Tropical Equilibration by Constraint Solving

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ODE System Reduction by Tropical Equilibration

1. rescale parameters using a small ϵ (round values)
2. search for a rescaling of variables $x_i = \epsilon^{a_i}\bar{x}_i$ $a_i \in \mathbb{Z}$ is an unknown
3. equilibrate the degrees of *at least* the biggest positive and the biggest negative term in some/all right sides of the ODEs
4. take care of conservation laws
5. profit!

CSP over integers

Express the problem as constraints over the a_i
Note: degrees are linear combinations of the a_i

We will need constraints of the form $E_1 < E_2$
And **reified constraints** of the form $B \Leftrightarrow (E_1 = E_2)$

Use a *Constraint Solver* to get solutions (reduce domains by propagation, if necessary enumerate over domains)

x_1 is `Cdc2`, x_2 `Cdc2~{p}`, x_3 `MPF` and x_4 `preMPF`

$$\frac{\partial x_1}{\partial t} = k_9 x_2 - k_8 x_1 + k_6 x_3$$

$\Rightarrow$

$$\frac{\partial \bar{x}_1}{\partial t} = \epsilon^{-3+a_2-a_1} \bar{k}_9 \bar{x}_2 - \epsilon^{-6} \bar{k}_8 \bar{x}_1 + \epsilon^{a_3-a_1} \bar{k}_6 \bar{x}_3$$

Do **not** enumerate!

```
equilibrate(LPos, LNeg) :-
    get_min(LPos, Min),
    get_min(LNeg, Min).
```

Conservations

$$x_1 + x_2 + x_3 + x_4 = 1$$

$\Rightarrow$

$$\epsilon^{a_1}\bar{x}_1 + \epsilon^{a_2}\bar{x}_2 + \epsilon^{a_3}\bar{x}_3 + \epsilon^{a_4}\bar{x}_4 = \epsilon^0$$

Ensure proper limit when $\epsilon \longrightarrow 0$

```
conserve(L, D) :-
    get_min_and_count(L, D, C),
    C #>= 2.
```

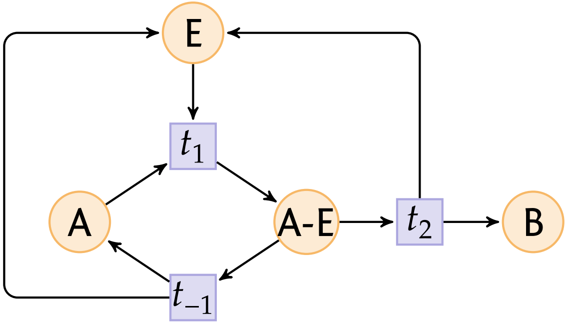
Actually...

```
get_min(L, M) :-
    get_min_and_count(L, M, C),
    C #>= 1.

get_min_and_count([H | T], M, C) :-
    M #=< H,
    B #<==> M #= H,
    C #= B + CC,
    get_min_and_count(T, M, CC).

get_min_and_count([], _, 0).
```

But how do we get conservation laws?

Petri-net view of a reaction model

Species are places and reactions are transitions, thus `A + E <=> A-E => B + E` corresponds to the following Petri-net:



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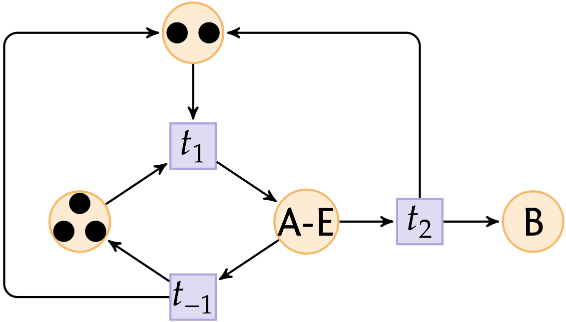

Consume a token in A and E to produce one in A-E (t_1), then do the exact opposite (t_{-1})

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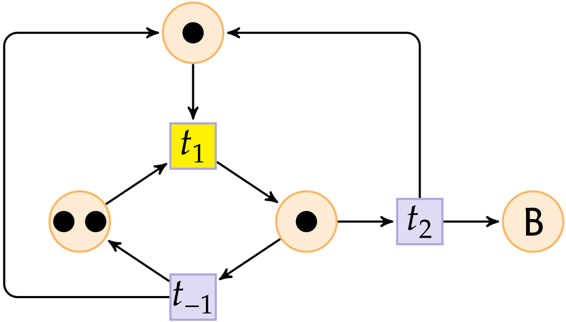

