Graph-based, dynamics-preserving reduction of (bio)chemical systems

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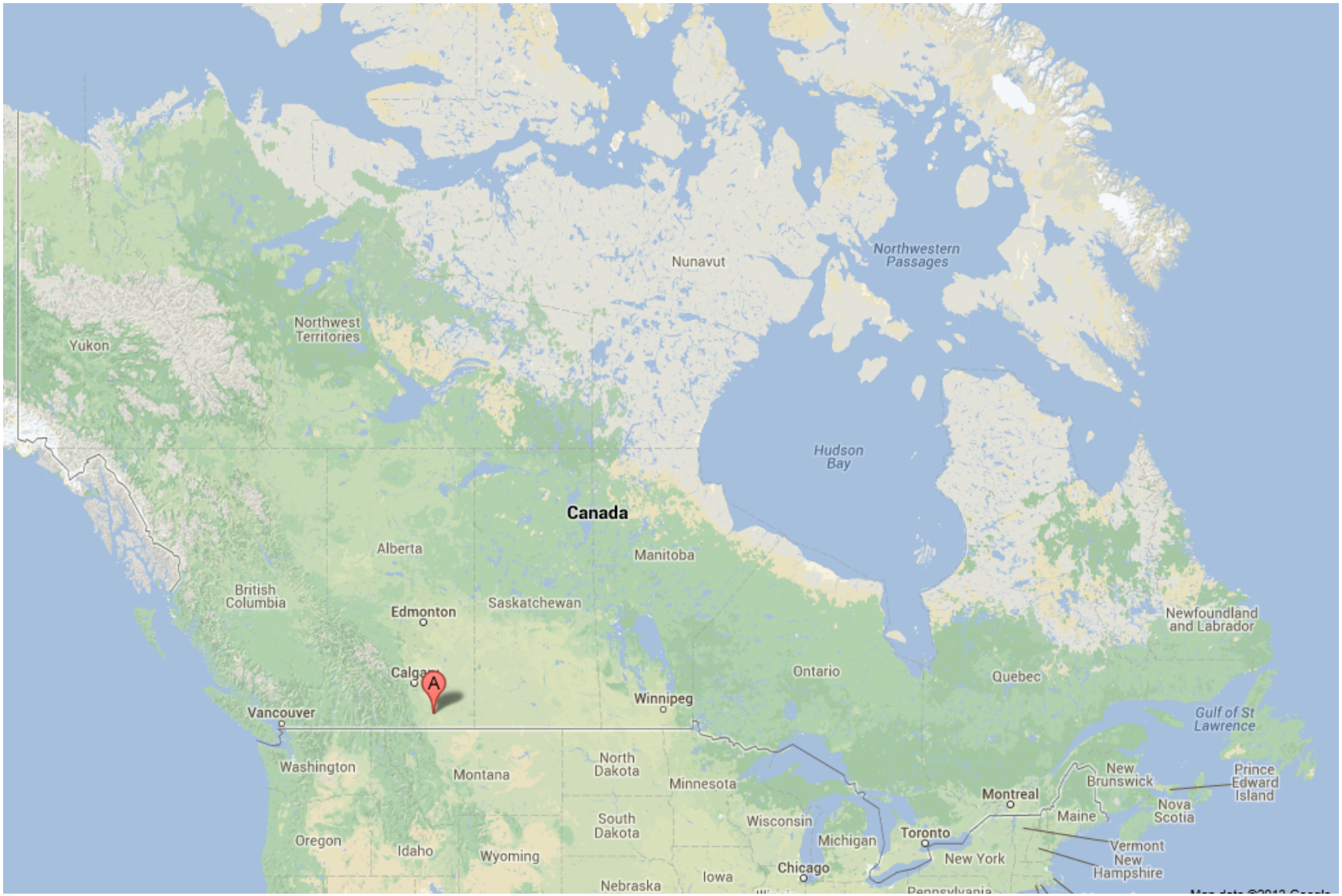
Where is Lethbridge?



University of Lethbridge campus

Thanks!

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Northern Illinois University

Catharine Roussel

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Part I

Introduction

Lots of interesting dynamics in cell biology

- Some cell/developmental events are associated with "clocks", i.e. oscillators.
  - Circadian oscillator
  - Somitogenesis
- Multiple cell fates from a single genome is an example of multistability.
  - Totipotency, pluripotency, ...
- Waves (e.g. of morphogens) often result from bistability.
  - 'Wave-pinning' in cell polarization
- Turing instabilities are often invoked as explanations for developmental patterning.
  - Animal coat patterns
  - Left-right asymmetry of internal organs?

