Published online: May 23, 2016

Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

molecular systems biology

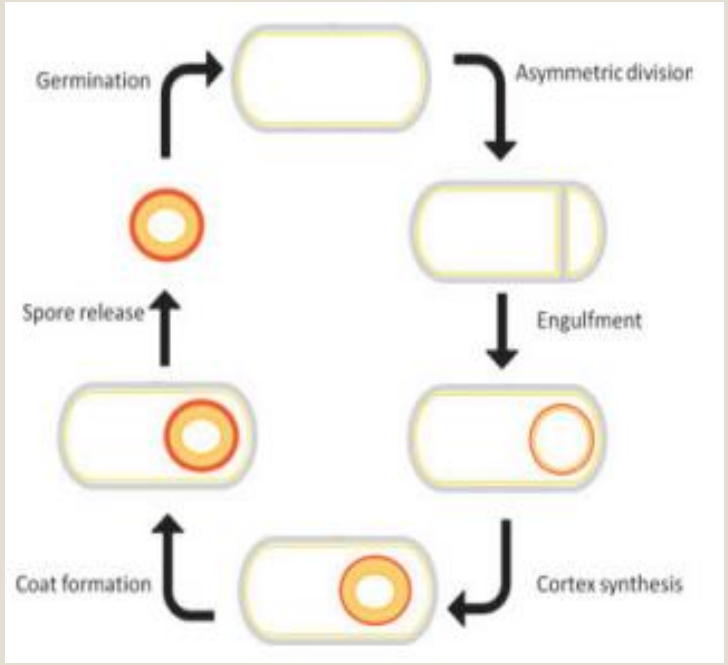
Slowdown of growth controls cellular differentiation

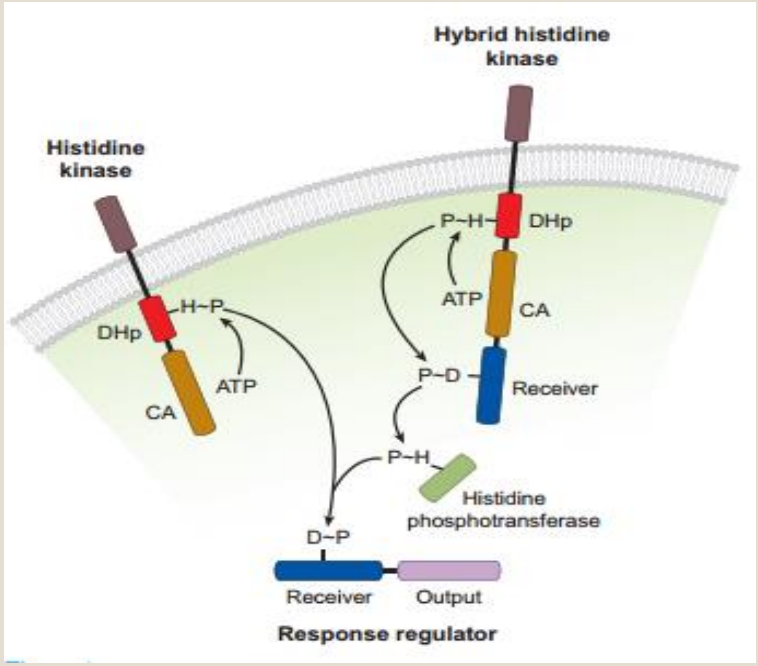
Jatin Narula[1,†], Anna Kuchina[2,†], Fang Zhang[2], Masaya Fujita[3], Gürol M Süel[2] & Oleg A Igoshin[1,*]

