P-invariants in Systems Biology

Modules, Conservations and Constraints

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Outline

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Thank you MOCA!

At the previous MOCA meeting, two talks gave *"definitions"* of modules for Systems Biology:

- Monika Heiner, using T-invariants;
- Andrei Zinovyev, using "minimal cycles".

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Intersection of both: a (minimal) P-invariant is a marking (with minimal support) of a Petri-net, representing a weighted sum that is invariant by all transitions.

Stating the obvious

A P-invariant is an invariant !

If **species are places** and **reactions are transitions**, a P-invariant defines a conservation law, whatever the dynamics (!!!).

Note that there are other ones, like the following when $k1 = k2$:

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MA(k1) for _ =[A]=> B.
MA(k2) for A => _.
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$$\frac{d[A]+[B]}{dt} = -k_2 * [A] + k_1 * [A] = (k_1 - k_2) * [A]$$

Finding (minimal) P-invariants is a CSP

For a Petri net with p places and t transitions $(L_i \longrightarrow R_i)$, a P-invariant is a vector $V \in \mathbb{N}^p$ s.t. $\forall 1 \leq i \leq t \; V \cdot L_i = V \cdot R_i$

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Ensure minimality by (labelling from small to big and) branch and bound on a partial base $\mathcal{B}$ of vectors: $\forall B \in \mathcal{B} \; \prod_{B_i \neq 0} V_i = 0$
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The problem is **EXPSPACE** and in CSP one difficulty is setting the upper bound of the domain...

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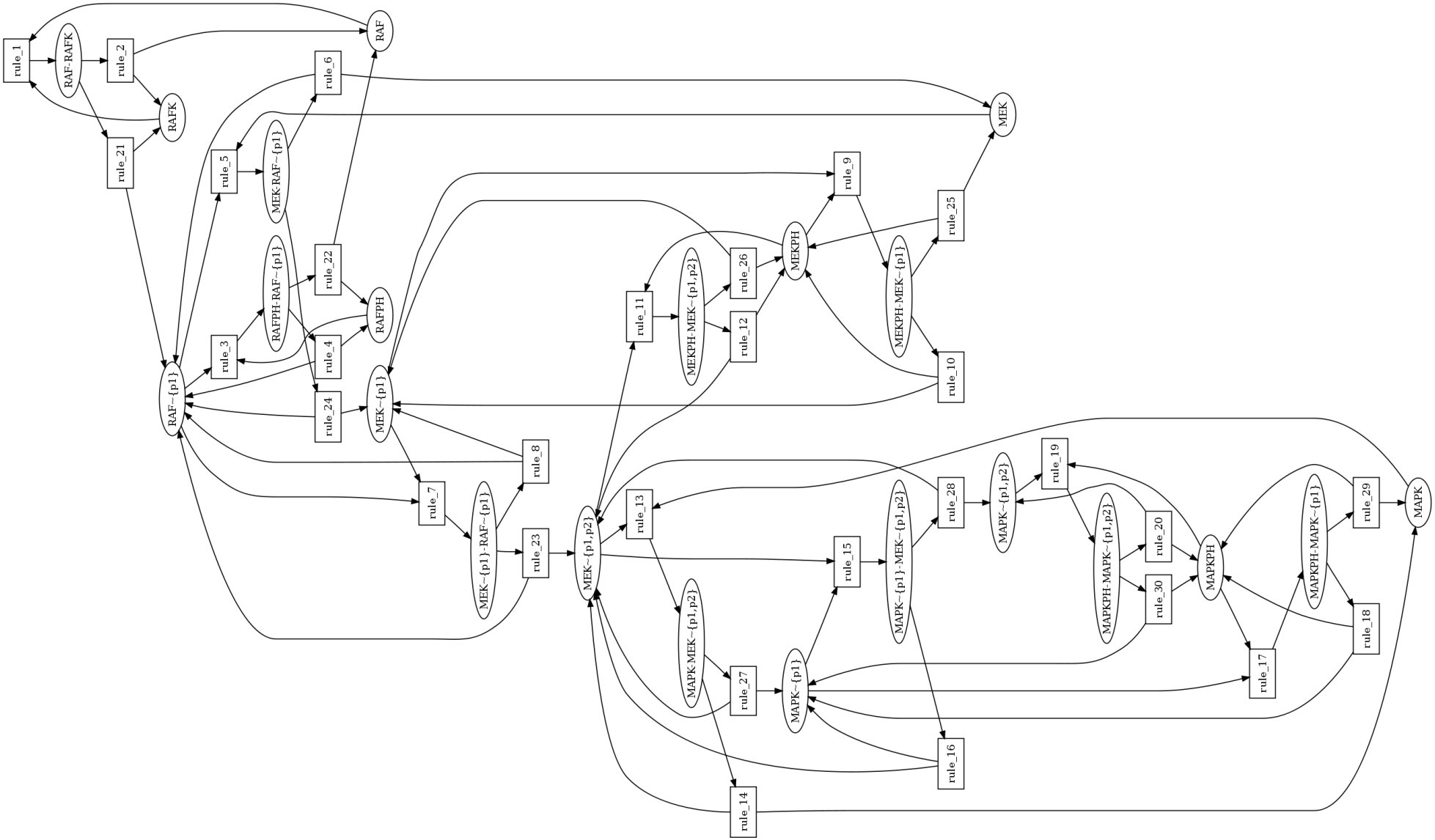
[Levchenko et al. PNAS 2000 (no scaffold)]