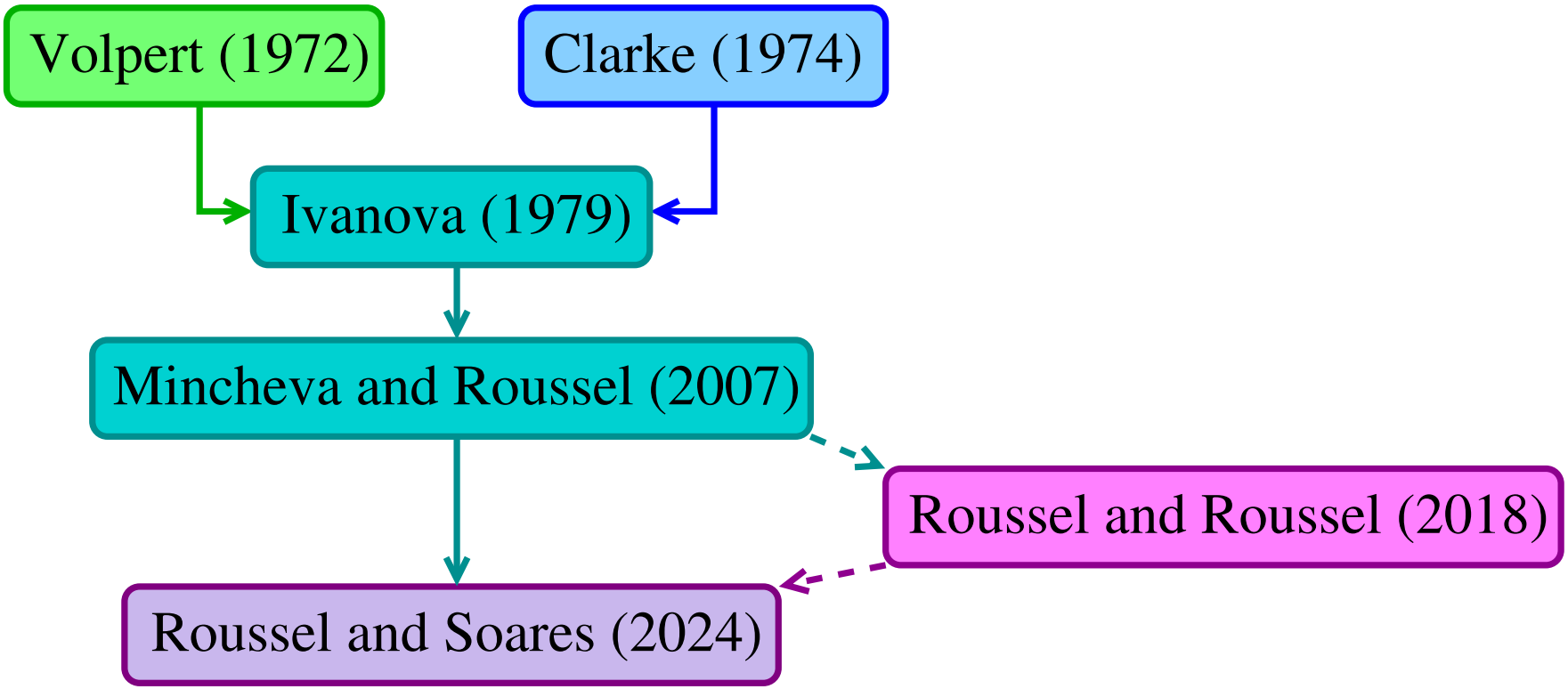
Problems with models in cell biology

- Models are often large.
- Few parameters available from the literature
- Available parameters often not "transferable"
- The models themselves are often subject to significant uncertainty.

Can we simplify a large model to create a smaller model that preserves the dynamics of the original without detailed knowledge of the parameters?

Qualitative stability analysis

- Long history of qualitative stability analysis
- Genealogy of our methods:



One-minute overview

- The Ivanova family of methods applies to mass-action systems.
- Roughly: build a (bipartite) graph of the reaction system and look for specific structures associated with instabilities.
- Provides a single, simple necessary condition for saddle-node bifurcations (multistability)
- We get a similarly simple condition for Turing bifurcations.
- For Andronov-Hopf bifurcations, there are two cases, one much simpler than the other.
- Simplification can preserve dynamics if it preserves the graphical conditions for bifurcations.

Part II

Bipartite graphs and Ivanova's critical fragments

The bipartite graph of a chemical reaction

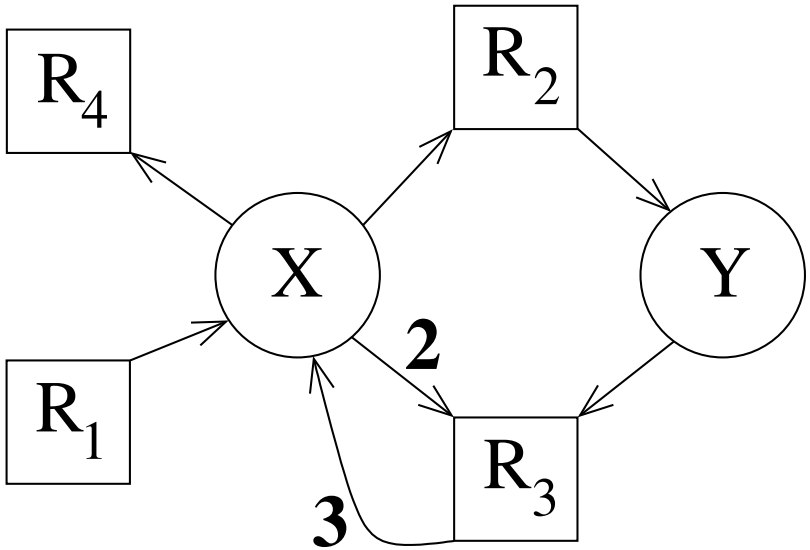
Example: the Brusselator

$$\xrightarrow{k_1} \mathrm{X}$$

$$\mathrm{X} \xrightarrow{k_2} \mathrm{Y}$$

$$2\,\mathrm{X} + \mathrm{Y} \xrightarrow{k_3} 3\,\mathrm{X}$$

$$\mathrm{X} \xrightarrow{k_4}$$



The bipartite graph and the characteristic polynomial

- Some subsets of the bipartite graph known as fragments have a 1:1 correspondence with terms in the characteristic polynomial.
- A fragment consists of k distinct chemical species and of k (not necessarily distinct) reactions.
- Specifically, a fragment containing k chemical species corresponds to one of the terms that appears in the coefficient of λ^{n-k}.

