IMT SCHOOL FOR ADVANCED STUDIES LUCCA

Evaluation and Reduction of ERODE Ordinary Differential Equations

http://sysma.imtlucca.it/tools/erode/

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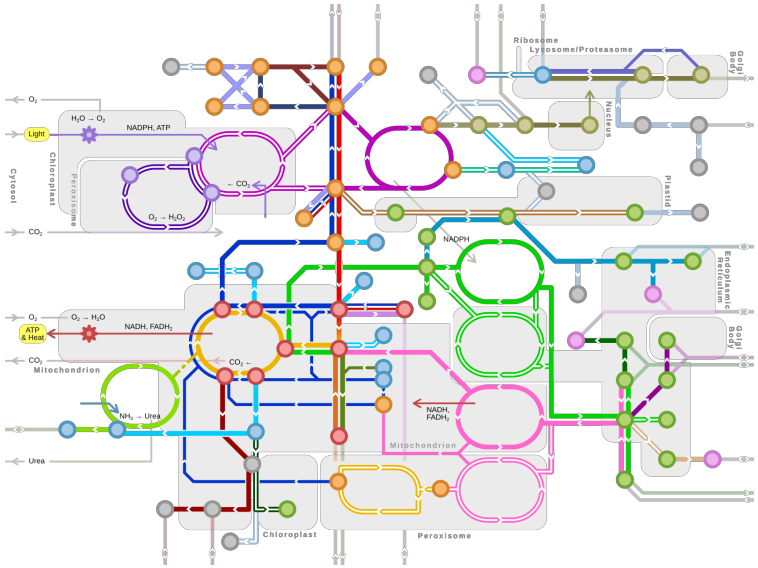
JOINT WORK WITH LUCA CARDELLI, MAX TSCHAIKOWSKI, AND ANDREA VANDIN

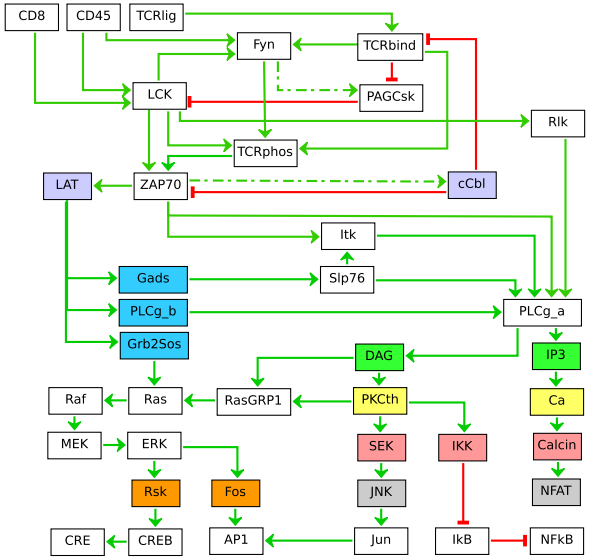
MAXIMAL AGGREGATION OF POLYNOMIAL DIFFERENTIAL EQUATIONS

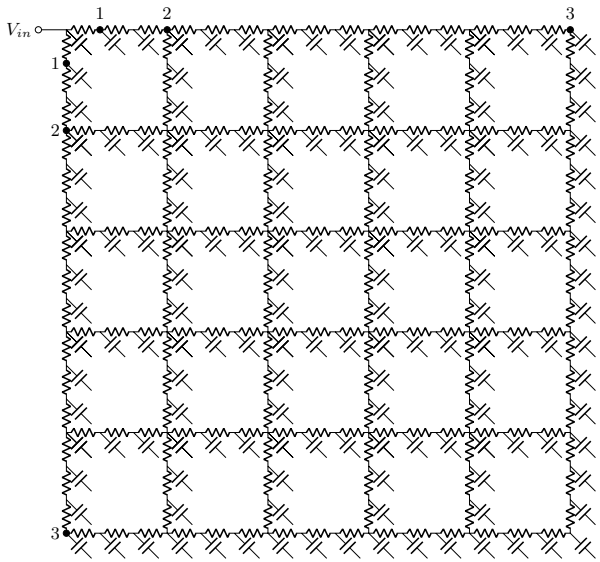
KOLCHIN SEMINAR

14 December 2018

MOTIVATION







(Bio-)chemistry **Systems biology** **Engineering**

- Ordinary differential equations as a universal mathematical modelling language
- System complexity leads to large-scale models (~ one equation per node)
- **Reduction/abstraction** needed to gain physical intelligibility and reduce analysis cost

POLYNOMIAL ODES

- **Polynomial ODEs** are the class of ODEs where the derivatives are multivariate polynomials (over the system's variables)
- They can also encode many nonlinearities (trigonometric, rational, exponential functions)
  - For applications in biochemistry, polynomial ODEs may encode other kinetics such as Hill, Michaelis-Menten, sigmoids, etc.

$$\dot{x} = 1 \qquad \dot{y} = \sin(x)$$

$$z := \sin(x), w := \cos(x)$$

$$\dot{x} = 1 \qquad \dot{y} = z \qquad \dot{z} = w \qquad \dot{w} = -z$$

- Liu J, et. al. (2015) Abstraction of elementary hybrid systems by variable transformation. In International Symposium on Formal Methods (FM).

