

Sporulation In Bacillus Subtilis

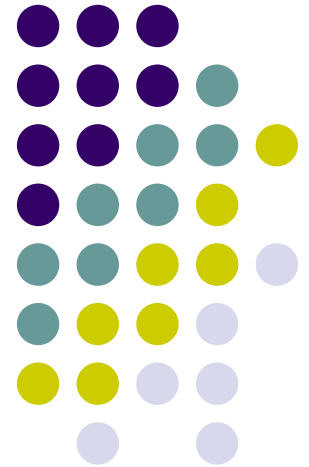
Raj Kulkarni

Henrik Sandberg

Tamas Keviczky

Jean-Charles Delvenne

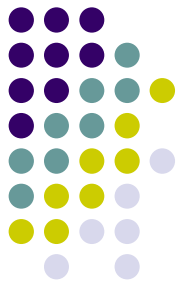
Genti Buzi



How do cells make decisions?

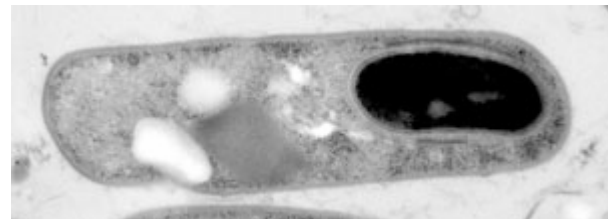


- Cells make decisions all the time
 - Differentiation
 - Response to environment
 - Etc...
-
- What regulatory networks underlie decision making processes?

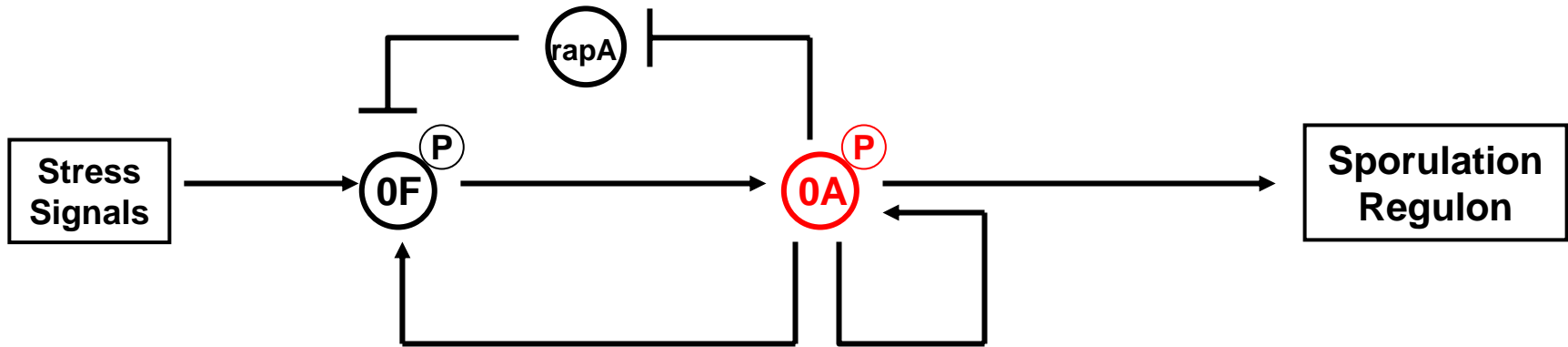


Tough Decisions of *B subtilis*!