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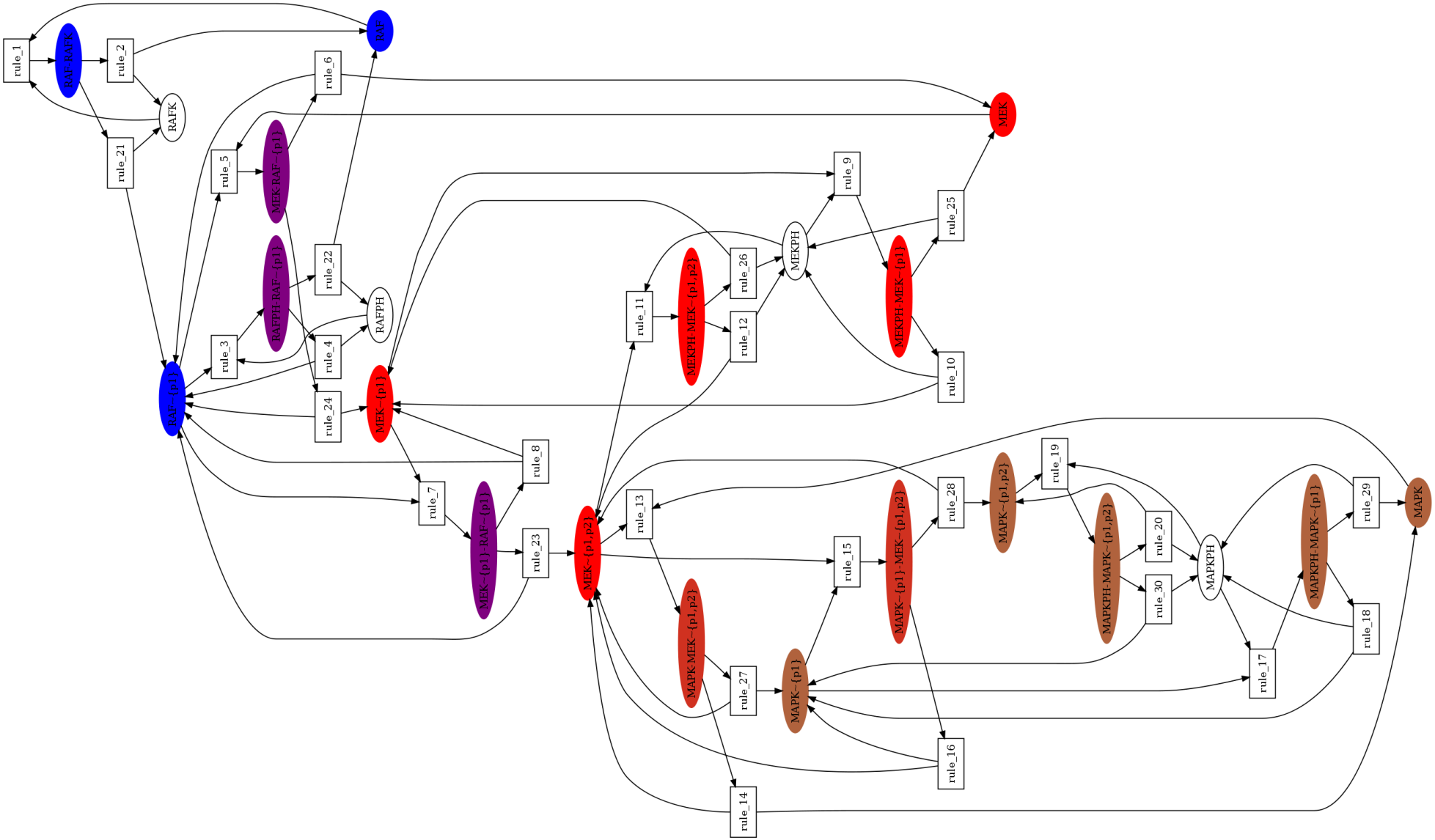
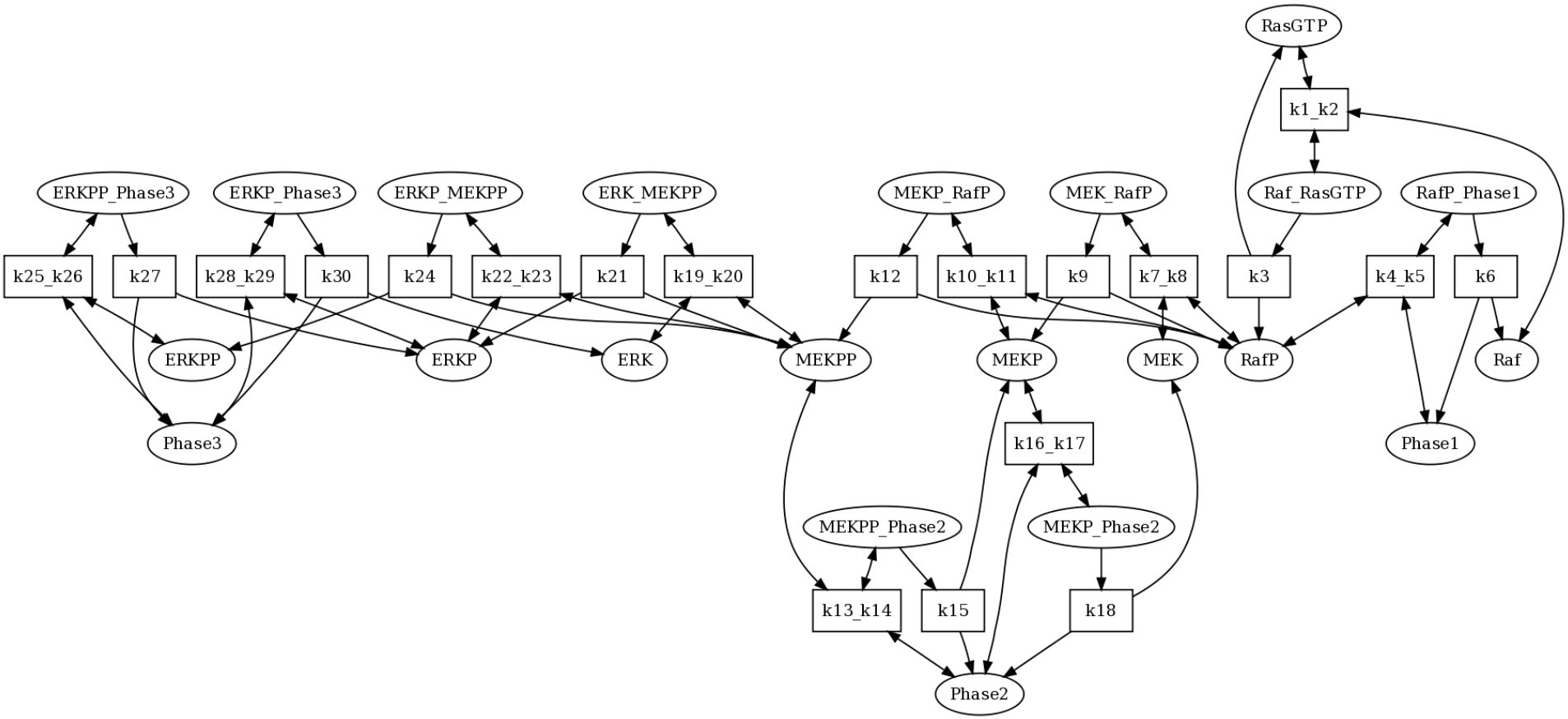