ANALYZING DIFFERENTIAL EQUATIONS

ODE SYSTEM

$$\frac{dx_1}{dt} = f_1(x_1, \ldots, x_n)$$

$$\frac{dx_2}{dt} = f_2(x_1, \ldots, x_n)$$

$$\ldots$$

$$\frac{dx_n}{dt} = f_n(x_1, \ldots, x_n)$$

NUMERICAL SOLUTION

- Approximate with finite differences

$$\frac{dx_i}{dt} \approx \frac{x_i(t + \Delta t) - x_i(t)}{\Delta t}$$

- Solve ODE iteratively (Euler's method)

$$x_i(t + \Delta t) = x_i(t) + \Delta t \cdot f_i\left(x_1(t), \ldots, x_n(t)\right)$$

Problem: numerical analysis affected by the number of variables as well as the complexity of the derivatives

SOLUTION: MODEL REDUCTION

ORIGINAL SYSTEM

$$\frac{dx_1}{dt} = f_1(x_1, \ldots, x_n)$$

$$\frac{dx_2}{dt} = f_2(x_1, \ldots, x_n)$$

$$\ldots$$

$$\frac{dx_n}{dt} = f_n(x_1, \ldots, x_n)$$

$m \ll n$

- Exact
- Observable preserving
- Automatic

REDUCED SYSTEM

$$\frac{dY_1}{dt} = F_1(Y_1, \ldots, Y_m)$$

$$\ldots$$

$$\frac{dY_m}{dt} = F_m(Y_1, \ldots, Y_m)$$

LUMPING DIFFERENTIAL EQUATIONS

- **Partition of variables** such that each block can be associated with a single equation *[Okino and Mavrovouniotis, 1998]*
- The **lumped ODE** preserves the original dynamics:
  - **Forward lumping** preserves sums of the solutions of the variables in each block
  - **Backward lumping** identifies variables with the same solution in each block
- ODE lumping is complementary to other techniques such as those for fast-slow decomposition (QE/QSSA)

FORWARD LUMPING AT A GLANCE

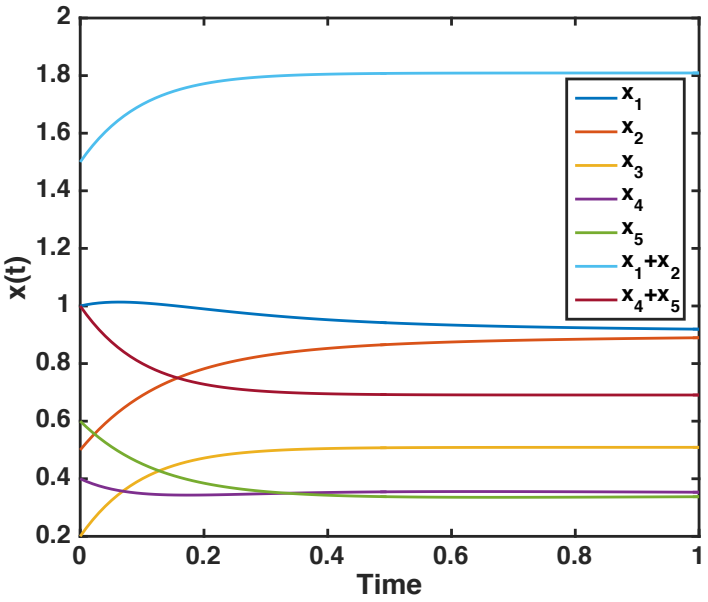
ORIGINAL SYSTEM

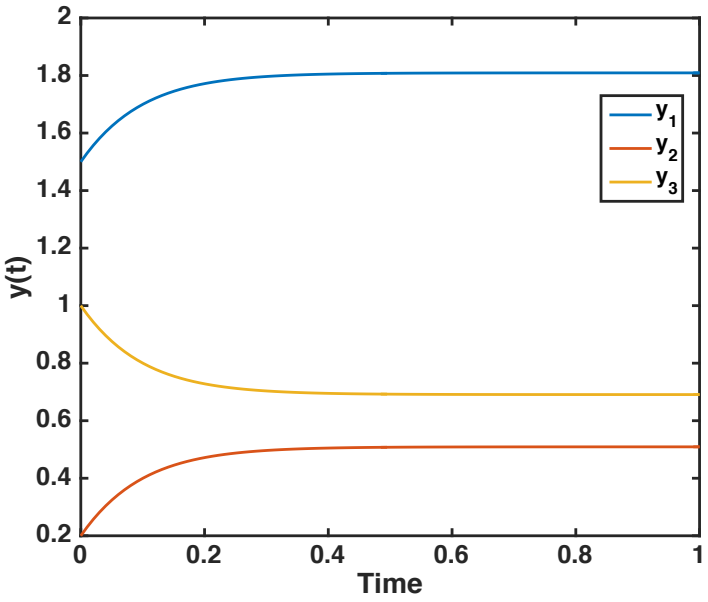
$$\dot{x}_1 = -x_1 + x_2 - 3x_1x_3 + 4x_4$$
$$\dot{x}_2 = +x_1 - x_2 - 3x_2x_3 + 4x_5$$
$$\dot{x}_3 = -3x_1x_3 + 4x_4 - 3x_2x_3 + 4x_5$$
$$\dot{x}_4 = 3x_1x_3 - 4x_4$$
$$\dot{x}_5 = 3x_2x_3 - 4x_5$$

$$Y_1 = x_1 + x_2$$
$$Y_2 = x_3$$
$$Y_3 = x_4 + x_5$$

REDUCED SYSTEM

$$\dot{Y}_1 = -3Y_1Y_2 + 4Y_3$$
$$\dot{Y}_2 = -3Y_1Y_2 + 4Y_3$$
$$\dot{Y}_3 = +3Y_1Y_2 - 4Y_3$$





BACKWARD LUMPING

- Identifies variables that have equal solution when starting with equal initial conditions