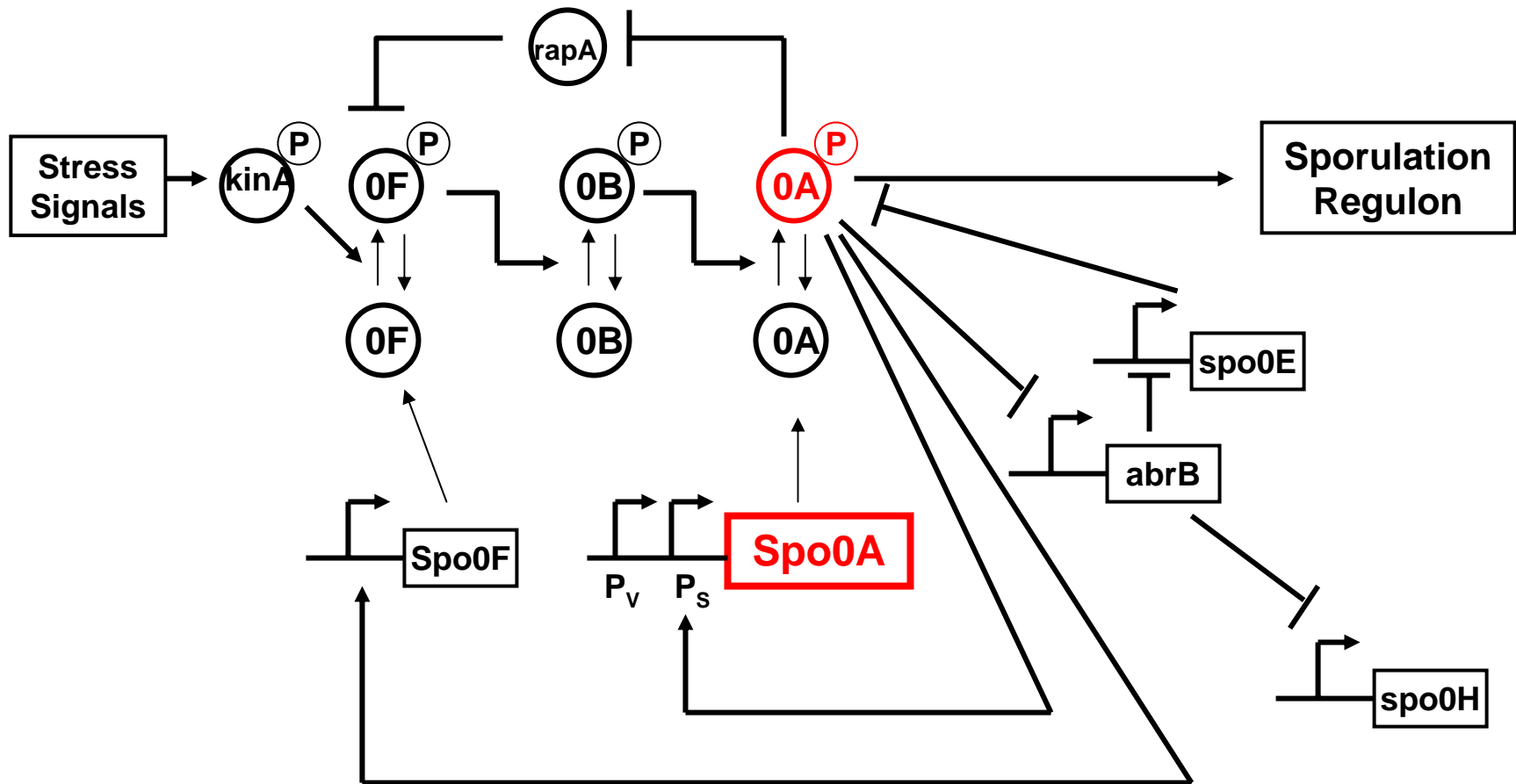
- Faced with nutrient limitation, *B subtilis* has many different stress responses...
 - Sporulation
 - Genetic Competence
 - Chemotaxing away...
 - Do nothing...?
- Study sporulation
 - The most drastic differentiation
 - The most rich control/regulation network

