Lecture 2: Analysis of Biomolecular Circuits

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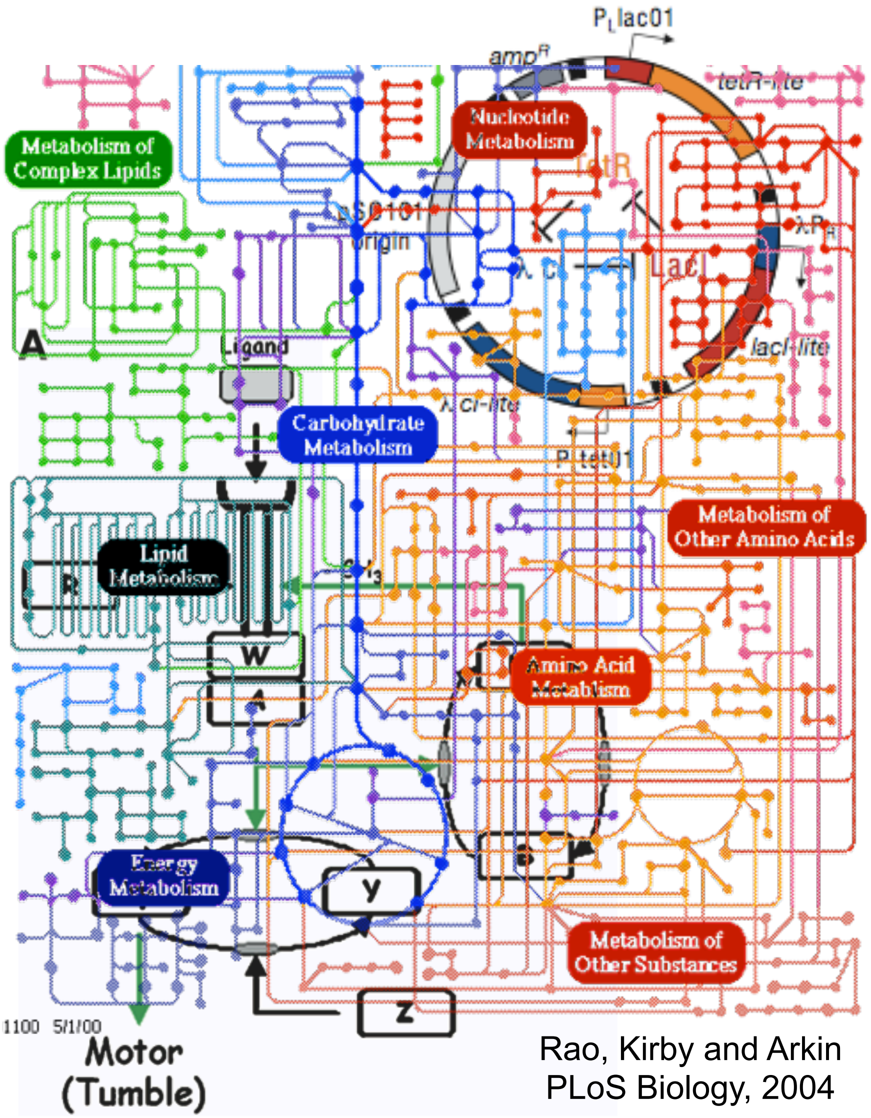
Goals:

- Give a short overview of the control techniques applied to biology
  - uncertainty management
  - system identification
  - design of dynamics
  - (fundamental limits of performance)

References

- D. Del Vecchio and R. M. Murray, *Biomolecular Feedback Systems,* 2009. http://www.cds.caltech.edu/~murray/amwiki/bfs

Control Theory for Biological Systems



Rao, Kirby and Arkin
PLoS Biology, 2004

What's different about biological systems

- *Complexity* - biological systems are *much* more complicated than engineered systems
- *Communications* - signal representations are very different (spikes, proteins, etc)
- *Uncertainty* - very large uncertainty in components; don't match current tools
- *Evolvability* - mutation, selection, etc

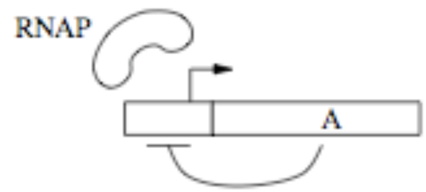
Potential application areas for control tools

- *System ID* - what are the appropriate component abstractions and models?
- *Analysis* - what are key biological feedback mechanisms that lead to robust behavior?
- *Design* - how to we (re-)design biological systems to provided desired function?
- *Fundamental limits* - what are the limits of performance and robustness for a given biological network topology?