ORIGINAL SYSTEM

$$\dot{x}_1 = -3x_1x_2 + 4x_3$$
$$\dot{x}_2 = -3x_1x_2 + 4x_3$$
$$\dot{x}_3 = +3x_1x_2 - 4x_3$$

$$x_1(0) = x_2(0)$$

$$Y_1 = x_1 = x_2$$
$$Y_2 = x_3$$

REDUCED SYSTEM

$$\dot{Y}_1 = -3Y_1^2 + 4Y_2$$
$$\dot{Y}_2 = +3Y_1^2 - 4Y_2$$

FORWARD AND BACKWARD LUMPING ARE NOT COMPARABLE

Forward does not imply backward

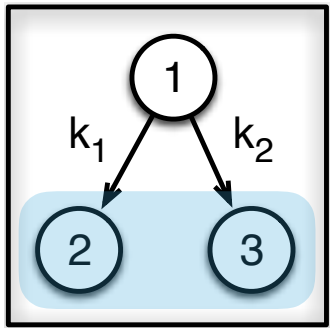
$$\dot{x}_1 = -x_2 + 1$$
$$\dot{x}_2 = -x_1$$

Backward does not imply forward

$$\dot{x}_1 = -x_1x_2$$
$$\dot{x}_2 = -x_1x_2$$

A PARALLEL WITH MARKOV CHAIN LUMPING

STRUCTURE



DYNAMICS

$$\dot{\pi}_1 = -(k_1 + k_2)\pi_1$$
$$\dot{\pi}_2 = k_1\pi_1$$
$$\dot{\pi}_3 = k_2\pi_1$$

LUMPED DYNAMICS

$$\dot{\Pi}_1 = -(k_1 + k_2)\Pi_1$$
$$\dot{\Pi}_2 = (k_1 + k_2)\Pi_1$$

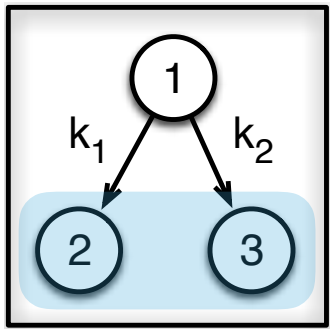
- A partition $\{X_1, X_2, \ldots, X_N\}$ of the state space of a CTMC is ordinarily lumpable if any two states in a block $x_{i_1}, x_{i_2} \in X_I$ have equal aggregate rate toward any block:

$$\sum_{j \in X_J} q_{i_1,j} =: q_{i_1,X_J} = q_{i_2,X_J} := \sum_{j \in X_J} q_{i_2,j}$$

- Preserves **sums of probabilities** *[Kemeny & Snell,1976]*

A PARALLEL WITH MARKOV CHAIN LUMPING

STRUCTURE



DYNAMICS

$$\dot{\pi}_1 = -(k_1 + k_2)\pi_1$$
$$\dot{\pi}_2 = k_1\pi_1$$
$$\dot{\pi}_3 = k_2\pi_1$$

LUMPED DYNAMICS

$$\dot{\Pi}_1 = -(k_1 + k_2)\Pi_1$$
$$\dot{\Pi}_2 = (k_1 + k_2)\Pi_1$$

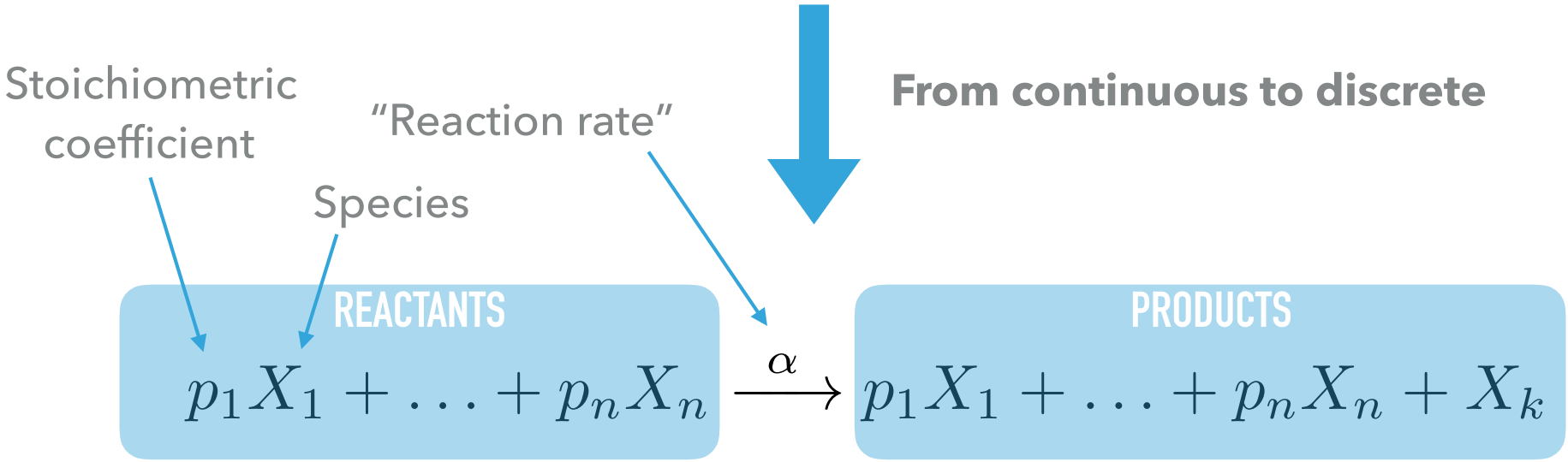
$$q_{2,1} = q_{3,1} = 0 \quad \Longrightarrow \quad \Pi_2(t) = \pi_2(t) + \pi_3(t)$$

- CTMC lumping as a special case of ODE lumping (as a specific class of linear ODEs)
- Condition on structure with implications on dynamics: can we **generalize** to nonlinear (polynomial) ODEs?
- What is the **structural analogous** to a transition matrix?