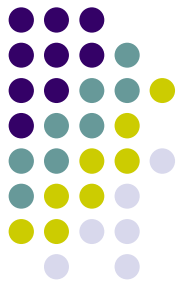


The network around *spo0A*



The network around *spo0A*

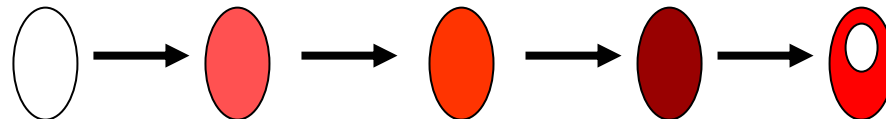
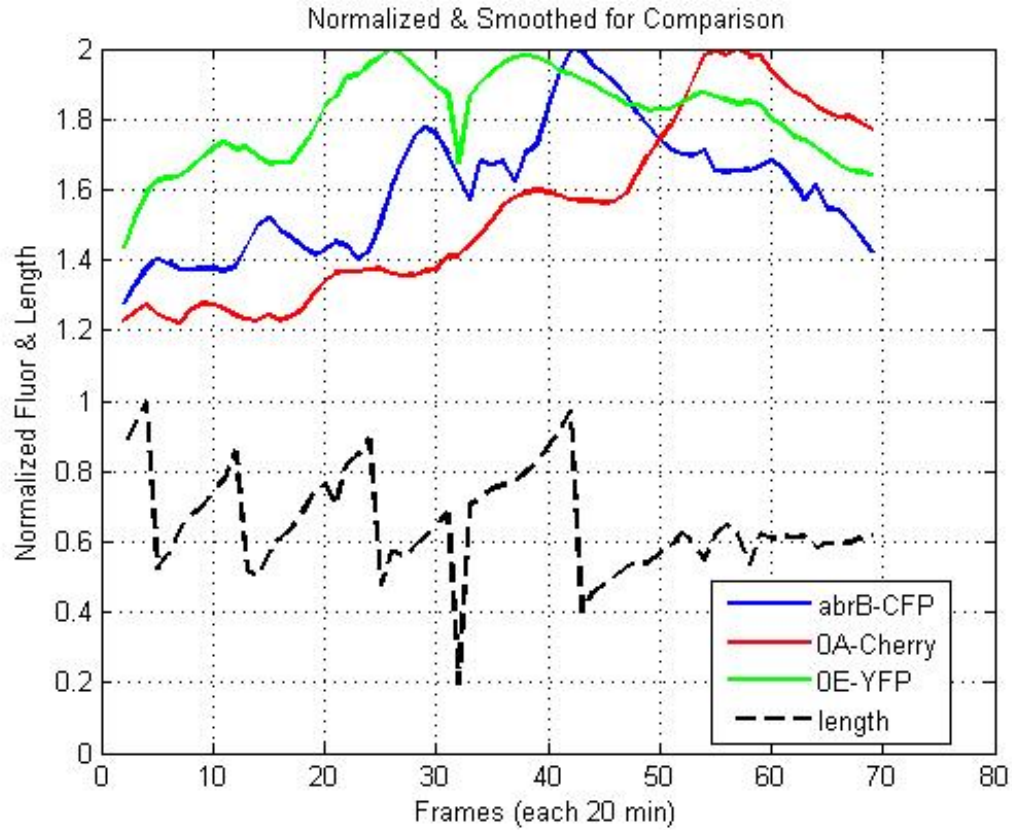




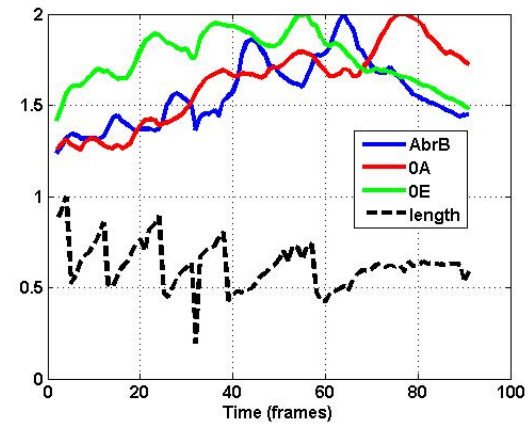
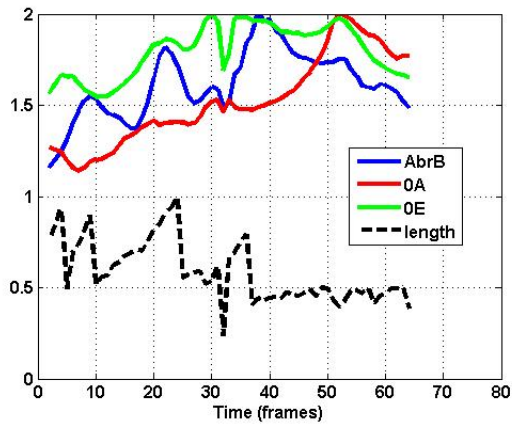
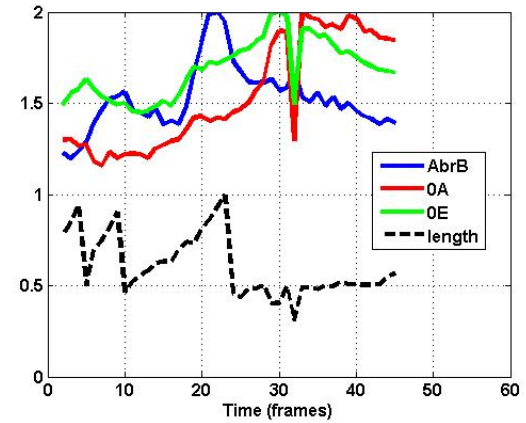
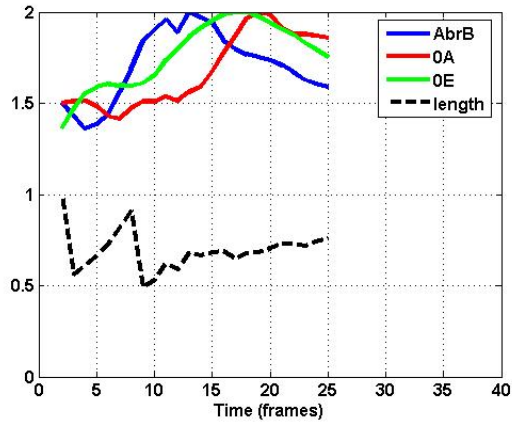
Looking at different loops