余文君
2016.12.21

- Introduction
- Result
- Conclusion
- Discussion

Introduction

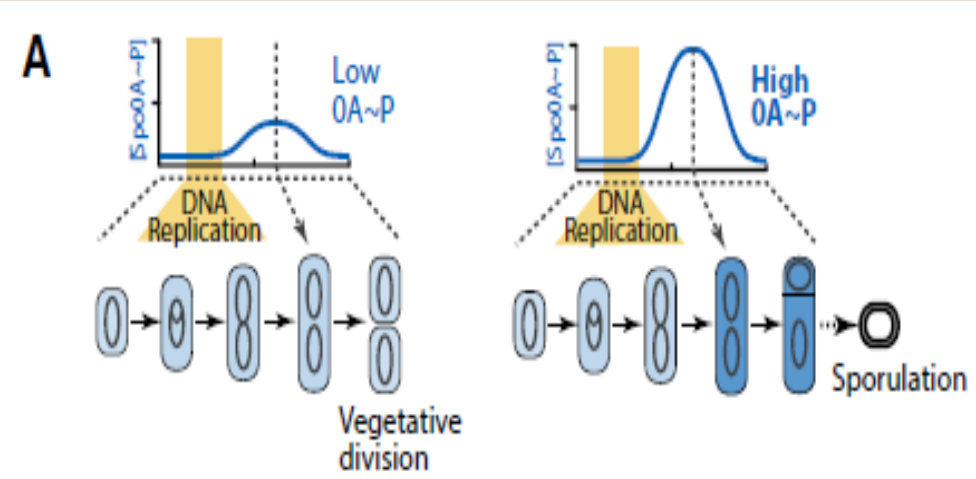


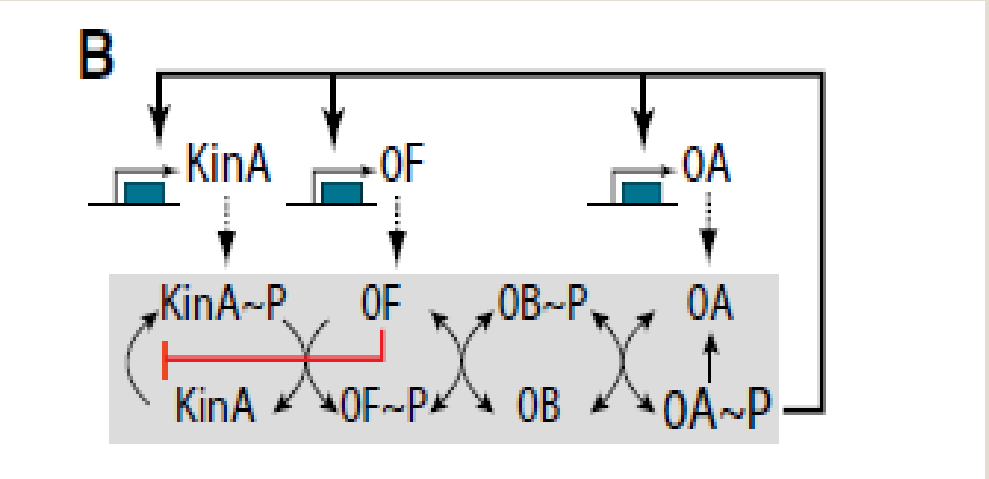


subtilis cells survive prolonged starvation by differentiating into stress-resistant and metabolically inert spores

A two-component signal transduction paradigm Bacillus

Laub M T, Goulian M. Specificity in two-component signal transduction pathways[J]. Annu. Rev. Genet., 2007, 41: 121-145
Higgins D, Dworkin J. Recent progress in Bacillus subtilis sporulation[J]. FEMS microbiology reviews, 2012, 36(1): 131-148.



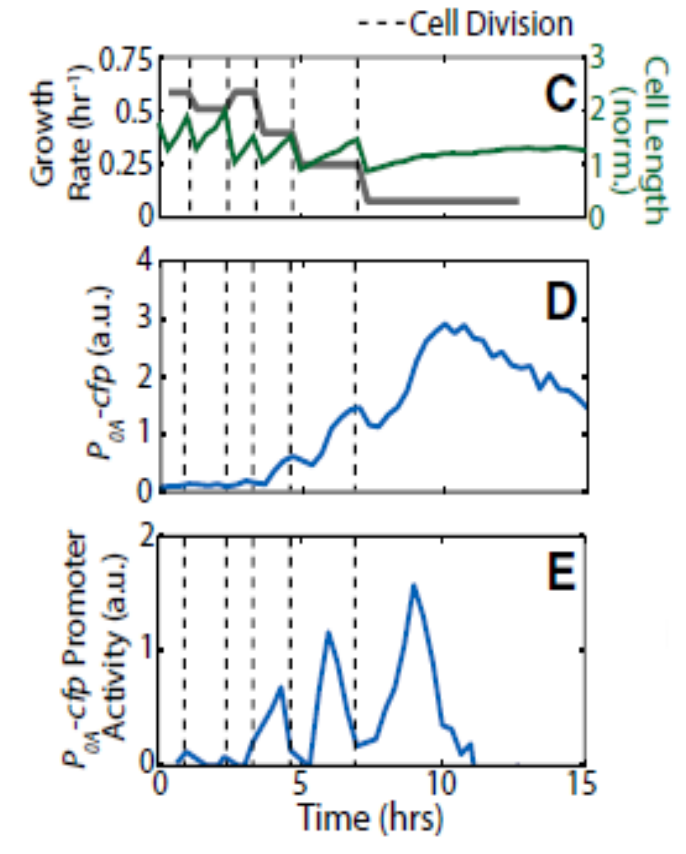


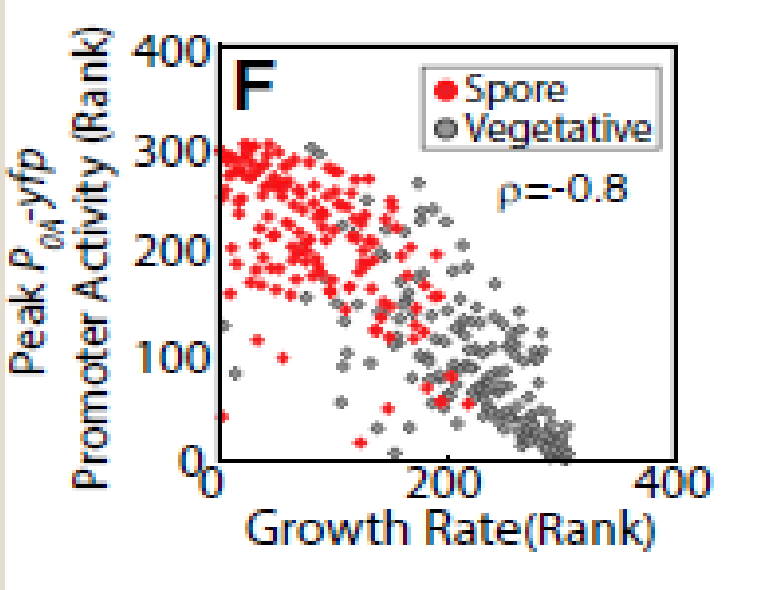
The decision to sporulate is based on the amplitude of the 0A~P pulse