FROM POLYNOMIAL ODES TO REACTION NETWORKS

- Main idea: take each monomial appearing in the derivative and transform it into an edge of a (labelled) bipartite multigraph: **a reaction**

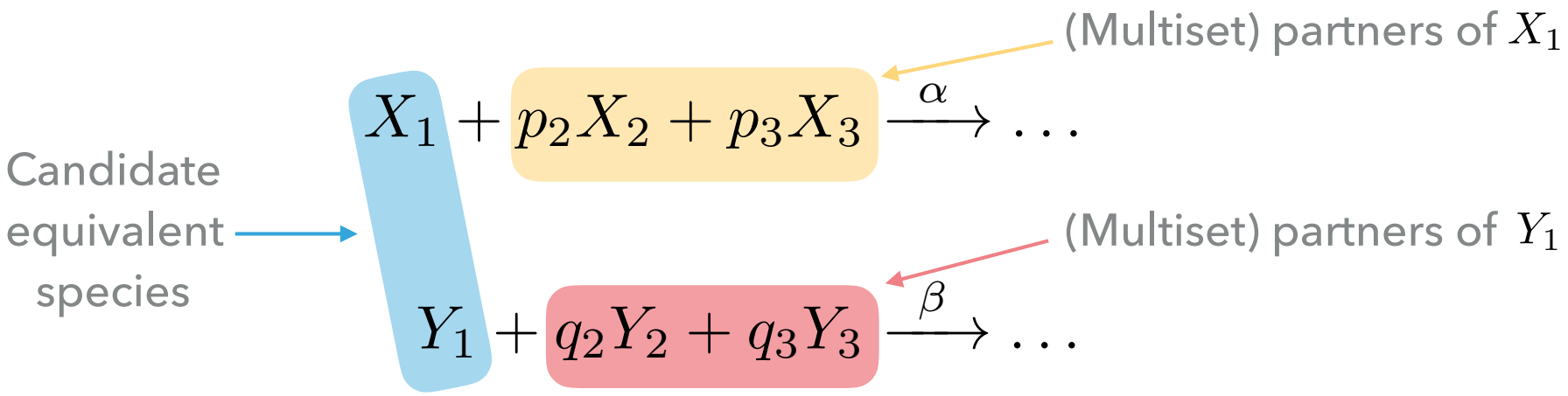
$$\dot{x}_k = \ldots + \alpha \prod_{i=1}^{n} x_i^{p_i} + \ldots$$



No physical meaning, used only for reasoning on equivalences

FORWARD EQUIVALENCE

- Main intuition (borrowed from process algebra): projected to a species, other reactants are partners/communication channels



- Two species are equivalent if they have equal aggregate rate toward any block, ***with any possible partners***

FORWARD EQUIVALENCE, FORMALLY

Multiset of reactants
ρ_i is the multiplicity of X_i

Multiset of products

$$\rho \xrightarrow{\alpha} \pi$$

FLUX NET STOICHIOMETRY

$$\phi(\rho, X_i) := \sum_{\text{all } \rho \xrightarrow{\alpha} \pi} \alpha(\pi_i - \rho_i)$$

FORWARD RATE

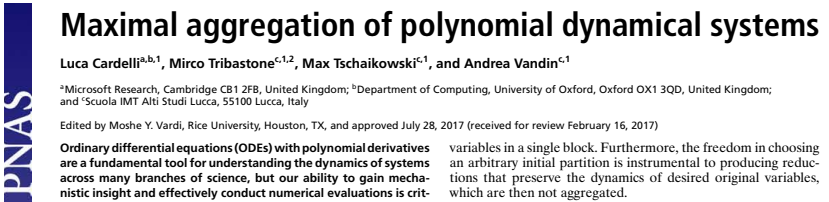
$$\mathbf{fr}(X_i, \rho, G) := \frac{\sum_{X_j \in G} \phi(X_i + \rho, X_j)}{[X_i + \rho]!}, \quad [\rho]! := \binom{\sum_i \rho_i}{\rho_1, \ldots, \rho_n}$$

- A partition of species is a forward equivalence if, for any two blocks H, H' and any two species X_i, X_j in H it holds that

$$\mathbf{fr}(X_i, \rho, H') = \mathbf{fr}(X_j, \rho, H')$$

for all multisets partners ρ

- **Characterisation result**, extending previous work **[CONCUR'15,TACAS'16]**



PNAS

Maximal aggregation of polynomial dynamical systems

Luca Cardelli[a,b,1], Mirco Tribastone[c,1,2], Max Tschaikowski[c,1], and Andrea Vandin[c,1]

[a]Microsoft Research, Cambridge CB1 2FB, United Kingdom; [b]Department of Computing, University of Oxford, Oxford OX1 3QD, United Kingdom; and [c]Scuola IMT Alti Studi Lucca, 55100 Lucca, Italy

Edited by Moshe Y. Vardi, Rice University, Houston, TX, and approved July 28, 2017 (received for review February 16, 2017)

Ordinary differential equations (ODEs) with polynomial derivatives are a fundamental tool for understanding the dynamics of systems across many branches of science, but our ability to gain mechanistic insight and effectively conduct numerical evaluations is crit-

variables in a single block. Furthermore, the freedom in choosing an arbitrary initial partition is instrumental to producing reductions that preserve the dynamics of desired original variables, which are then not aggregated.