Example: Self-Repression (from Astrom & Murray '08)

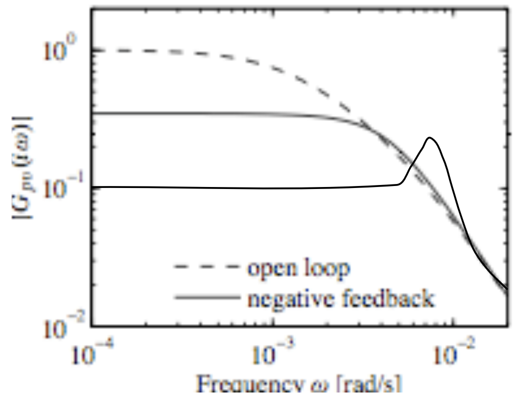
Common motif in transcriptional regulation

- A binds to its own promotor region
- If A is bound, represses binding of RNA polymerase



Use #1: decrease sensitivity to input disturbances

- Frequency responses demonstrates effect



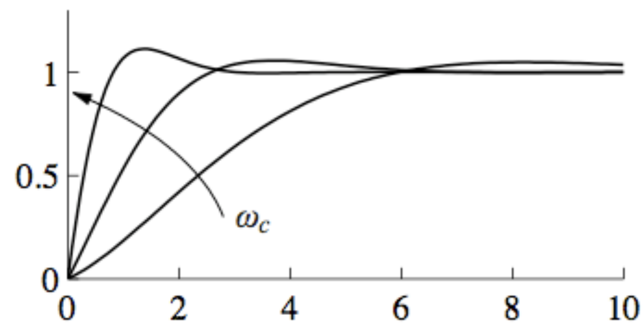
$$\frac{dm}{dt} = \alpha(p) - \gamma m - v, \qquad \frac{dp}{dt} = \beta m - \delta p$$

$$G^{\text{ol}}_{pv}(s) = \frac{-\beta}{(s+\gamma)(s+\delta)}$$

$$G^{\text{cl}}_{pv}(s) = \frac{\beta}{(s+\gamma)(s+\delta)+\beta\sigma}, \qquad \sigma = \frac{n\alpha_1 k p_e^{n-1}}{(1+kp_e^n)^2}$$

Use #2: use to decrease response time

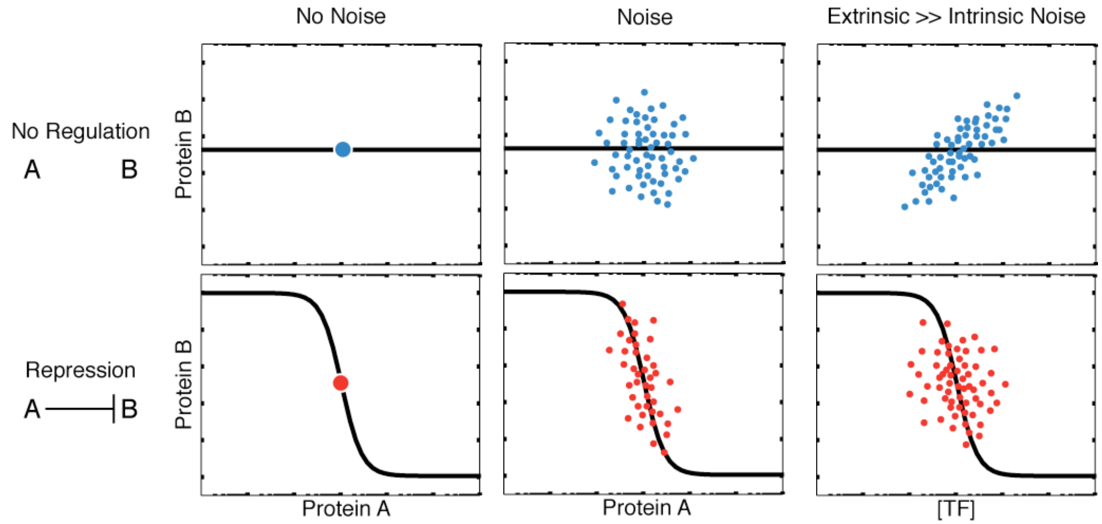
- Use a stronger promotor to increase low freq gain
- Increases bandwidth ⇒ faster response