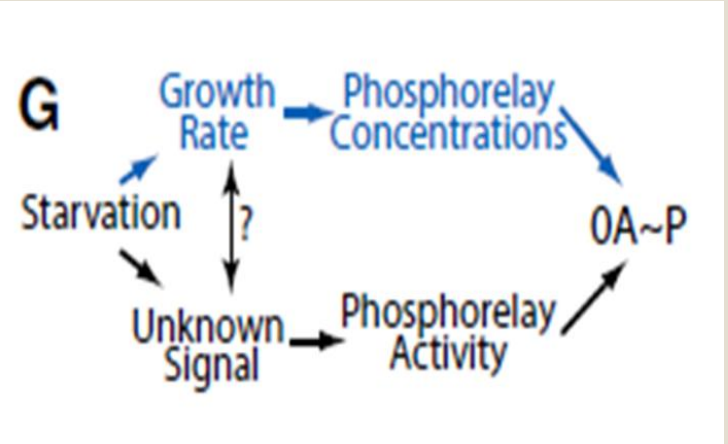
The sporulation phosphorelay network that controls 0A~P formation

Result

0A~P pulse amplitudes are correlated with cell growth rate

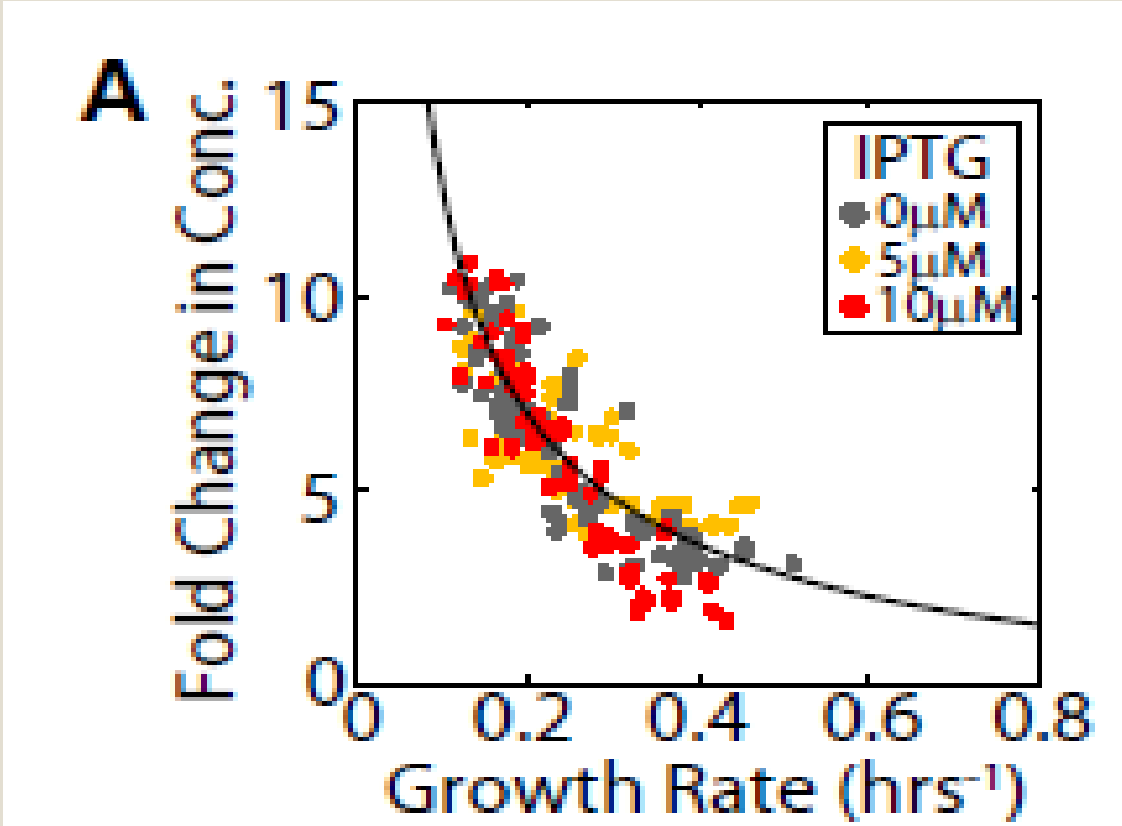