BACKWARD EQUIVALENCE

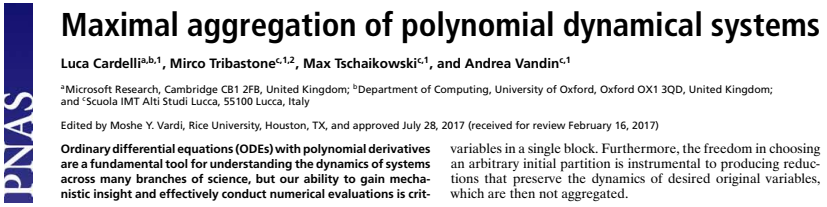
- Definition in the same style, **with a twist:**

$$\mathbf{br}(X_i, \mathcal{M}, H) = \mathbf{br}(X_j, \mathcal{M}, H)$$

where $\mathcal{M}$ is an equivalence relation on multisets of species naturally induced by the equivalence over species, e.g.:

$$A \sim B \implies A + B + C \sim_{\mathcal{M}} 2B + C$$

- **Characterisation result:** extension of **[CONCUR'15]**



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MAXIMAL AGGREGATION THROUGH PARTITION REFINEMENT

FORWARD RATE

$$\mathbf{fr}(X_i, \rho, H') = \mathbf{fr}(X_j, \rho, H')$$

BACKWARD RATE

$$\mathbf{br}(X_i, \mathcal{M}, H) = \mathbf{br}(X_j, \mathcal{M}, H)$$

- Both in the same style of Larsen and Skou's **probabilistic bisimulation** (where the partners are analogues of action type)
- Intuition for computing the maximal aggregation through a **partition refinement algorithm**
  - **Polynomial time and space complexity** (in the number of species, number of monomials and maximum degree)
  - Extensions of the works of *Derisavi et al.*, *Valmari & Franceschinis*, *Baier et al.*, our own **[MFCS'15,TACAS'16]**

PARTITION REFINEMENT EXAMPLE

Reaction Network

$$A_{u,u} \xrightarrow{k_1} A_{p,u}$$
$$A_{p,u} \xrightarrow{k_2} A_{u,u}$$
$$A_{u,u} \xrightarrow{k_1} A_{u,p}$$
$$A_{u,p} \xrightarrow{k_2} A_{u,u}$$
$$A_{p,u} + B \xrightarrow{k_3} A_{p,u}B$$
$$A_{p,u}B \xrightarrow{k_4} A_{p,u} + B$$
$$A_{u,p} + B \xrightarrow{k_3} A_{u,p}B$$
$$A_{u,p}B \xrightarrow{k_4} A_{u,p} + B$$

- **Binding model**
  - Occurs over one of two binding sites when it is phosphorylated
- Classic, basic model in biochemistry
- Intuition: if the binding sites are identical then, by symmetry, explicit identity is unimportant

PARTITION REFINEMENT EXAMPLE

Reaction Network

$$A_{u,u} \xrightarrow{k_1} A_{p,u}$$
$$A_{p,u} \xrightarrow{k_2} A_{u,u}$$
$$A_{u,u} \xrightarrow{k_1} A_{u,p}$$
$$A_{u,p} \xrightarrow{k_2} A_{u,u}$$
$$A_{p,u} + B \xrightarrow{k_3} A_{p,u}B$$
$$A_{p,u}B \xrightarrow{k_4} A_{p,u} + B$$
$$A_{u,p} + B \xrightarrow{k_3} A_{u,p}B$$
$$A_{u,p}B \xrightarrow{k_4} A_{u,p} + B$$

Current partition

$$\{\{A_{u,u}, A_{p,u}, A_{u,p}, B, A_{p,u}B, A_{u,p}B\}\}$$

First iteration

Set of splitters

$$\{\{A_{u,u}, A_{p,u}, A_{u,p}, B, A_{p,u}B, A_{u,p}B\}\}$$

sp

Non-zero values

$$\mathbf{fr}(A_{p,u}, B, sp) = -3$$
$$\mathbf{fr}(A_{u,p}, B, sp) = -3$$
$$\mathbf{fr}(B, A_{p,u}, sp) = -3$$
$$\mathbf{fr}(B, A_{u,p}, sp) = -3$$
$$\mathbf{fr}(A_{p,u}B, \emptyset, sp) = 4$$
$$\mathbf{fr}(A_{u,p}B, \emptyset, sp) = 4$$

- The initial partition may be arbitrary
  - Useful to **single out observables** that are not to be aggregated