System Identification Using Cell Noise

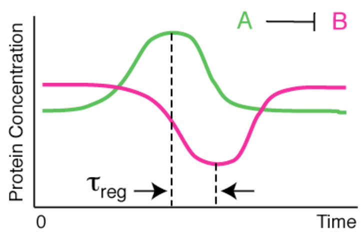
Traditional systems identification

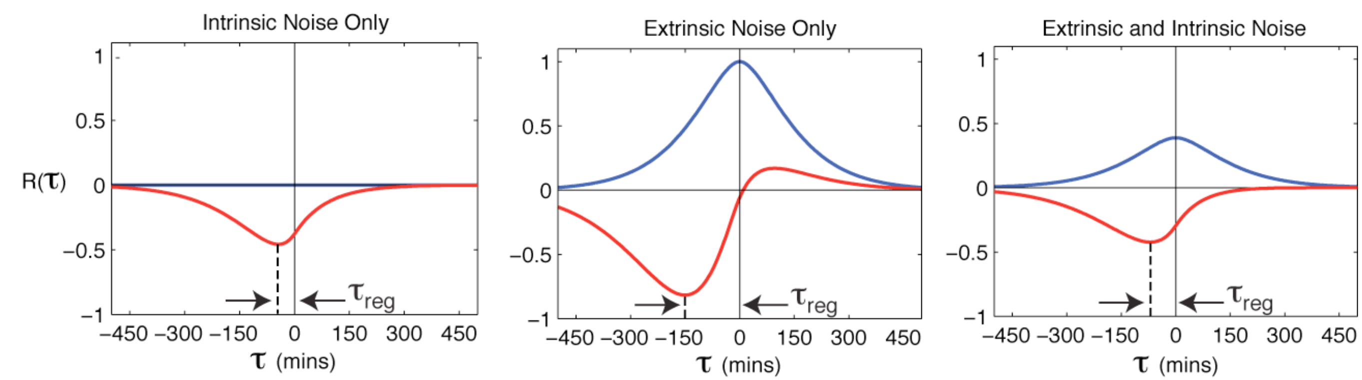
- Engineering: forced response. Difficult to do in in vivo (eg, sinusoids are tricky)
- Biology: gene knockouts; steady state measurements using gene arrays



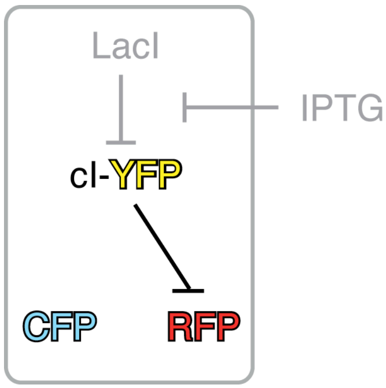
Idea: use noise as a forcing function

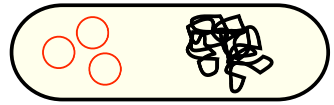
- Steady state distributions are not enough if extrinsic noise is present
- Need to use correlation data instead