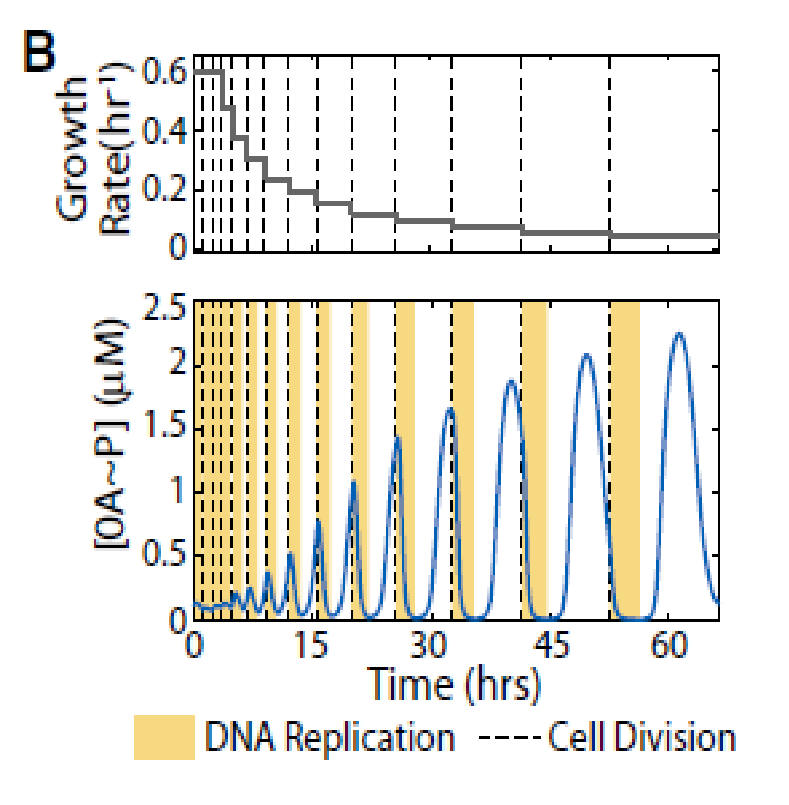


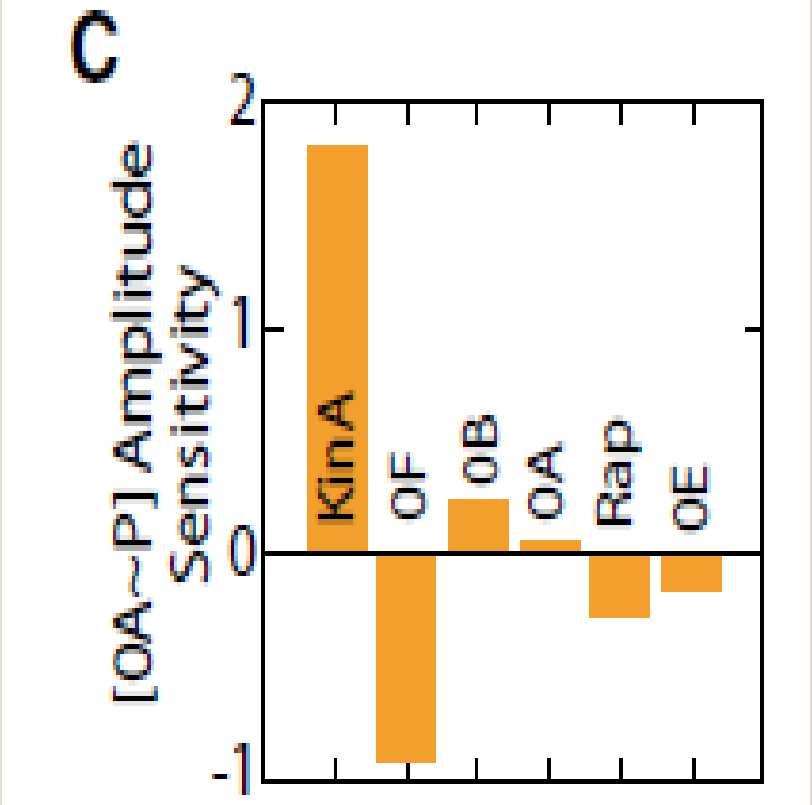
Decrease in growth rate leads to accumulation of stable proteins

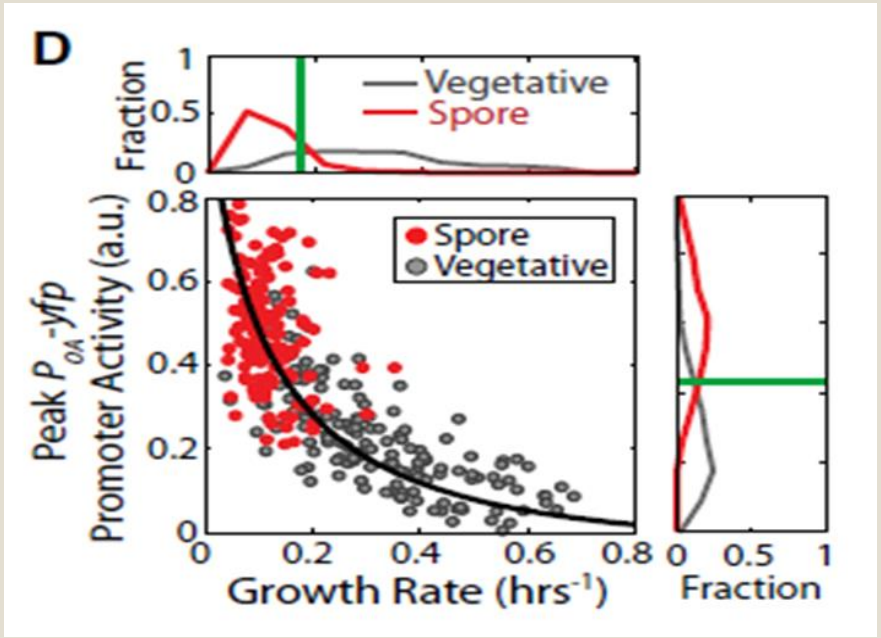
$$C(\mu) = \frac{P}{V(\mu)(k_{\text{deg}} + \mu)}$$