$$S_k^{(\eta)} \begin{pmatrix} A_{i_1} & A_{i_2} & \dots & A_{i_k} \\ R_{j_1} & R_{j_2} & \dots & R_{j_k} \end{pmatrix}$$

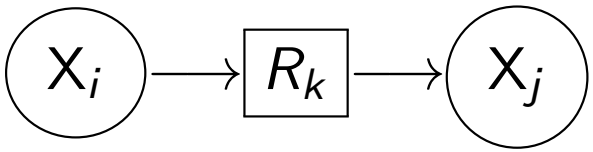
$$\Updownarrow$$

$$p(\lambda) = \lambda^n + a_1\lambda^{n-1} + \ldots + \lambda^{n-k}\left(\ldots + K_{S_k^{(\eta)}} \frac{v_{j_1} v_{j_2} \ldots v_{j_k}}{c_{i_1} c_{i_2} \ldots c_{i_k}} + \ldots\right) + \ldots + a_n$$

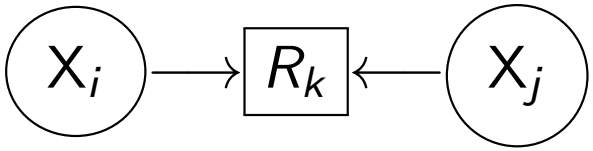
Fragments

- Fragments are unions of subgraphs, which in turn consist of unions of cycles and reactant-to-reaction edges with each chemical species at the origin of only one edge in each subgraph.

- A cycle is made of paths.

  Positive path:  denoted $[\mathrm{X}_i, R_k, \mathrm{X}_j]$,

  encodes a reactant-to-product relationship

  Negative path:  denoted $\overline{[\mathrm{X}_i, R_k, \mathrm{X}_j]}$,

  encodes a co-reactant relationship

- A positive cycle has an even number of negative paths, and a negative cycle has an odd number.

Calculation of the coefficient of a fragment, K_{S_k}

$$K_{S_k^{(\eta)}} = \sum_{g \in S_k^{(\eta)}} K_g$$

Reaction j: $\sum_i \alpha_{ji} \mathrm{X}_i \to \sum_i \beta_{ji} \mathrm{X}_i$

$$K_g = \prod_{[\mathrm{X}_i, v_j] \in g} \alpha_{ji}^2 \prod_{C \in g} K_C$$

$$K_C = - \prod_{\overline{[\mathrm{X}_k, v_j, \mathrm{X}_i]}} (-\alpha_{jk}\alpha_{ji}) \prod_{[\mathrm{X}_k, v_j, \mathrm{X}_i]} \alpha_{jk}\beta_{ji}$$

- We say that a fragment is critical if $K_{S_k^{(\eta)}} < 0$.
- A critical fragment must contain at least one subgraph with an odd number of positive cycles.

Some easily applied theorems

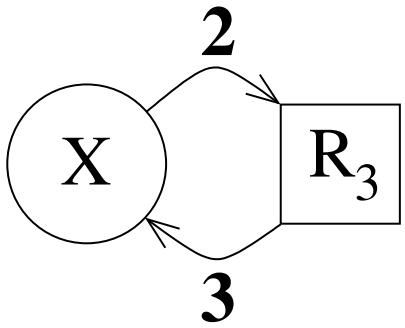
Theorem 1: A critical fragment of order n is a necessary condition for a saddle-node bifurcation.
(n = number of independent chemical species)

Theorem 2: A critical fragment of order $k < n$ is a necessary condition for an Andronov-Hopf bifurcation due to positive feedback.
Mincheva and Roussel, *J. Math. Biol.* **55**, 61 (2007)

Theorem 3: A critical fragment is a necessary condition for a Turing bifurcation.
Mincheva and Roussel, *J. Chem. Phys.* **125**, 204102 (2006)

A simple example: the Brusselator

- Critical fragment:



$$K_{S_1^{(2)}} = -2$$

- Characteristic polynomial:

$$p(\lambda) = \lambda^2 + \lambda \left(\frac{v_2}{x} + \frac{-2v_3}{x} + \frac{v_4}{x} + \frac{v_3}{y} \right)_{(x^*,y^*)} + \left. \frac{v_3}{y} \frac{v_4}{x} \right|_{(x^*,y^*)}$$

What about negative feedback?