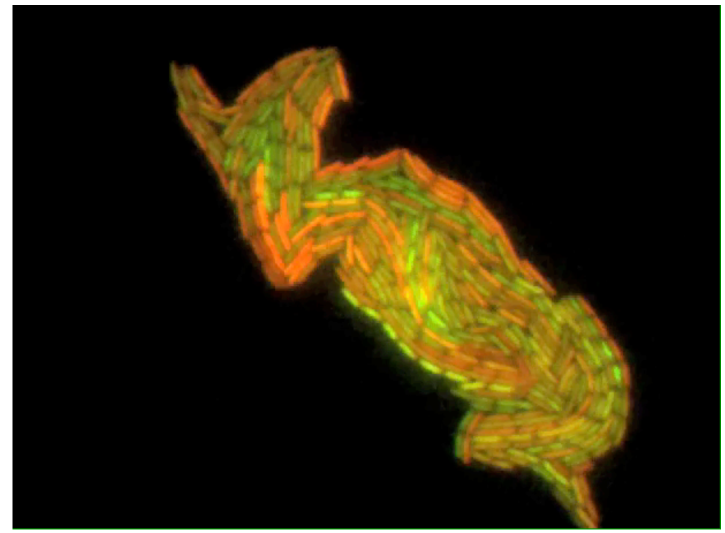


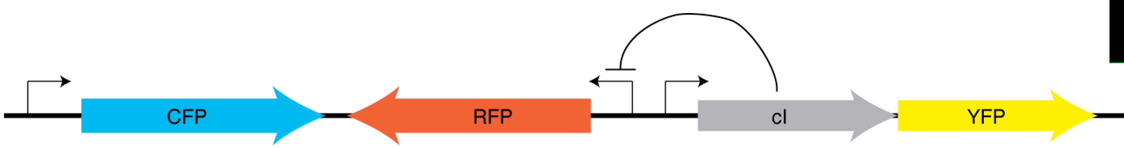


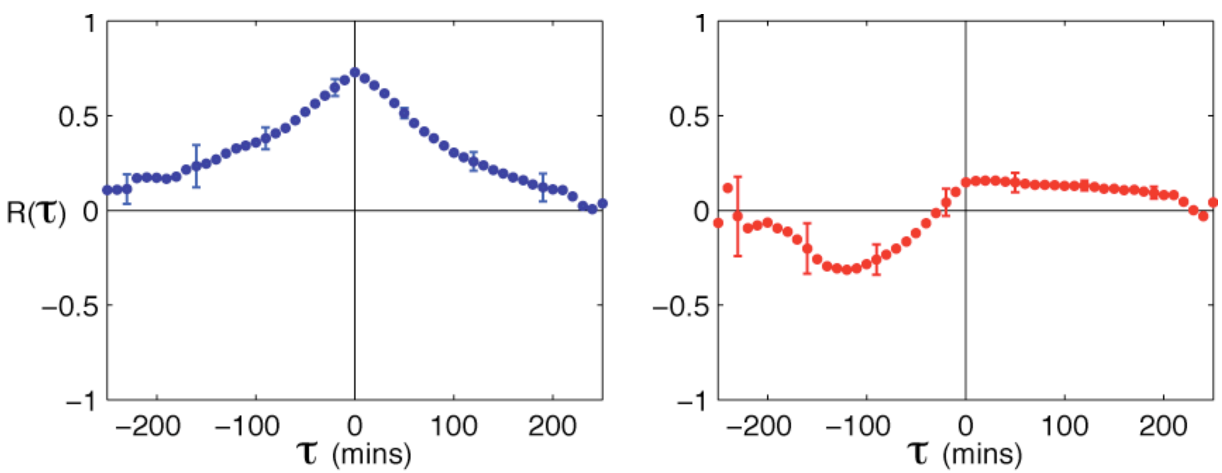
System ID of a Synthetic Circuit (Dunlop, Elowitz & M)