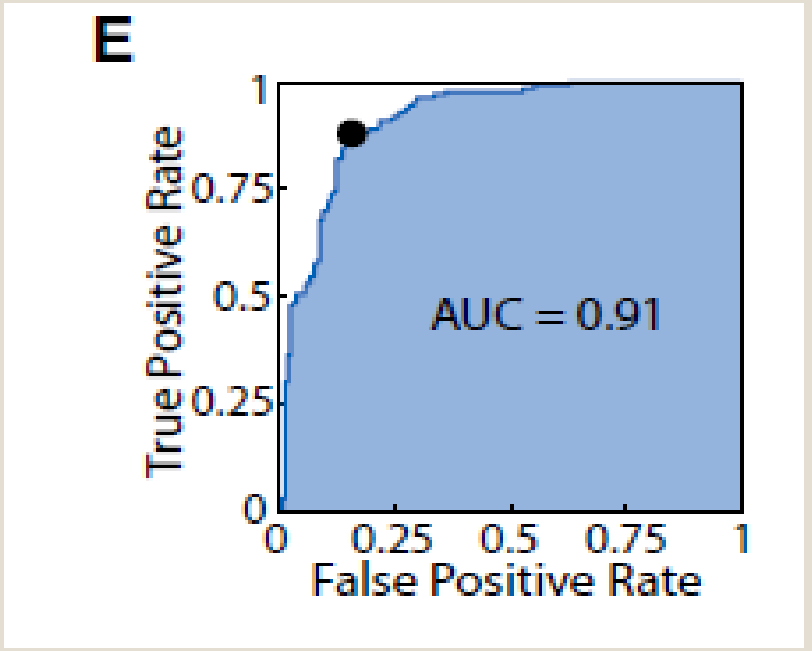


Accumulation of phosphorelay proteins is sufficient to explain observed increase in 0A~P levels

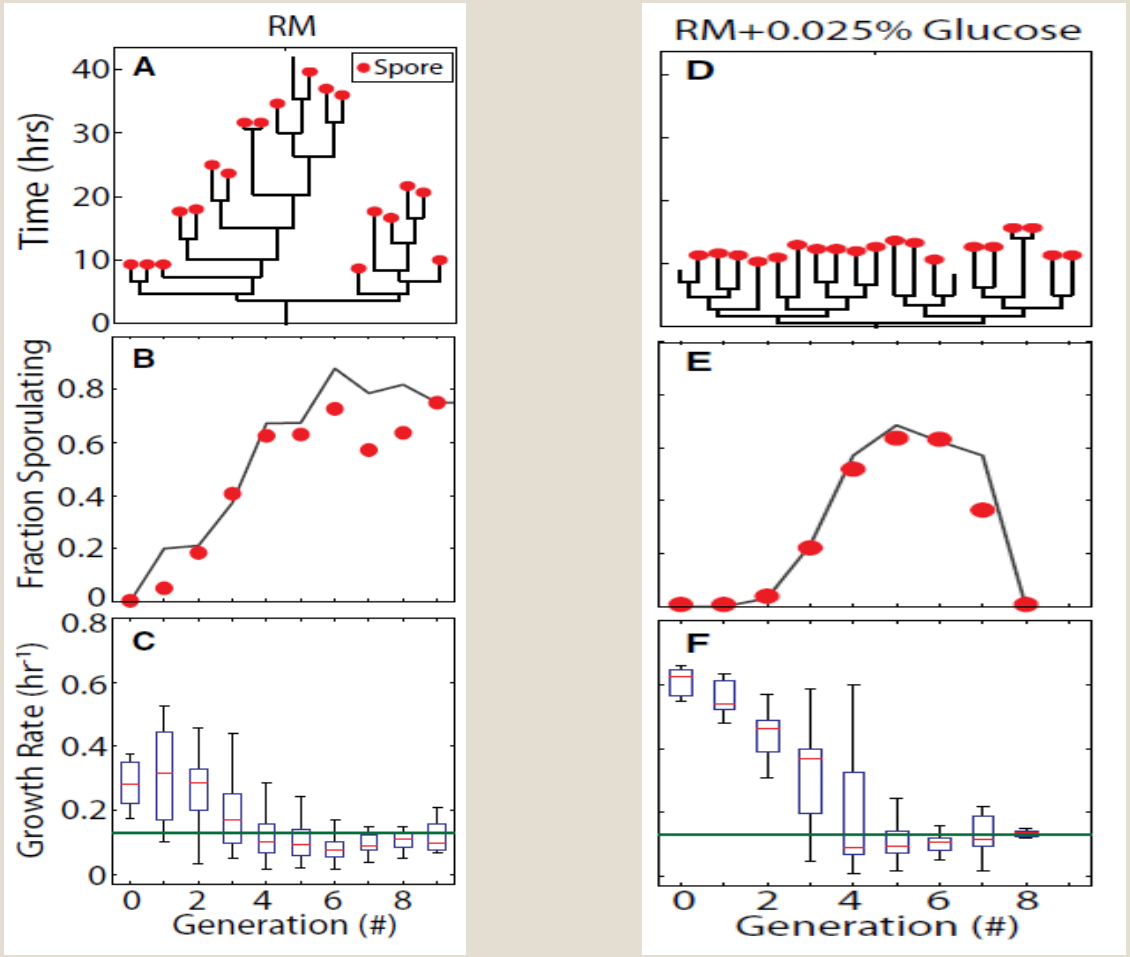





D
Fraction
1
0.5
0
Vegetative
Spore
Peak P_{0A}-yfp
Promoter Activity (a.u.)
0.8
0.6
0.4
0.2
0
Spore
Vegetative
0
0.2
0.4
0.6
0.8
Growth Rate (hrs^{-1})
0
0.5
1
Fraction