- The case of oscillations due to negative feedback is much harder. Mincheva, *Bull. Math. Biol.* **73**, 2277 (2012)

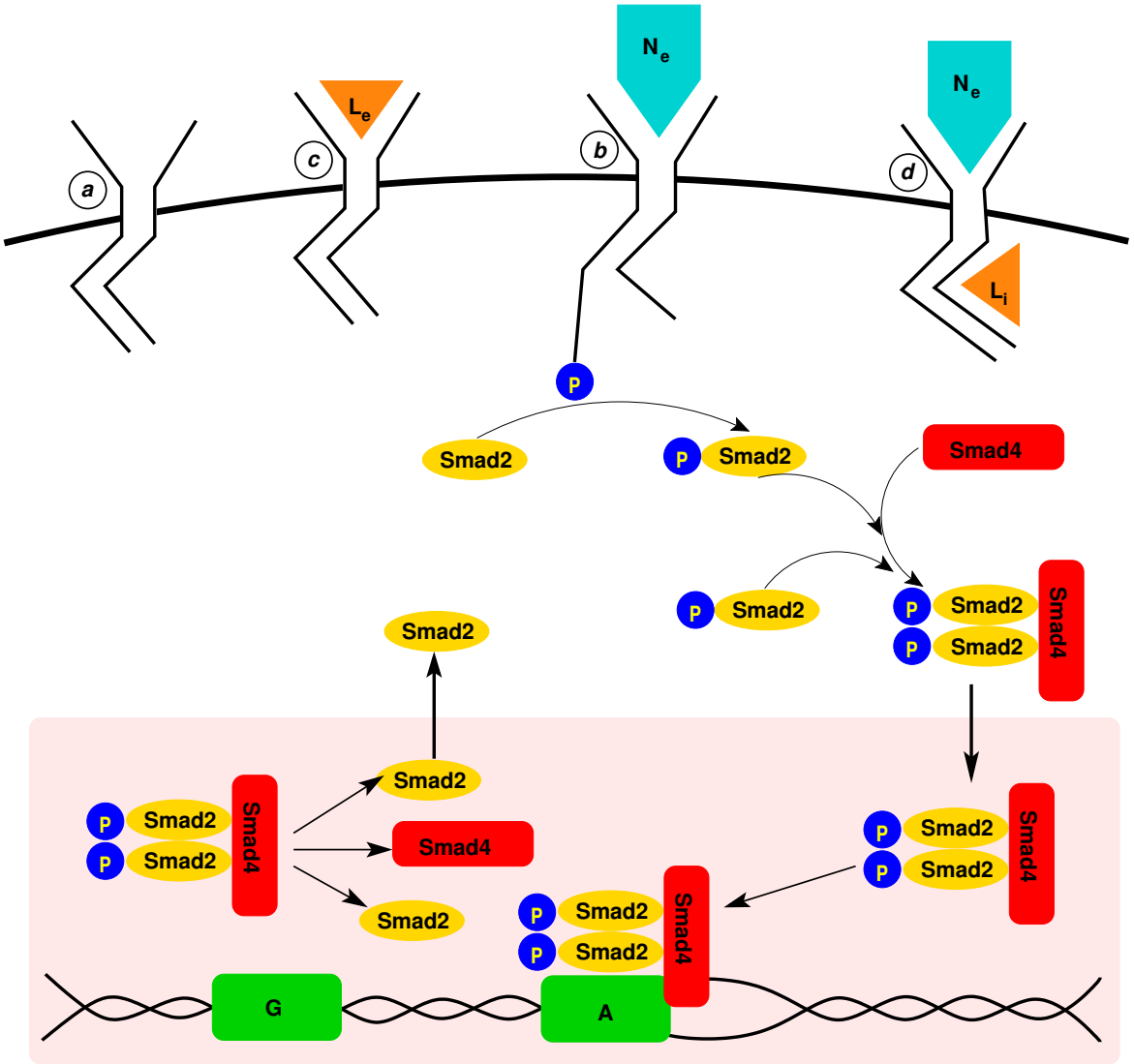
- It involves finding two positive fragments of orders $k+1$ and $k-2$ satisfying a complicated condition.

- A necessary (but far from sufficient) condition is that one of the pair of fragments contains a cycle of order 3 or more.