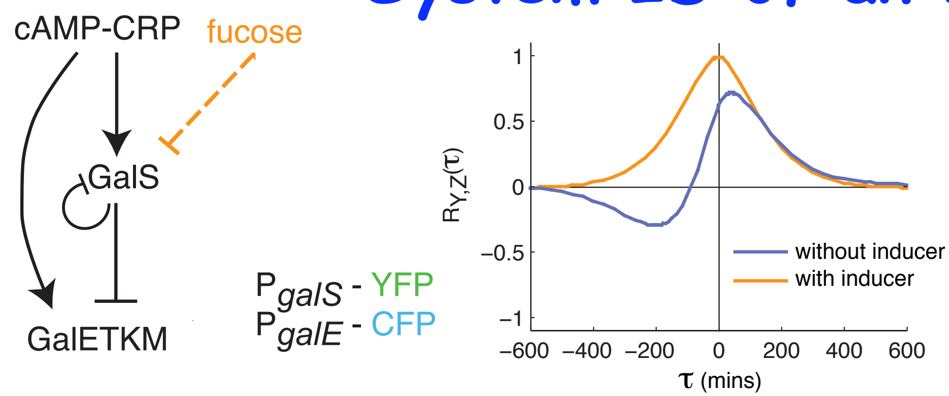


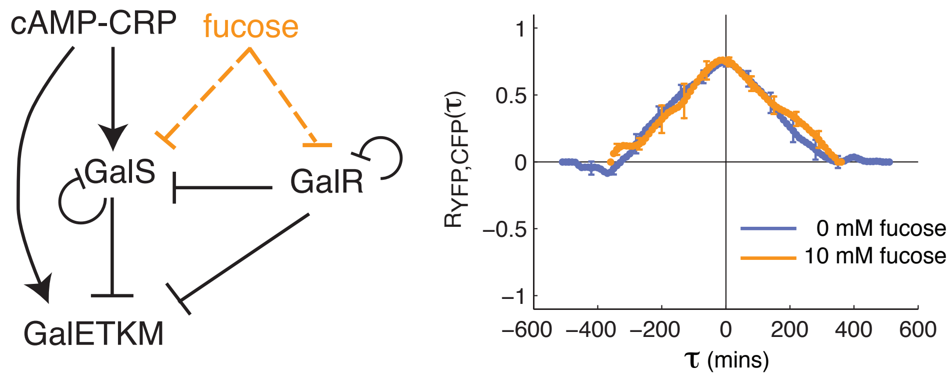


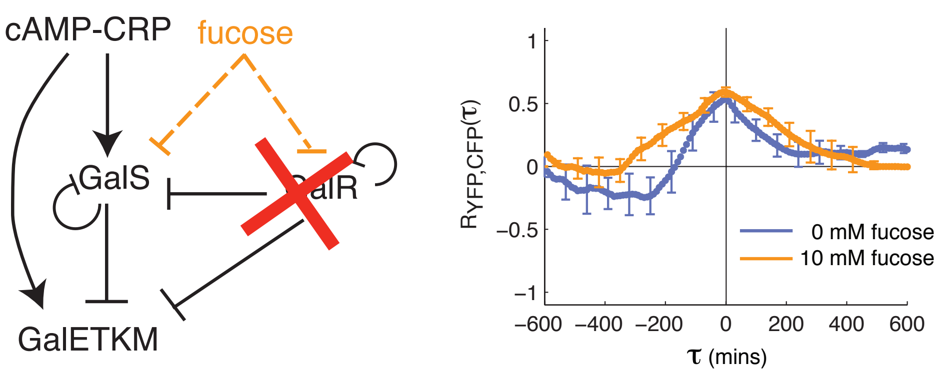
Results to date

- Synthetic circuit demonstrates viability of approach
- Implemented on natural circuit (using promoter fusion)

System ID of an in vivo circuit







Galactose regulation in *E. coli*

- GalE regulated by CRP via a feedforward loop
- GalR represses feedforward loop when fucose is present
- Promoter fusions measure GalS and GalE concentrations

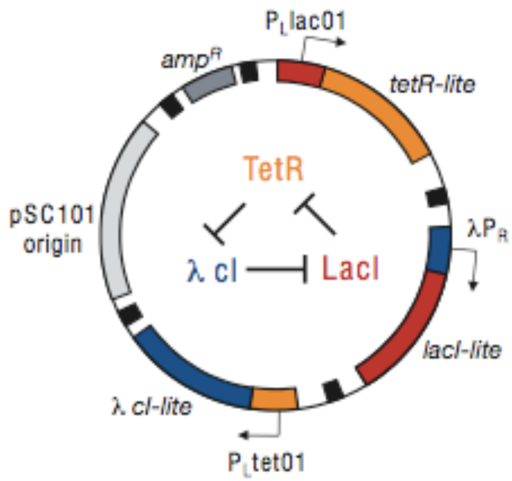
System ID shows FFL is not active

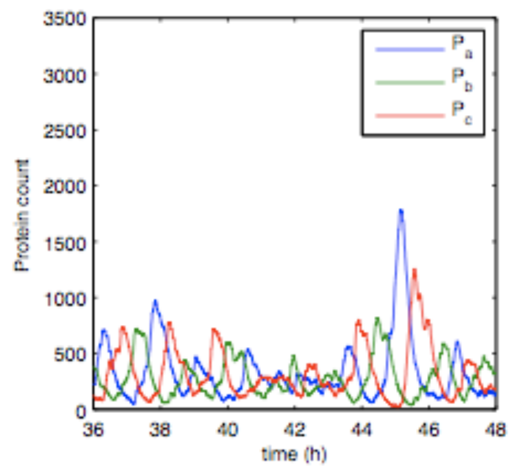
- Addition of fucose shows no change in correlations => GalS is not actively regulating GalE