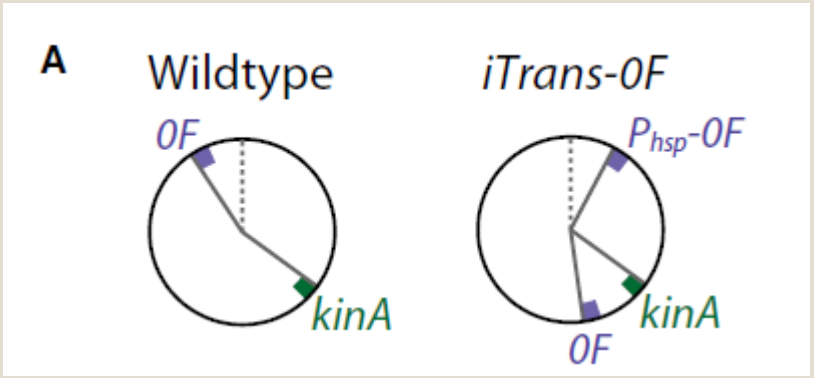

E
True Positive Rate
1
0.75
0.5
0.25
0
AUC = 0.91
0
0.25
0.5
0.75
1
False Positive Rate

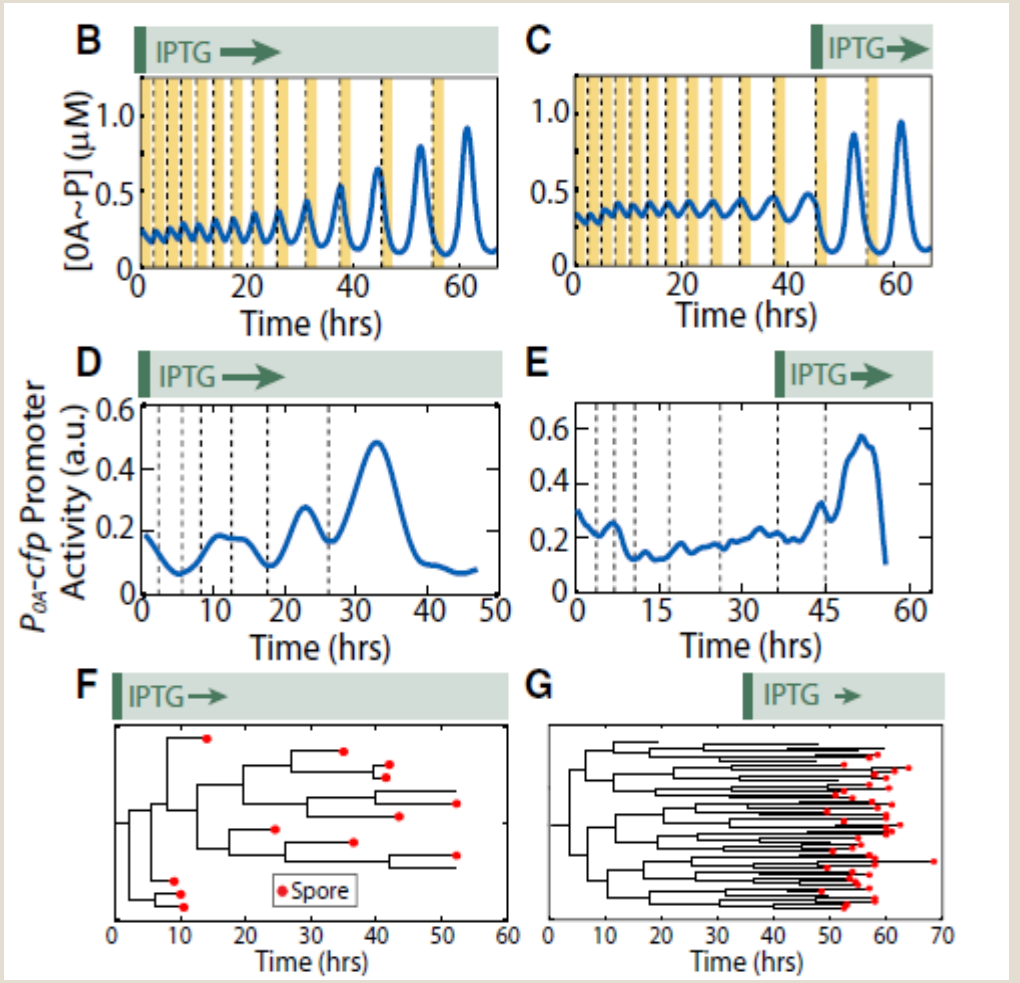
Test the effectiveness of growth rate as a predictor of cell fates