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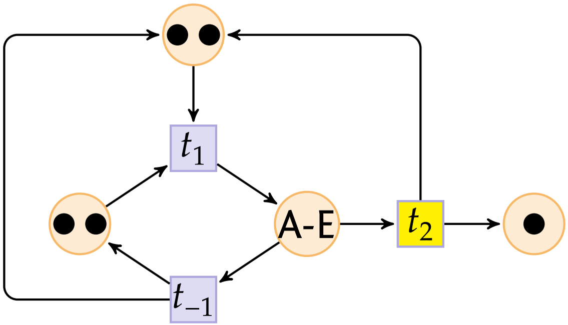


Consume a token in A and E to produce one in A-E (t_1), then do the exact opposite (t_{-1}) or remove the A-E token to add one B and one E (t_2).

P-invariants

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

$$V \cdot M = 0$$

A P-invariant defines a conservation law, whatever the semantics and the dynamics. There are other ones, e.g.:

```
MA(k1) for _ =[A]=> B.
MA(k2) for A => _.
```

when $k_1 = k_2$

Finding (minimal) P-invariants as a CSP

For a Petri net with p places and t transitions, a P-invariant is a vector $V \in \mathbb{N}^p$ s.t.
$\forall 1 \leq i \leq t \quad V \cdot L_i = V \cdot R_i$
$\Rightarrow t$ (linear) equality constraints on p Finite Domain variables

Non trivial iff $V \cdot \mathbf{1} > 0$

Ensure minimality by (labelling from small to big and) branch and bound on a partial base $\mathscr{B}$ of vectors: $\forall B \in \mathscr{B} \ \prod_{B_i \neq 0} V_i = 0$

Removing some subsumed P-invariants remains necessary.

Example

Using the Petri-net of our example we have:

`A + E => A-E`
`A-E => A + E`
`A-E => B + E`
	$A + E = AE$ (1)
	$AE = A + E$ (2)
	$AE = B + E$ (3)

where obviously equation (2) is redundant.

We add $A + E + AE + B > 0$.

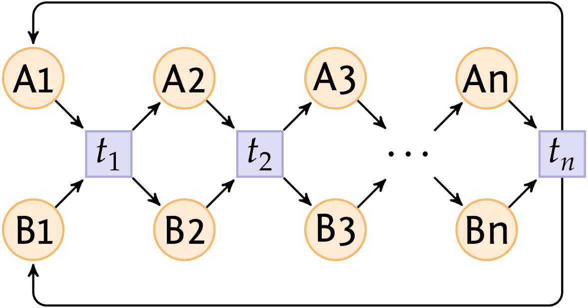
And find two minimal semi-positive P-invariants:

- $E = AE = 1$ and $A = B = 0$
- $A = B = AE = 1$ and $E = 0$

Exponential blow-up

Bad news, the problem actually has an exponential number of solutions

```
A1+B1=>A2+B2
A2+B2=>A3+B3
...
An+Bn=>A1+B1
```



Use CSPs symmetry breaking
(similar to *Equality classes* optimization for FM)

Evaluation

Minimal semi-positive P-invariant computation on big models of biochemical reaction networks is quite efficient: all < 1s

Model	t	p	#	Invariant size
Schoeberl's MAPK [N. Biotech 02]	125	105	14	from 2 to 44 ODE model!
Curie's E2F/Rb [MSB 08]	$\sim$500	$\sim$400	79	from 1 (EP300) to $\sim$230 (E2F1 box)
Kohn's map [MBC 99]	$\sim$800	$\sim$500	65	from 1 (Myt1) to $\sim$200 (e.g., cdk2)

All curated models of `biomodels.net` also < 1s

Conclusion

+ Conservation law computation is a CSP
+ Tropical Equilibration is a CSP
+ Reasonable performance

- Not symbolic
- Rounding errors

"If debugging is the process of removing software bugs, then programming must be the process of putting them in."

– Edsger Dijkstra