Part III

A model and an observation

An example: left-right development



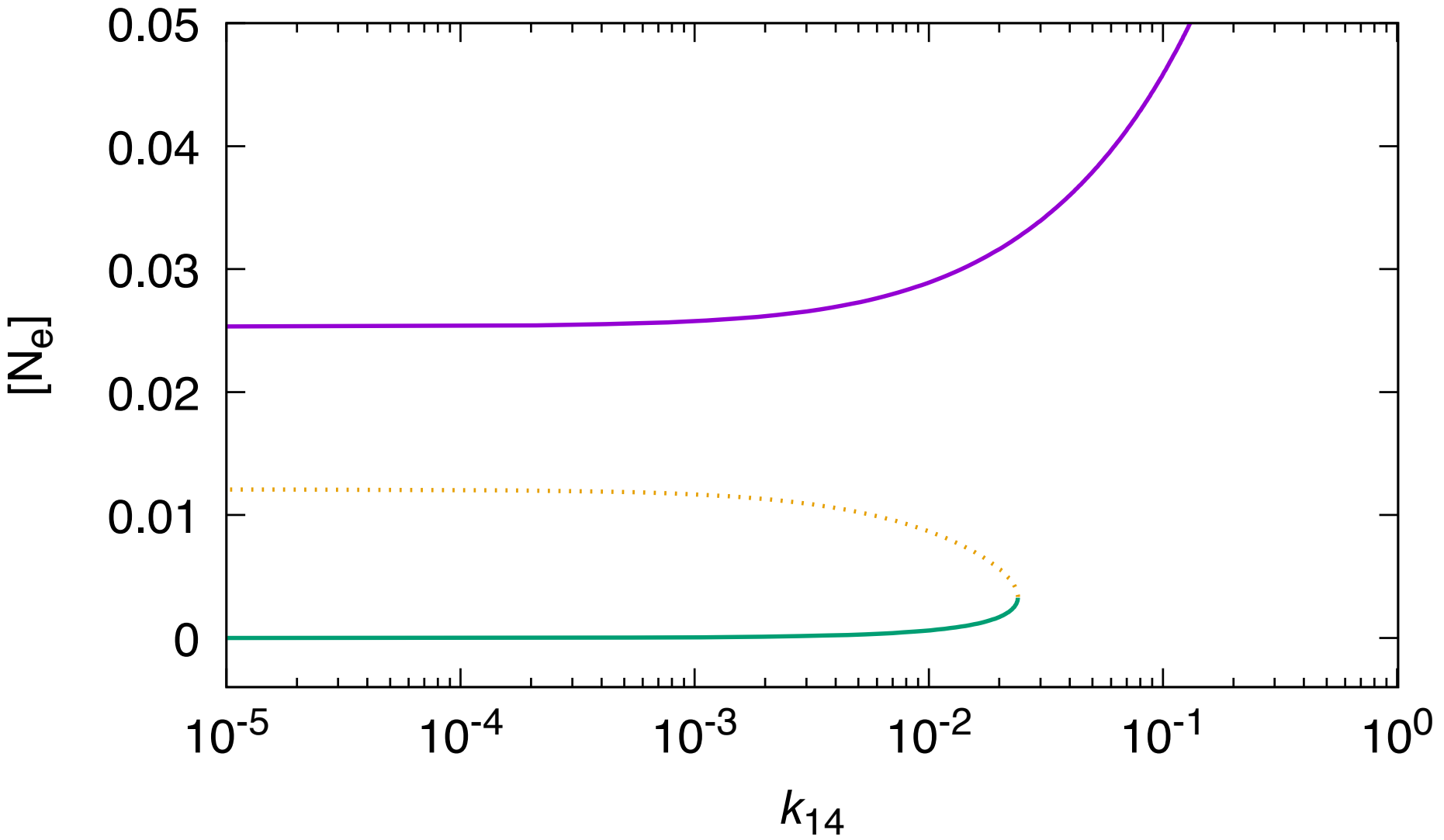
18 chemical species

5 conservation relations

$n = 13$

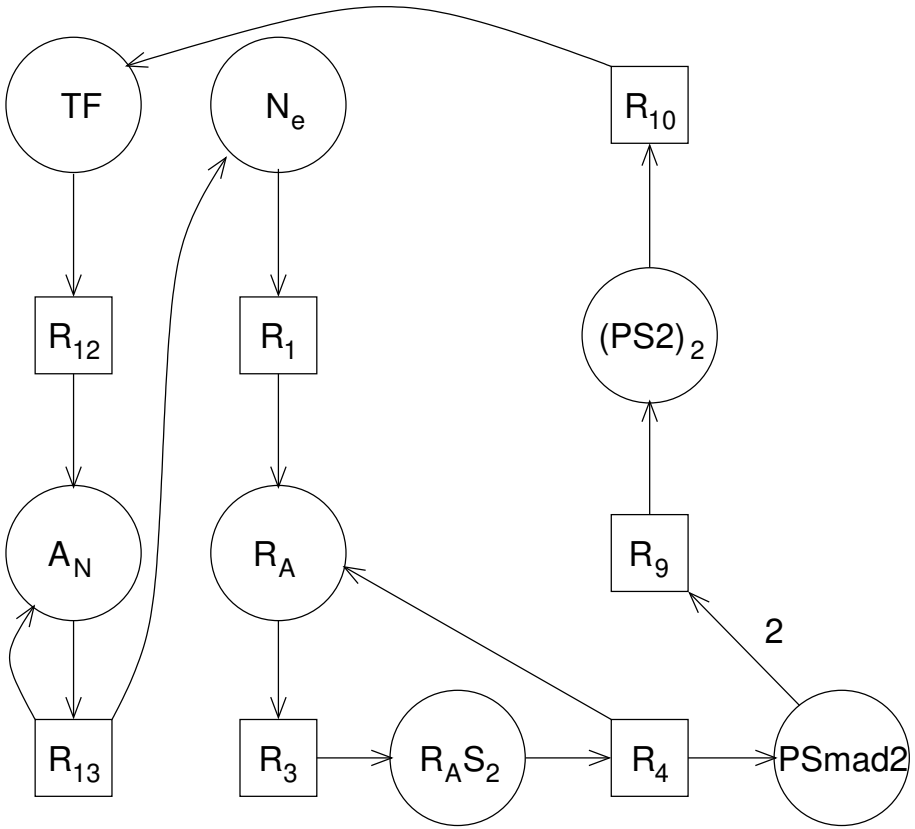
Roussel and Roussel, *BioSystems* **173**, 281 (2018)