- Spo0A on itself (+)
 - Complex promoter structure (next slide)
- SinI/SinR (+)
 - SinR might not repress P-spo0A (Kearns *et al* 2005)
- Spo0F (+)
 - Response regulator, aspartate kinase, transfer to Spo0B
- RapA (+)
 - 0Ap represses RapA, which dephosphorylates Spo0F
- SigH (+?)
 - Required for most of the feedback promoters
- KinA-C (?)
- AbrB-0E (-)

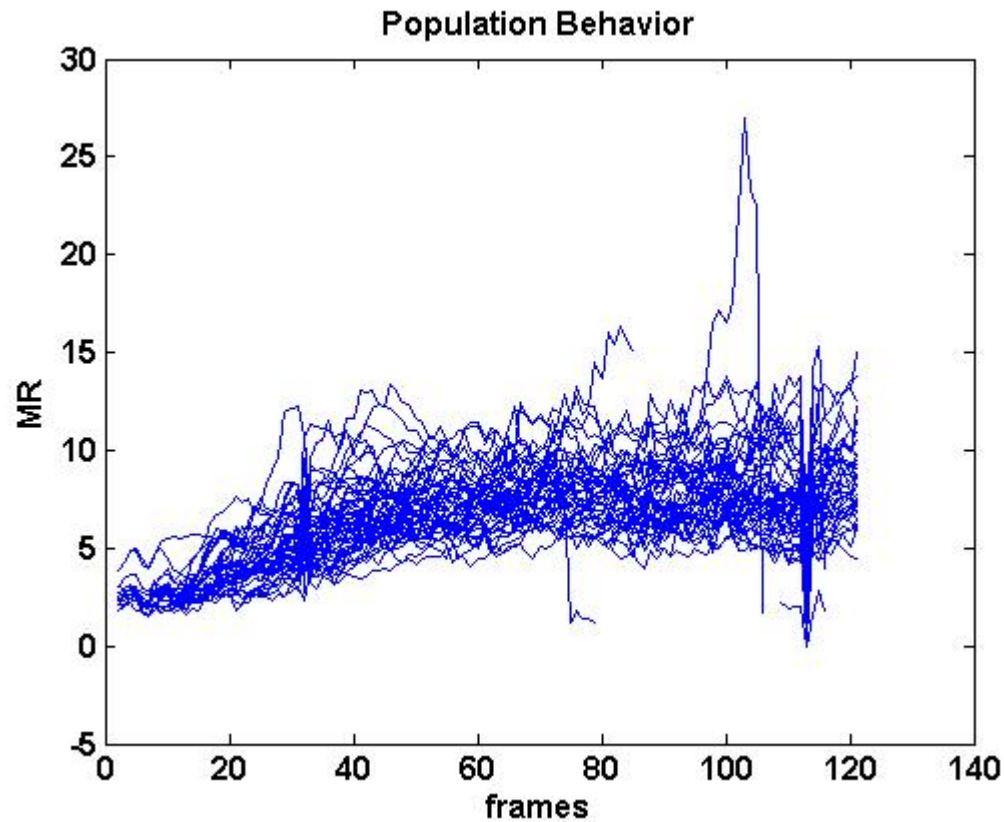
Single Cell P-spo0A behavior



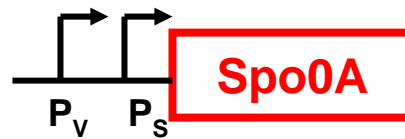
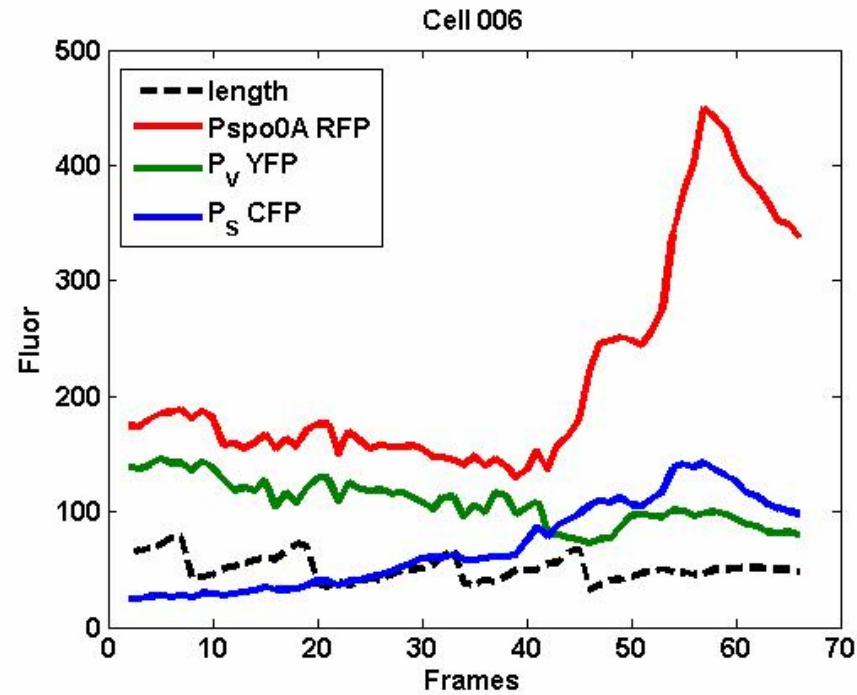
Example Traces