PARTITION REFINEMENT EXAMPLE

Current partition

$$\{\{A_{u,u}\}, \{A_{p,u}, A_{u,p}\}, \{B\}, \{A_{p,u}B, A_{u,p}B\}\}$$

Second iteration

Set of splitters

$\{\{A_{u,u}\}, \{B\}, \{A_{p,u}B, A_{u,p}B\}\}$

sp

$\mathbf{fr}(A_{u,u}, \emptyset, sp) = -2$

$\mathbf{fr}(A_{p,u}, \emptyset, sp) = 2$

$\mathbf{fr}(A_{u,p}, \emptyset, sp) = 2$

Third iteration

Set of splitters

$\{\{B\}, \{A_{p,u}B, A_{u,p}B\}\}$

sp

$\mathbf{fr}(A_{p,u}, B, sp) = -3$

$\mathbf{fr}(A_{u,p}, B, sp) = -3$

$\mathbf{fr}(B, A_{p,u}, sp) = -3$

$\mathbf{fr}(B, A_{u,p}, sp) = -3$

$\mathbf{fr}(A_{p,u}B, \emptyset, sp) = 4$

$\mathbf{fr}(A_{u,p}B, \emptyset, sp) = 4$

Fourth iteration

Set of splitters

$\{\{A_{p,u}B, A_{u,p}B\}\}$

sp

$\mathbf{fr}(A_{p,u}, B, sp) = 3$

$\mathbf{fr}(A_{u,p}, B, sp) = 3$

$\mathbf{fr}(B, A_{p,u}, sp) = 3$

$\mathbf{fr}(B, A_{u,p}, sp) = 3$

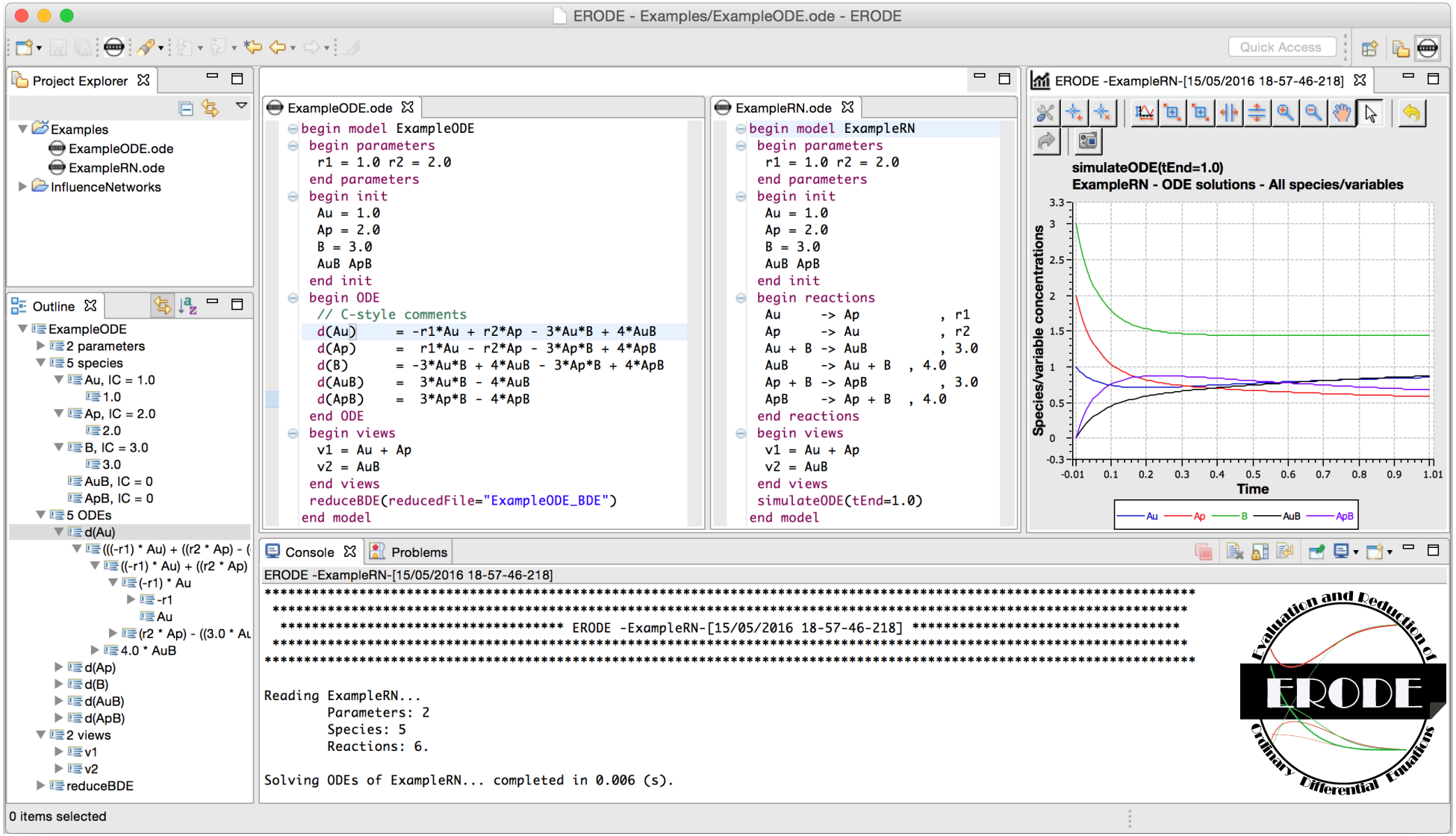
$\mathbf{fr}(A_{p,u}B, \emptyset, sp) = -4$

$\mathbf{fr}(A_{u,p}B, \emptyset, sp) = -4$

- Splitters do not distinguish current equivalences classes
- Terminates with the maximal aggregation that refines the input partition
- Similar approach for backward equivalence

EVALUATION AND REDUCTION OF ORDINARY DIFFERENTIAL EQUATIONS

Scalability: 2.5M variables and 5M reactions analysed in ~5 minutes on an ordinary laptop



http://sysma.imtlucca.it/tools/erode/

[TACAS'17]