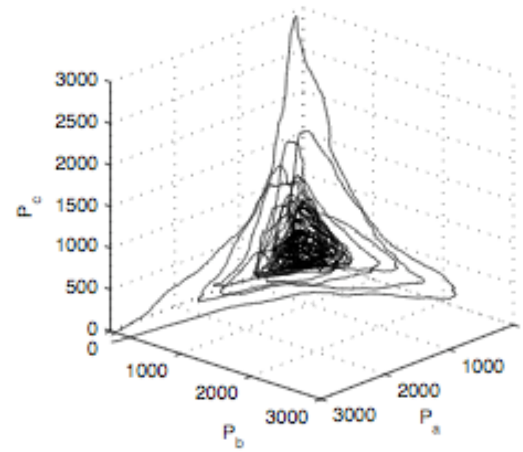
Hypothesis: GalR repression dominant

- If repression by GalR is large, GalS is always “off” => no connection
- Removal of GalR recovers expected correlations

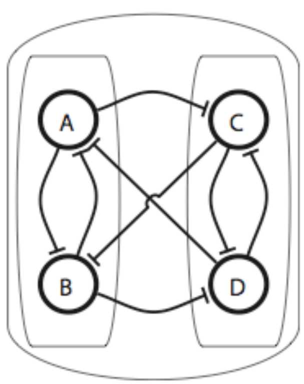
Improving the Performance of Oscillators