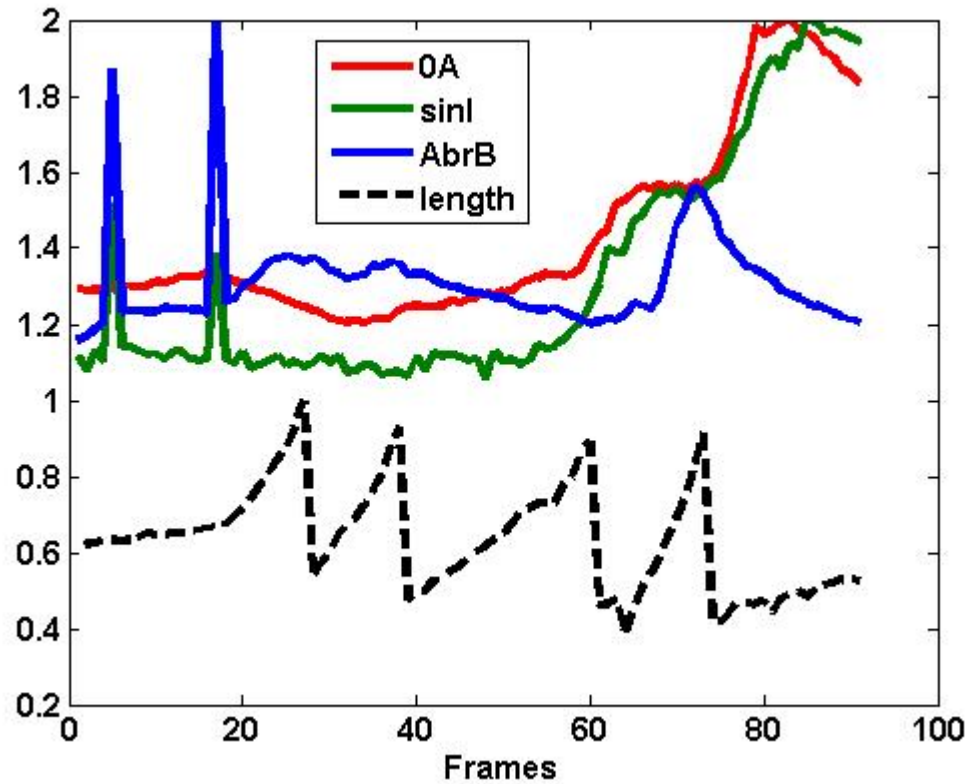
Population behavior of spo0A



Spo0A autoactivation loop



SinI loop



Goals

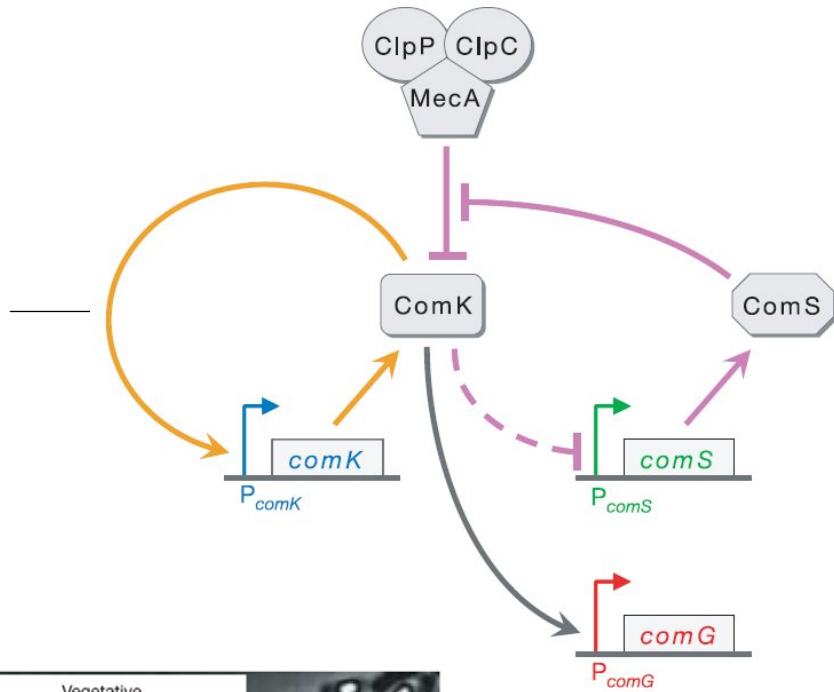


- Build a mathematical model that
 - Explains the experimental data
 - Gives insights to how the pathway works and makes meaningful predictions that can be experimentally verified
 - Shows how this pathway might interact with the other competing pathways

