	1236.6	1524.9

Test set of 176 instances with 50 – 250 states. Time limit 1h.

Conclusion

Summary

- First MIP model for detecting cyclic clustering of non-reversible Markov State Models
- Various (facet-defining) valid inequalities for the cycle-clustering polytope
- Very brief description of problem-tailored primal heuristics

References

- Model: Witzig, J., Beckenbach, I., Eifler, L., Fackeldey, K., Gleixner, A., Grever, A., & Weber, M. (2018). Mixed-Integer Programming for Cycle Detection in Nonreversible Markov Processes. Multiscale Modeling & Simulation, 16(1), 248-265.
- Methods: Master thesis of Leon Eifler, publication coming soon...

The End

Thank you for your attention.

Questions?