MODEL FORMATS

- ERODE has two internal specification formats

```
begin model ExampleODE
 begin parameters
  r1 = 1.0 r2 = 2.0
 end parameters
 begin init
  Au = 1.0 Ap = 2.0 B = 3.0
  AuB ApB
 end init
 begin partition
  {Au,Ap}, {AuB}, {B,ApB}
 end partition
 begin ODE
  // C-style comments
  d(Au)   = -r1*Au + r2*Ap - 3*Au*B + 4*AuB
  d(Ap)   =  r1*Au - r2*Ap - 3*Ap*B + 4*ApB
  d(B)    = -3*Au*B + 4*AuB - 3*Ap*B + 4*ApB
  d(AuB)  =  3*Au*B - 4*AuB
  d(ApB)  =  3*Ap*B - 4*ApB
 end ODE
 begin views
  v1 = Au + Ap
  v2 = AuB
 end views
 reduceBDE(reducedFile="ExampleODE_BDE.ode")
end model
```

```
begin model ExampleRN
 begin parameters
  r1 = 1.0 r2 = 2.0
 end parameters
 begin init
  Au = 1.0 Ap = 2.0 B = 3.0
  AuB ApB
 end init
 begin partition
   {Au,Ap}, {AuB}
  end partition
 begin reactions
  Au      -> Ap       , r1
  Ap      -> Au       , r2
  Au + B -> AuB      , 3.0
  AuB     -> Au + B   , 4.0
  Ap + B -> ApB      , 3.0
  ApB     -> Ap + B   , 4.0
 end reactions
 begin views
  v1 = Au + Ap
  v2 = AuB
 end views
 simulateODE(tEnd=1.0)
end model
```

- Basic support for:
  - BioNetGen (net format)
  - SBML
  - MATLAB
- Planned support:
  - GINSIM
  - BioModels
  - …

SOME BENCHMARKS

Original Model			Forward		Backward	
ID	Reactions	Vars	Vars	Time	Vars	Time
CRN1	**3,538,944**	**262,146**	222	**7.5 s**	222	**12.0 s**
CRN5	194,054	14,531	10,855	0.4 s	6,634	0.6 s
CRN13	24	18	18	4 ms	7	4 ms
AFF2	8,814,880	1,270,433	160,951	~ 10 min	639,509	~ 3 min

- Original CRN could not be solved on our machine

Sneddon M W, et al. (2011) Efficient modeling, simulation and coarse-graining of biological complexity with NFsim. In Nature Methods

SOME BENCHMARKS

Original Model			Forward		Backward	
ID	Reactions	Vars	Vars	Time	Vars	Time
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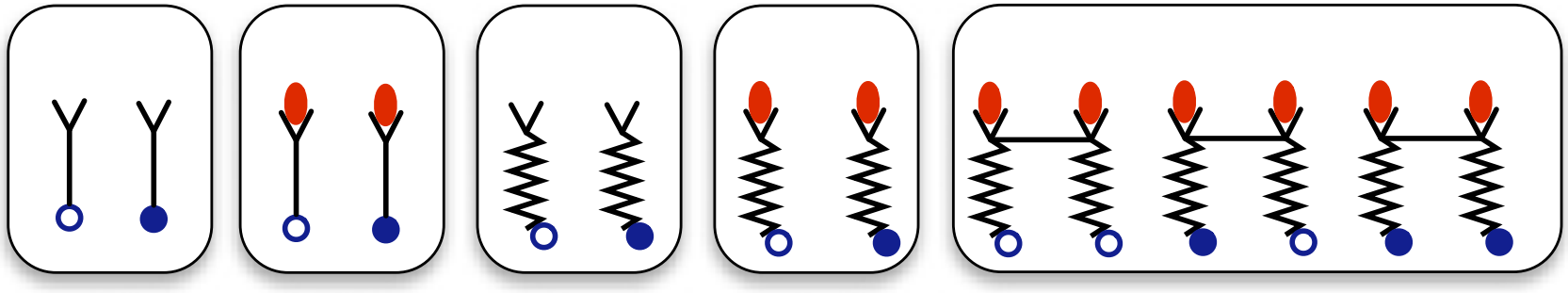
CRN13	24	18	18	4 ms	7	4 ms
AFF2	8,814,880	1,270,433	160,951	~ 10 min	639,509	~ 3 min

- Forward and backward equivalence are not comparable

Suderman R, et al. (2013) Machines vs. ensembles: Effective MAPK signaling through heterogeneous sets of protein complexes . In PLOS Computational Biology.

WHAT DOES AGGREGATION PRESERVE?



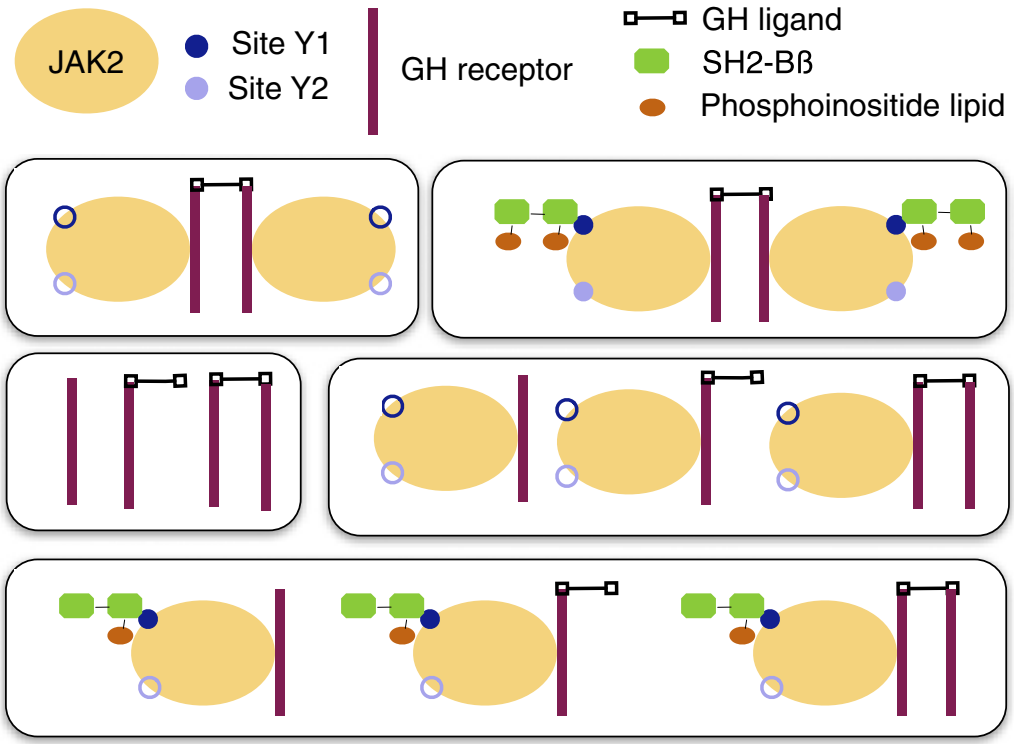
- Equal complexes up to the states of the phosphorylation site (hollow/solid blue circles) of EGFR independently of:
  - Conformational change of the cytosolic tail
  - EGF binding state
  - Conformational of cytosolic tail
  - Cross-linking