More Modest Goals

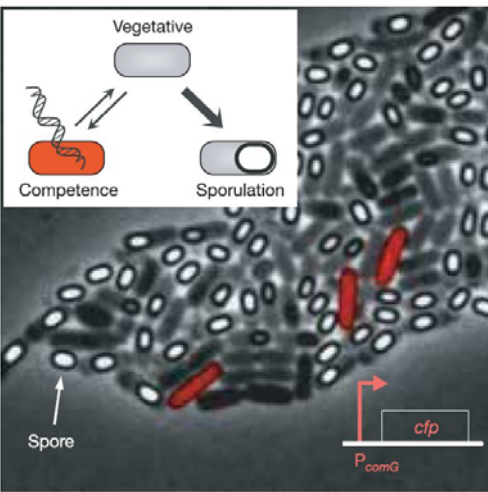
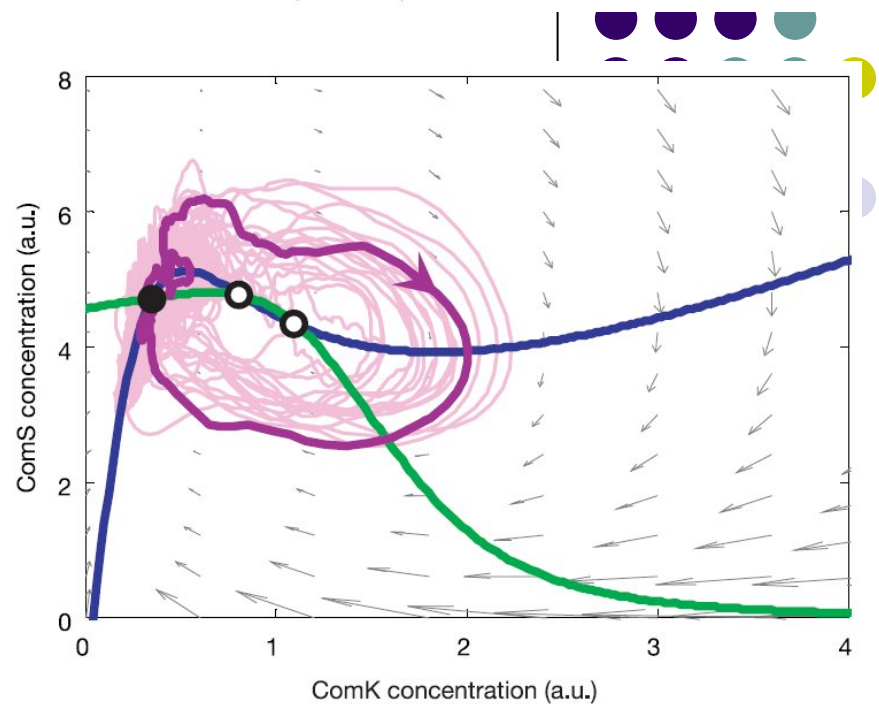
- Build a model for the part of the network that
 - Explains the relevant experimental data
 - Makes meaningful predictions that can be experimentally verified
- Extract qualitative/quantitative features of the network that might guide future experiments