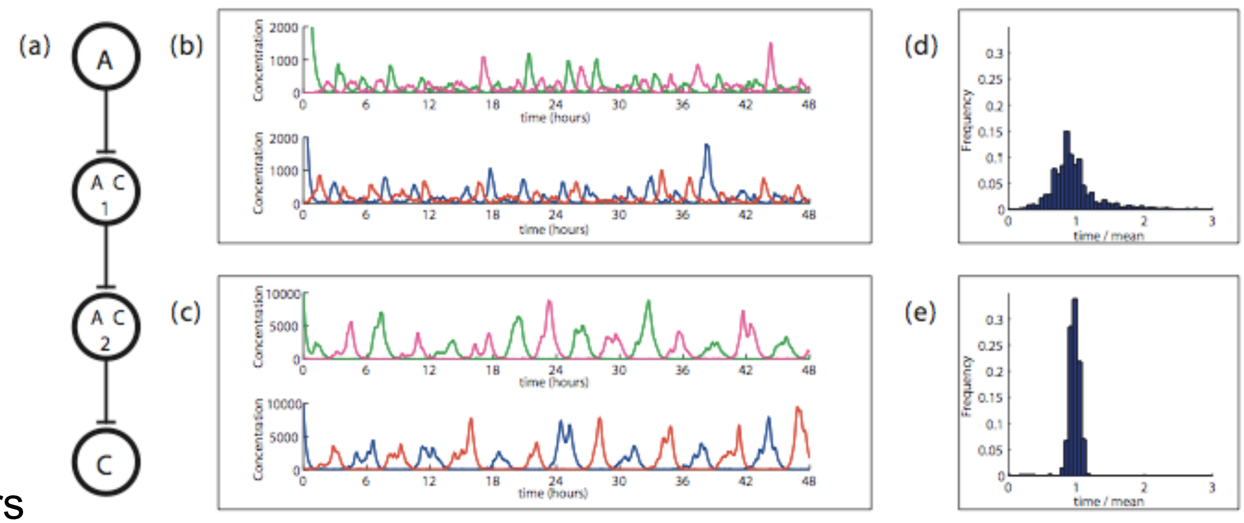






Toggelator

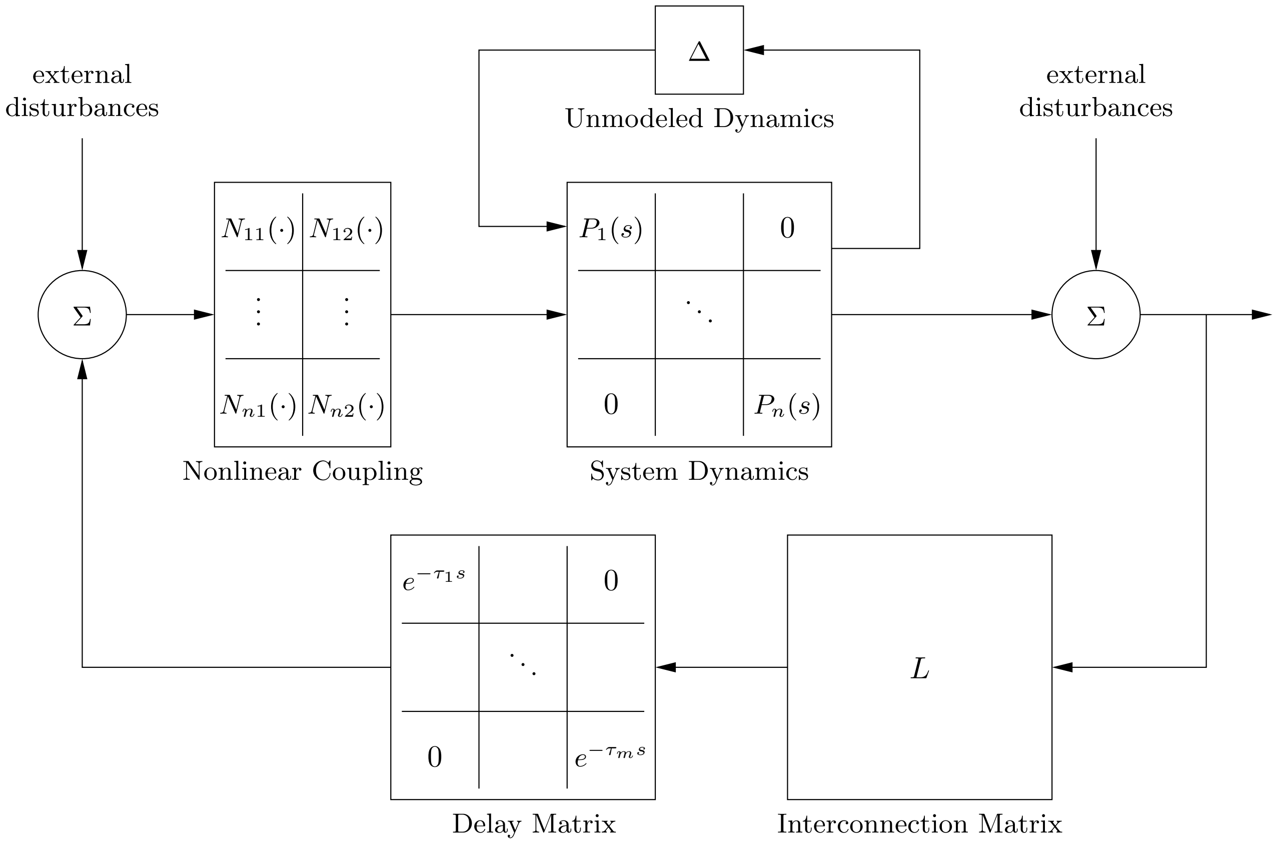




- Coupled oscillators
- Add additional "delay" (ACi)

Uganders, Dunlop & M, ACC 07

Possible Framework for Analysis and Design



Analysis via loop gain

Design the easy parts

- Interconnection matrix
- Time delay matrix

Design tools exist for pairwise combinations

- Linear + uncertain = robust control theory
- Linear + nonlinear = describing functions
- Linear + network = formation stabilization
- Linear + delay = Floquet analysis

Open questions

- What is the class of feedback compensators we can obtain using L and τ ?
- How do we specify robustness and performance in highly stochastic settings?
- Can feedback be used to design robust dynamics that implements useful functionality?