FROM 923 SPECIES AND 11,918 REACTIONS TO 87 SPECIES AND 705 REACTIONS

Kozer N, et al. (2013) Exploring higher-order EGFR oligomerisation and phosphorylation - a combined experimental and theoretical approach. Mol Biosyst 9: 1849-1863

WHAT DOES AGGREGATION PRESERVE?

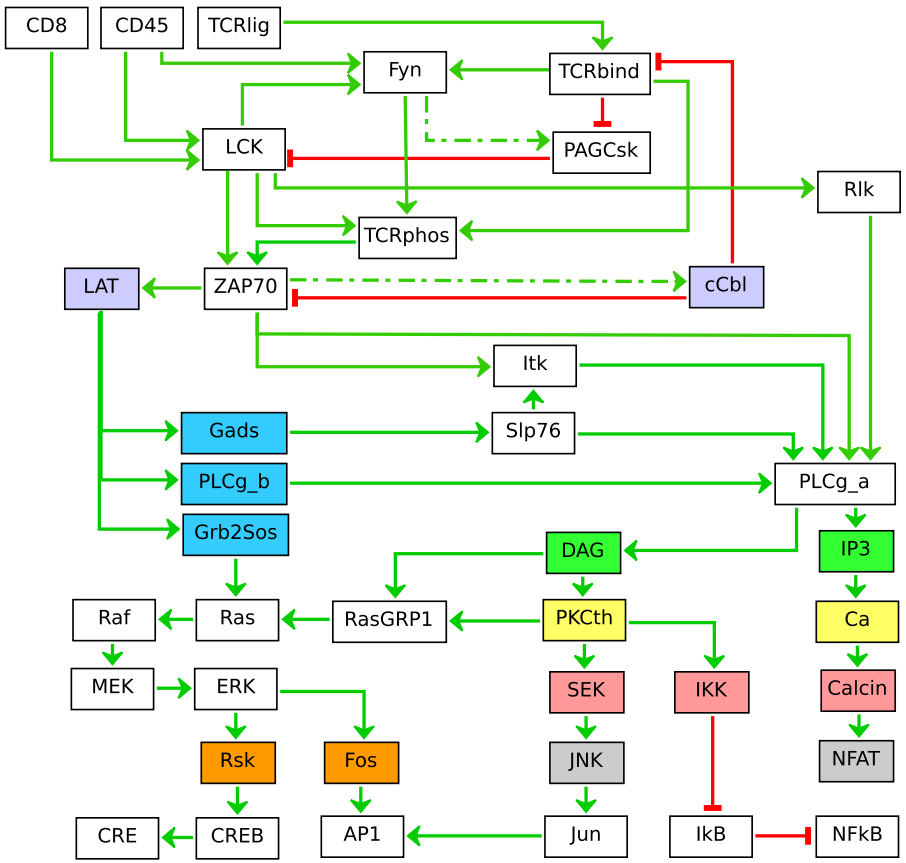
- Molecular complexes with different structure but equivalent dynamics
- Only holds when the complex is endocytosed



FROM 471 SPECIES AND 5,033 REACTIONS TO 345 SPECIES AND 4,068 REACTIONS

Barua D, Faeder JR, Haugh JM (2009) A bipolar clamp mechanism for activation of Jak-family protein tyrosine kinases. PLoS Comput Biol 5:e1000364

REDUCTION OF GENE REGULATORY NETWORKS



- Differential-equation semantics for gene networks
- Each node is a an ODE variable
- Update agrees with the boolean semantics for 0/1 inputs
- Result is a polynomial ODE of arbitrary degree

$$y = x_1 \wedge x_2 \Longrightarrow \dot{y} = x_1 x_2$$

- **Wittmann DM, et al. (2009) Transforming boolean models to continuous models: Methodology and application to t-cell receptor signaling. BMC Syst Biol 3:1-21**
- **Le Novere N (2015) Quantitative and logic modelling of molecular and gene networks. Nat Rev Genet 16:146-158**

CHAINS OF SYMMETRIES: EQUIVALENT NODES RECEIVE EQUIVALENT INFLUENCES

ONGOING AND FUTURE WORK

- All our algorithms so far are for **exact reductions**
  - Approximate reductions as perturbations of exact ones ***[QEST'18]***
- **Differential-algebraic equations *[CDC'18]***
  - Continuous dynamics with constraints (mass conservation, rigid-body dynamics, current and voltage laws, …)
  - Popular in many branches of science and engineering
- **Applications in new areas** (e.g., brain network models)

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quanticol

http://quanticol.eu

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