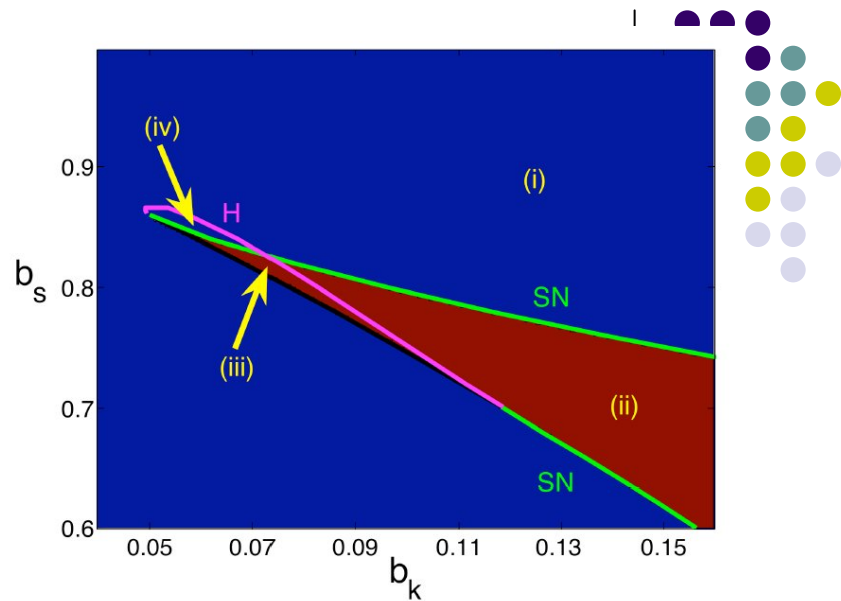
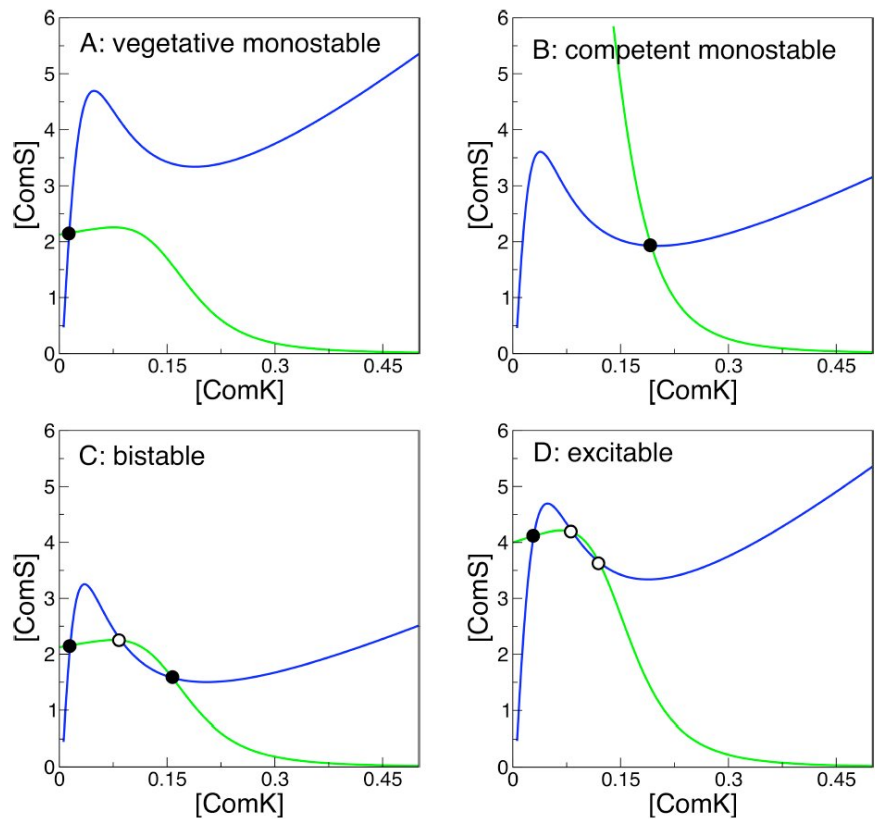
Modeling of the competence network of *Bacillus subtilis* (M. Elowitz et al.)