[Heiner et al. CMSB' 07 (Chickarmane et al. JTB 2006)]



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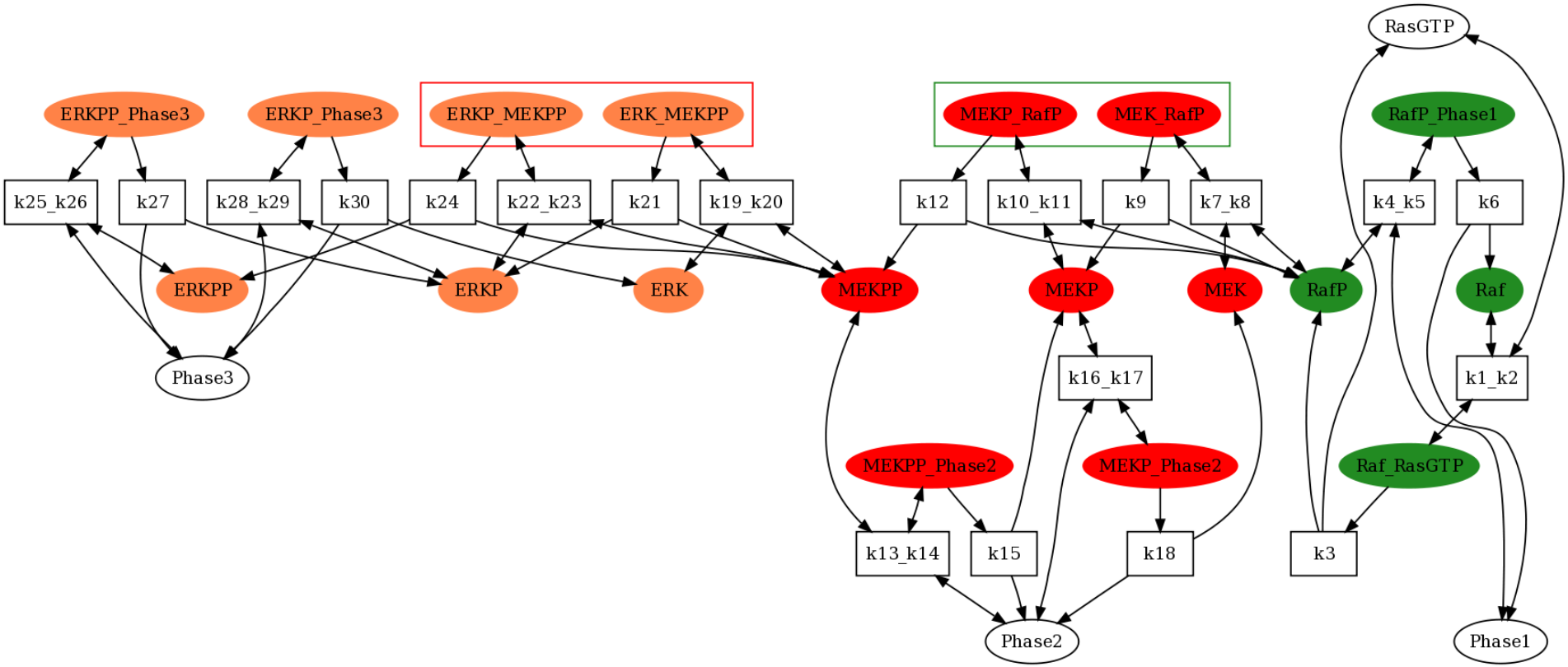