Bistability in model



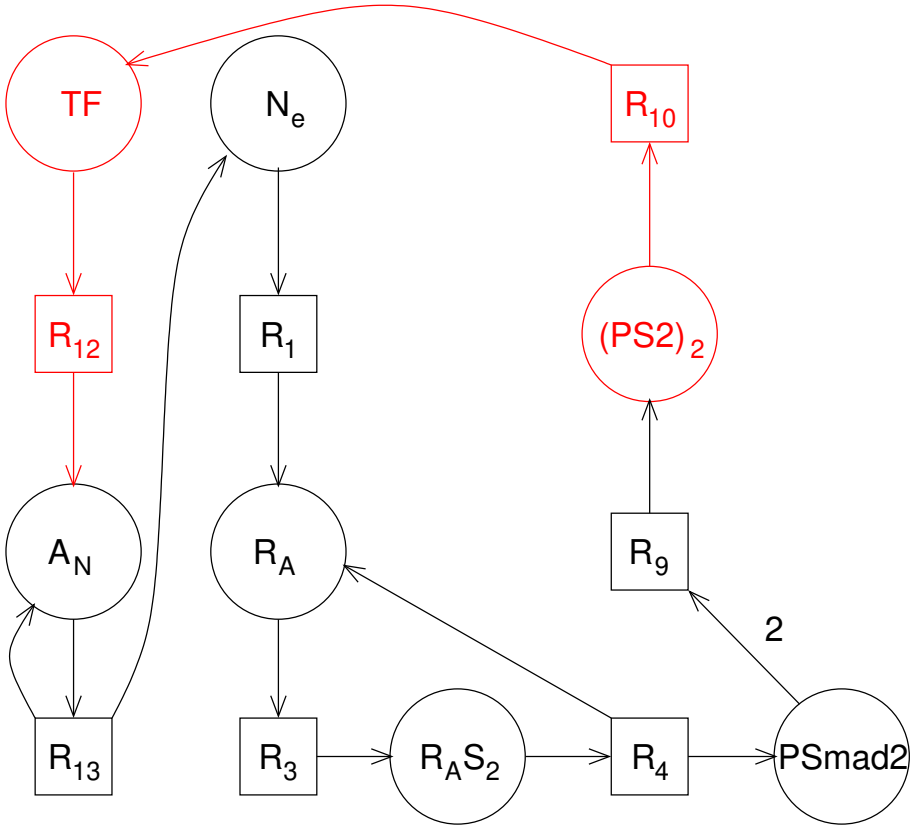
$G_N \xrightarrow{k_{14}} G_N + N_e$ (leaky expression of Nodal)

The smallest critical fragment



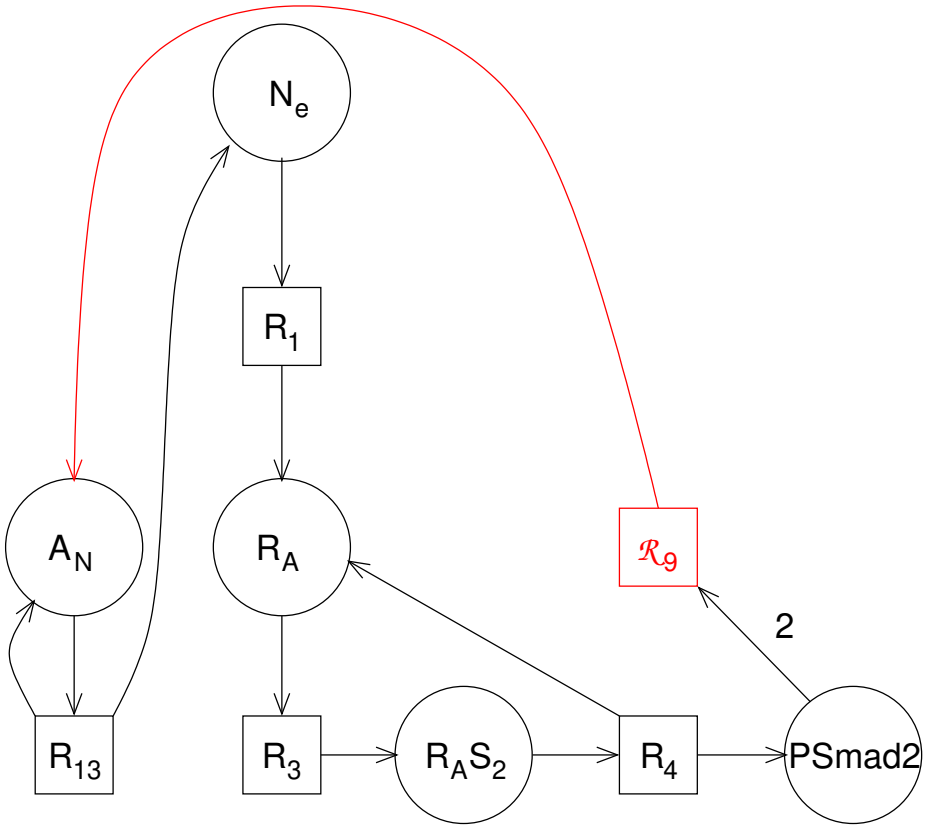
- $k = 7 < n \ldots$
- $\ldots$ but $k = n$ in a model without Lefty

An opportunity for model simplification



Observation: the fragment would remain critical if we removed the highlighted vertices of the cycle.

Simplified critical fragment



- Simplified model can be verified to still be bistable
- Simplification highlights the importance of the involvement of two molecules of Smad2 in the transcription factor
- Dynamically, assembly on the Smad4 scaffold or binding to other proteins to form the transcription factor not important

Part IV

A formal approach

Dynamics-preserving model reduction

Goals and potential issues

- We often don't know what the critical fragment is, particularly in a large mechanism with a large number of reactions and species.
- Can we simplify the model without knowing the critical fragment?
- And if we know the critical fragment, does that give us additional freedom?