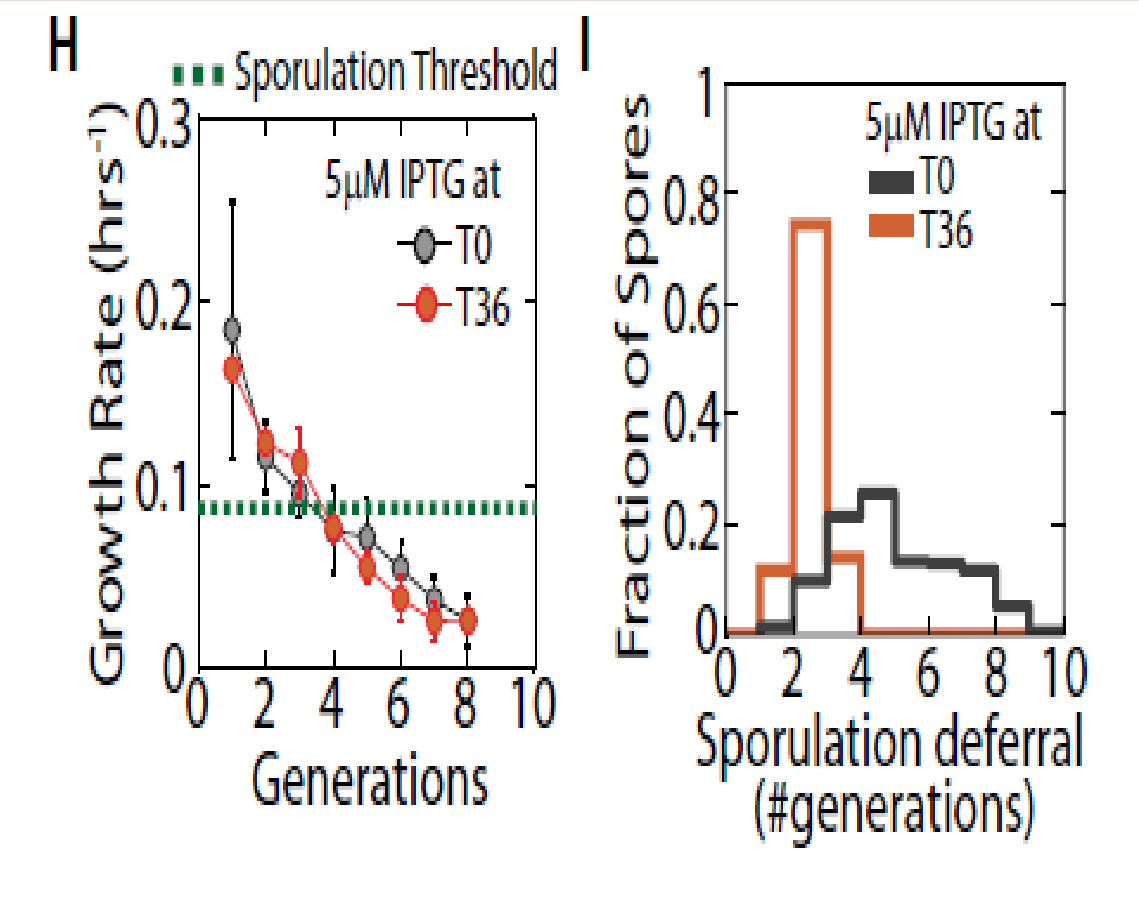


perturbed growth dynamics with nutrient addition to test the ability of the growth threshold model to explain cell-fate decisions in different conditions

Growth slowdown controls sporulation deferral.