$$\frac{dK}{dt} = a_k + \frac{b_k K^n}{k_0^n + K^n} - \frac{K}{1 + K + S}$$

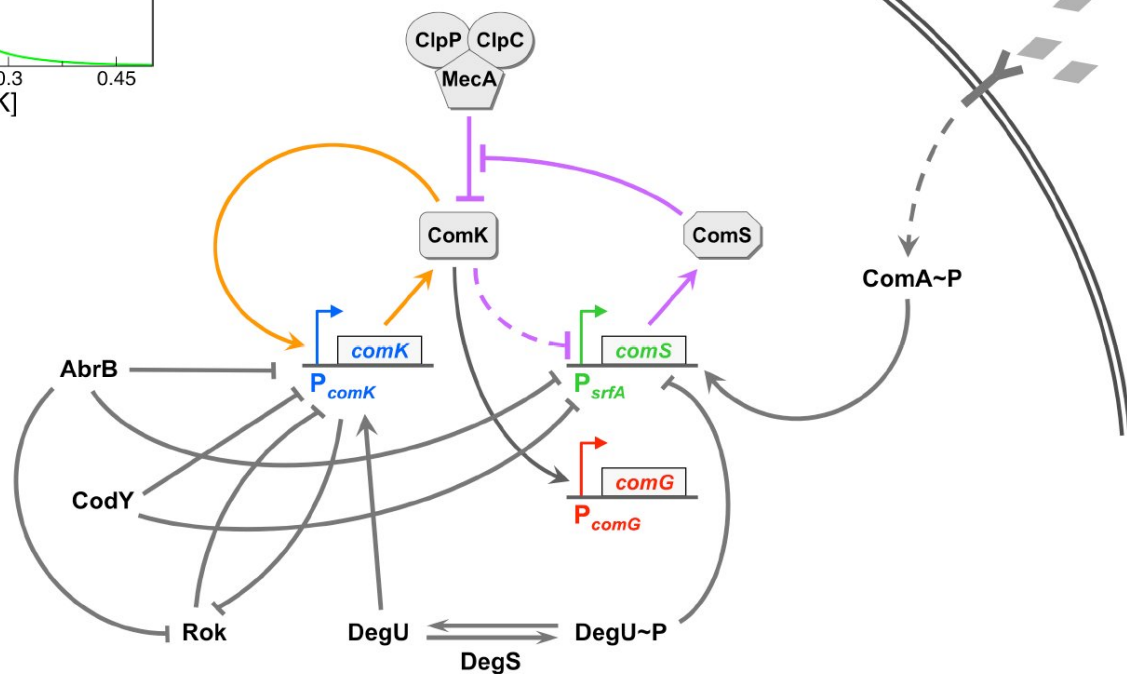
$$\frac{dS}{dt} = \frac{b_s}{1 + (K/k_1)^p} - \frac{S}{1 + K + S} + \xi(t)$$





$$\frac{dK}{dt} = a_k + \frac{b_k K^n}{k_0^n + K^n} - \frac{K}{1 + K + S}$$

$$\frac{dS}{dt} = \frac{b_s}{1 + (K/k_1)^p} - \frac{S}{1 + K + S} + \xi(t)$$



What's next



- Analyze the Data
 - Pre-Filtering, Normalization, etc.
 - Statistical analysis, data mining and feature extraction
- Building the Model
 - Start with simple finite difference models and ODE
 - Build the models for the simple sub-networks
 - Other models (Hybrid, SDE etc)
- Analyzing the Model
 - Model Reduction
 - Etc.