Some definitions

Conservative reductions avoid removals that may change the number or types of cycles in the overall bipartite graph.

Unidirectional cycles can only be traversed in one direction.

An entry vertex of a cycle has a connection outside of the cycle.

Roussel and Soares, *J. Math. Biol.* **89**, 42 (2024)

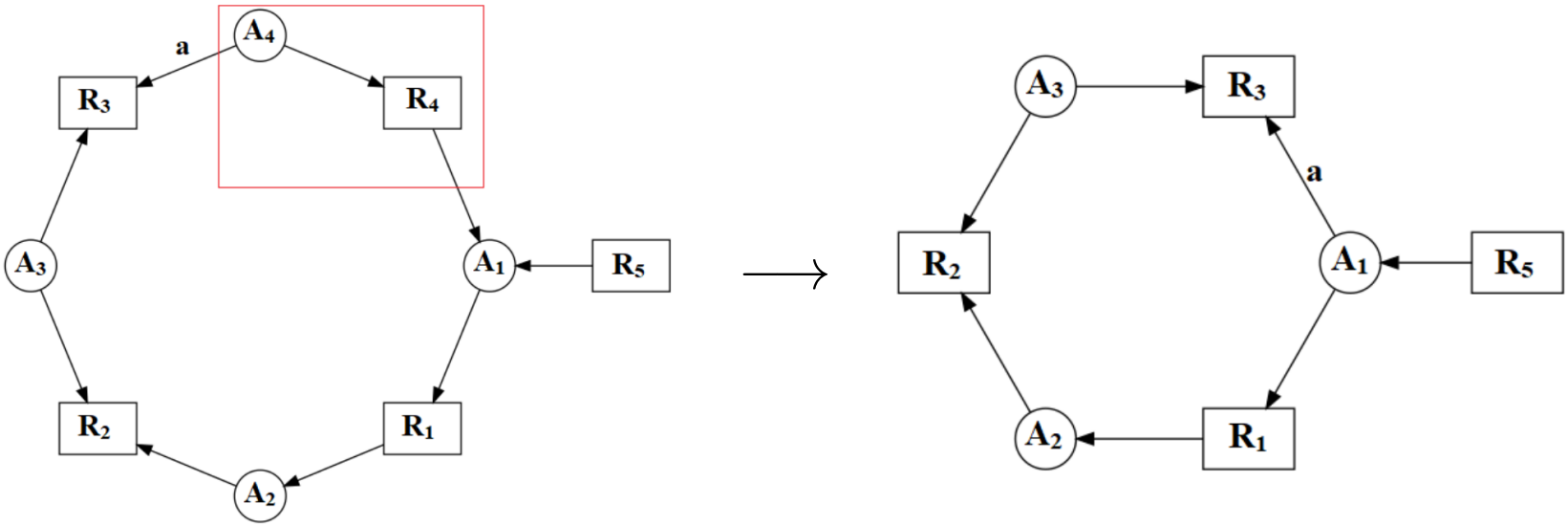
Rules of thumb for conservative reductions

- Don't try to simplify cycles that aren't unidirectional.
- Don't mess up unidirectionality.
- Don't eliminate cycles or create new ones.
- Generally avoid touching entry vertices.

Roussel and Soares, *J. Math. Biol.* **89**, 42 (2024)

A graphical tour of the reduction theorems

Theorem 1: removing positive paths



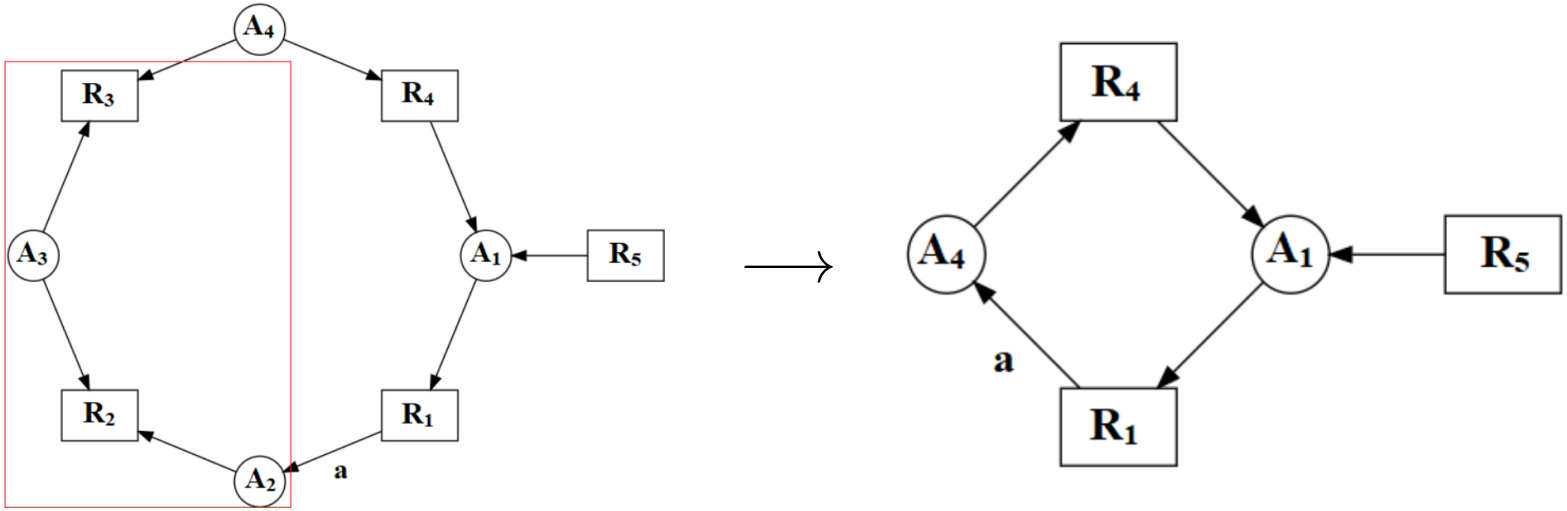
Corresponds to stoichiometric elimination:

$$\begin{array}{rl} R_3 & A_3 + aA_4 \to \\ -\,aR_4 & -\,a\,(A_4 \to A_1) \\ \hline \mathcal{R}_3 & A_3 + aA_1 \to \end{array}$$

A graphical tour of the reduction theorems

Theorem 2: removing consecutive negative paths

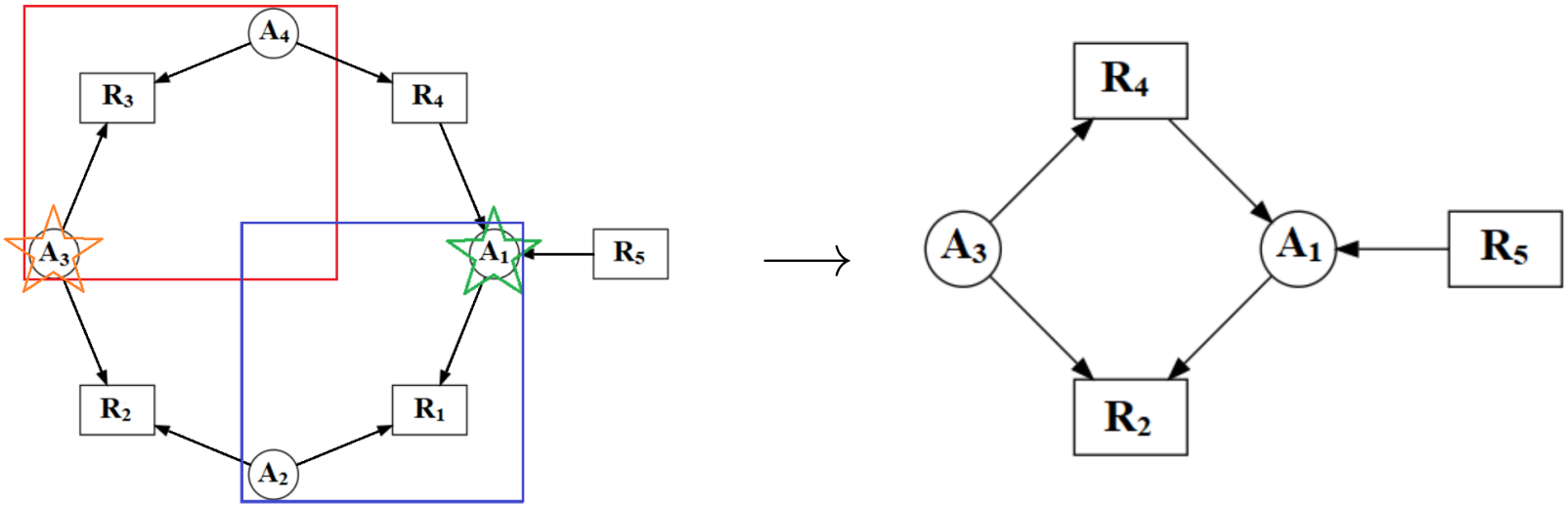
In pairs!



$$\begin{array}{rl} \mathsf{R}_1 & \mathsf{A}_1 \to a\mathsf{A}_2 \\ + a\mathsf{R}_2 & + a\,(\mathsf{A}_2 + \mathsf{A}_3 \to) \\ - a\mathsf{R}_3 & - a\,(\mathsf{A}_3 + \mathsf{A}_4 \to) \\ \hline \mathcal{R}_1 & \mathsf{A}_1 \to a\mathsf{A}_4 \end{array}$$

A graphical tour of the reduction theorems

Theorem 3: removing disjoint negative paths



$\mathcal{R}_2 = \mathrm{R}_3 - \mathrm{R}_4$ and $\mathcal{R}_4 = \mathrm{R}_2 - \mathrm{R}_1$

Aggressive reductions

- Reduction of Lefty-Nodal model violates conservative reduction rules $\Longrightarrow$ eliminates entry vertices (reactions with Smad4)

- OK (but not provably so) because we knew the critical fragment and could show it was retained in the simplified model

- For very large models, suggests multi-step reduction process:
  1. Carry out all possible conservative reductions.
  2. Identify critical fragment.
  3. Carry out aggressive reductions.

Part V

Conclusions

Future work

- Examples!
- Same ideas could be applied to other qualitative stability analysis methods
- More refined theorems to cover more complex cases
- Reduced models often have a simple chemical interpretation, and sometimes not.
  Can we come up with stricter rules such that the reduced models always make sense?
- Classification of oscillators and multistable models based on their maximally reduced critical fragments

Thanks!