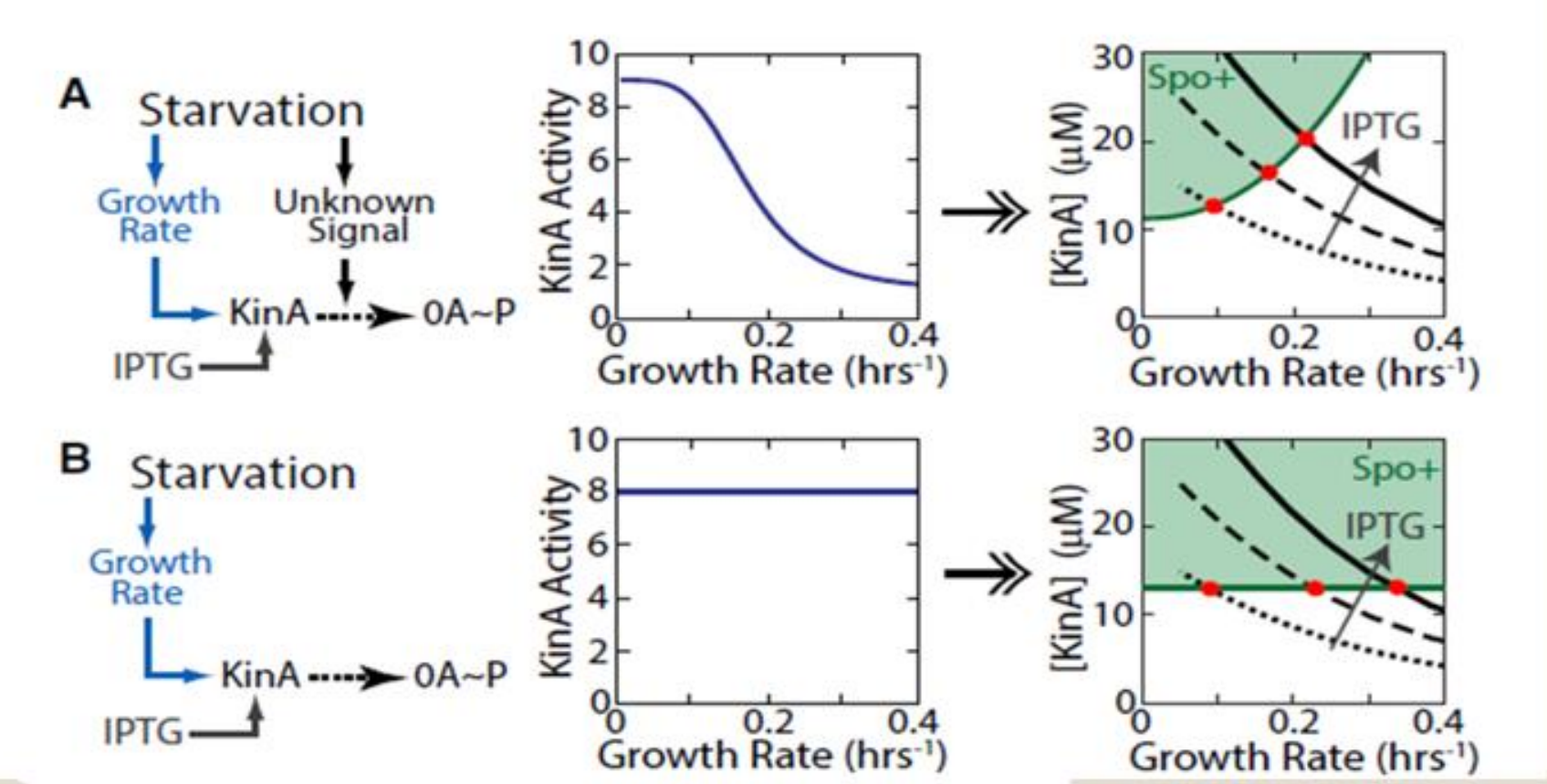


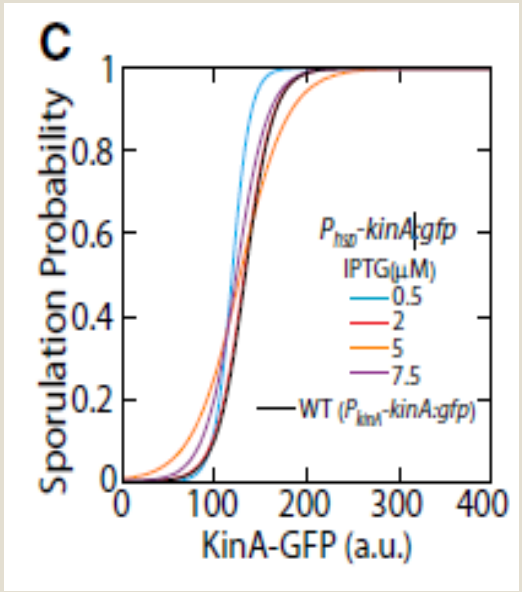
the timing of IPTG addition affected the 0A activity dynamics but not the average growth dynamics

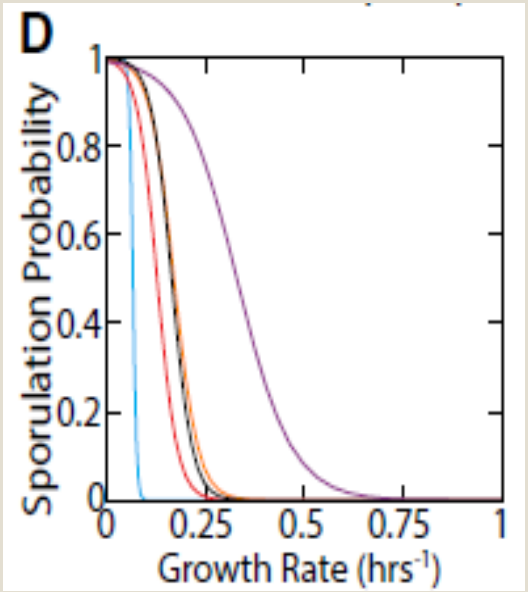
sporulation was deferred and its deferral was heterogeneous when IPTG was added early

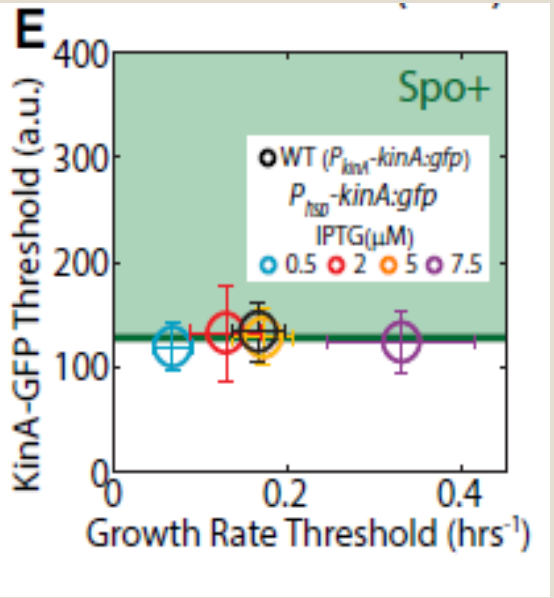
when IPTG was added late,cells sporulated immediately upon IPTG addition without any deferral

KinA activity does not depend on the growth rate




C
Sporulation Probability
1
0.8
0.6
0.4
0.2
0
0
100
200
300
400
KinA-GFP (a.u.)
P_{hsp}-kinA:gfp
IPTG(μM)
0.5
2
5
7.5
WT (P_{kinA}-kinA:gfp)


D
Sporulation Probability
1
0.8
0.6
0.4
0.2
0
0
0.25
0.5
0.75
1
Growth Rate (hrs^{-1})


E
KinA-GFP Threshold (a.u.)
400
300
200
100
0
0
0.2
0.4
Growth Rate Threshold (hrs^{-1})
Spo+
WT (P_{kinA}-kinA:gfp)
P_{hsp}-kinA:gfp
IPTG(μM)
0.5
2
5
7.5

conclusion

- only cells growing slower than a certain rate reach ***threshold*** Spo0A activity necessary for sporulation.
- This ***growth threshold model*** accurately predicts cell fates.
- sensing the ***growth rates*** enables cells to indirectly ***detect*** starvation without the need for evaluating specific stress signals.

Discussion

- **Advantage**

focused on the role of cell growth in determining the phosphorelay response.

Apply in a wide range of other systems.

- **Disadvantage**

other signals may also affect the phosphorelay.

Why growth slowdown controls sporulation deferral.

- **Inspiration**

Network Model

Thanks for your watching!