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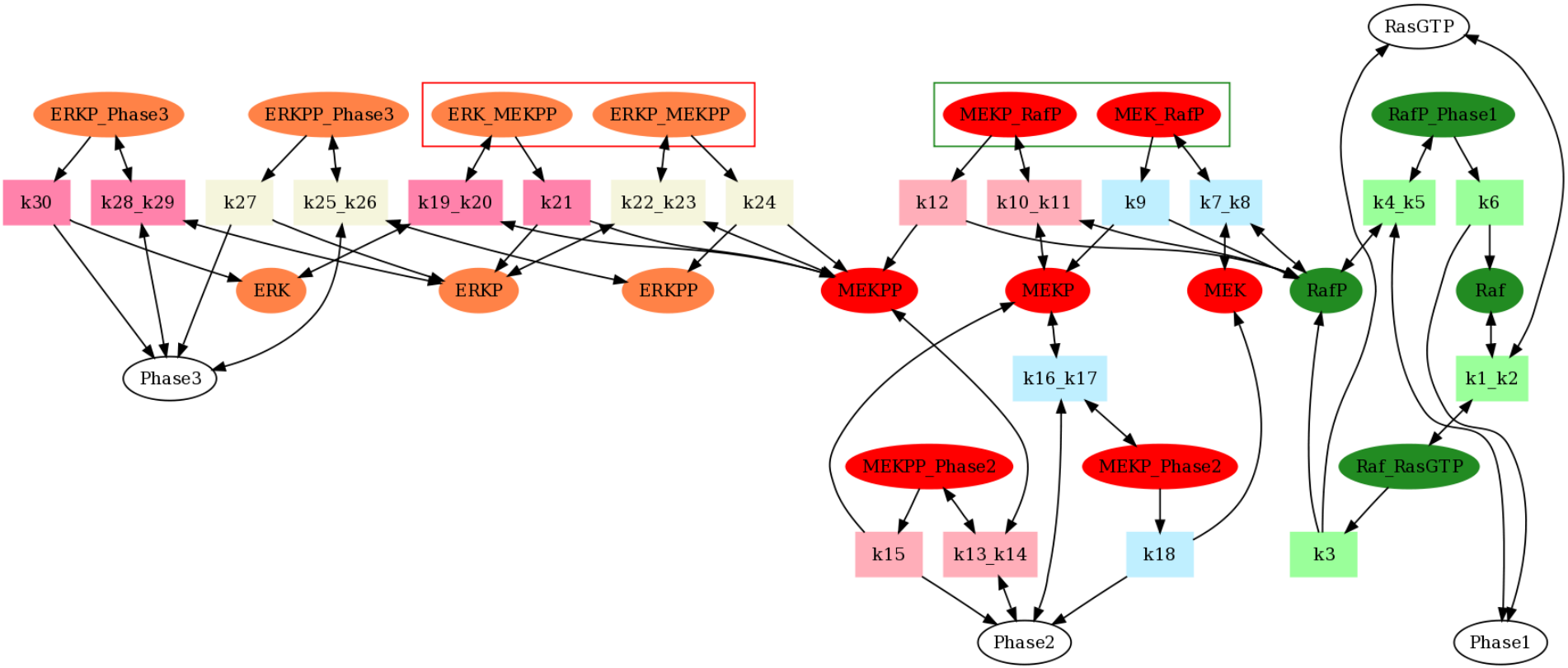

What else?

- Heiner's MAPK model: 30 reactions, 22 molecules, 7 P-invariants;
- Schoeberl's model: 125 reactions, 105 molecules, 14 P-invariants (<1s);
- Curie's (old) Rb model: ∼500 reactions, ∼400 molecules, 79 P-invariants (max=8 ⇒ ∼10s), from size 1 (s220) to about 230 (s715, s716, . . .);
- Kohn's 99 map: ∼800 reactions, ∼500 molecules, 65 P-invariants (max=8 ⇒ ∼40s), from size 1 (Myt1) to about 200 (pRb or cdk2);
- Domitille's reduced FSH model: 8 reactions, 9 molecules, 2 P-invariants (should have been 3!!!).

Error detection, module decomposition, model reduction!

What now?

- handling of unbounded models;
- catalysts absent from the incidence matrix;
- evaluation of this notion of modules;
- comparison with "Structural analysis" of Copasi;
- combining with T-invariant analysis?

"Those who agree with us may not be right, but we admire their astuteness."
– Cullen Hightower