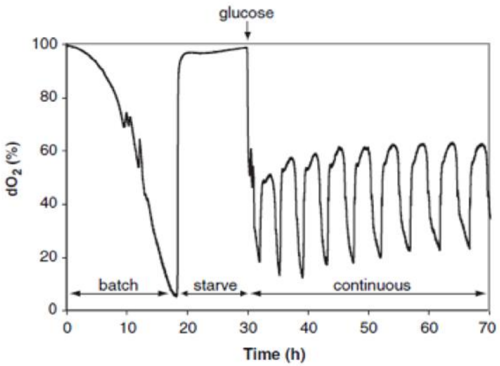
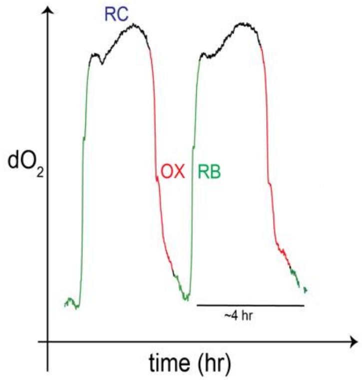
Hysteretic oscillations in a well-mixed population of budding yeast

Sandeep Krishna and Sunil Laxman



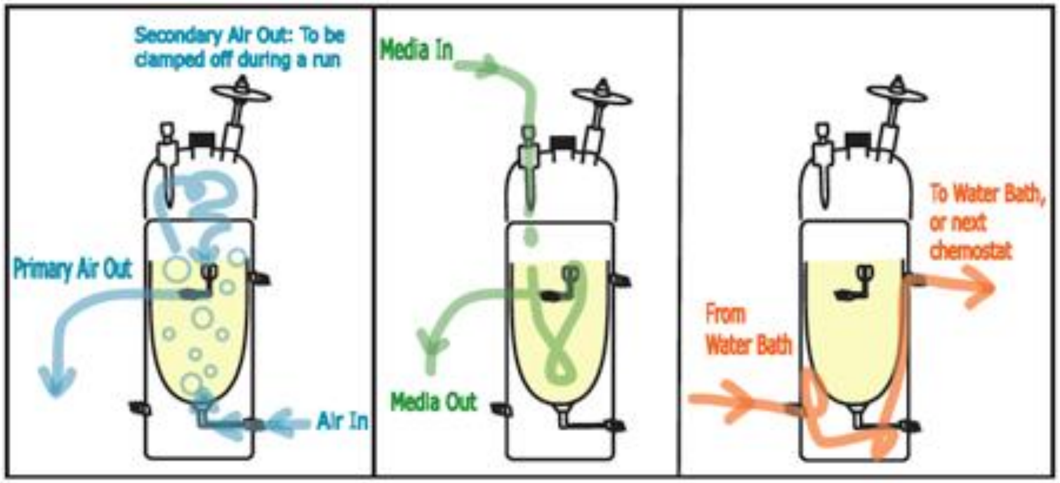
(From Tu et al, Science 2005)

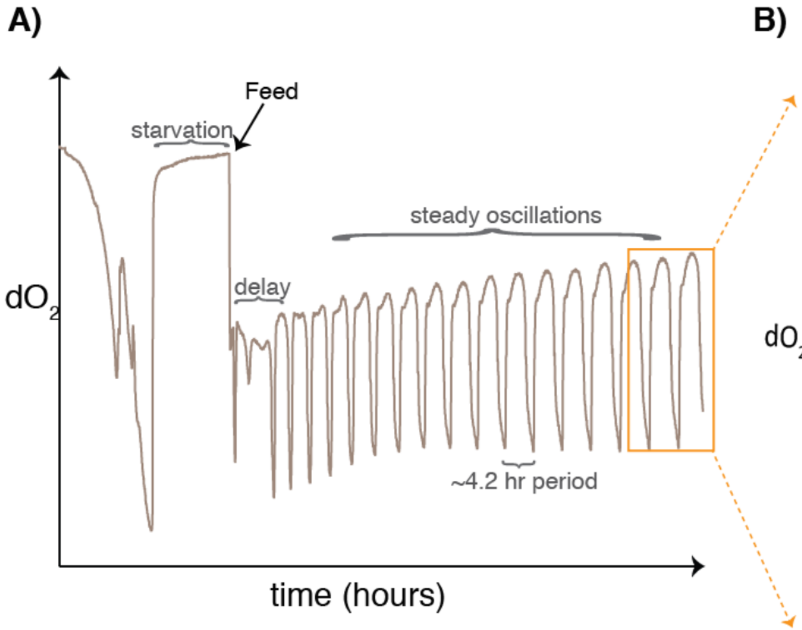


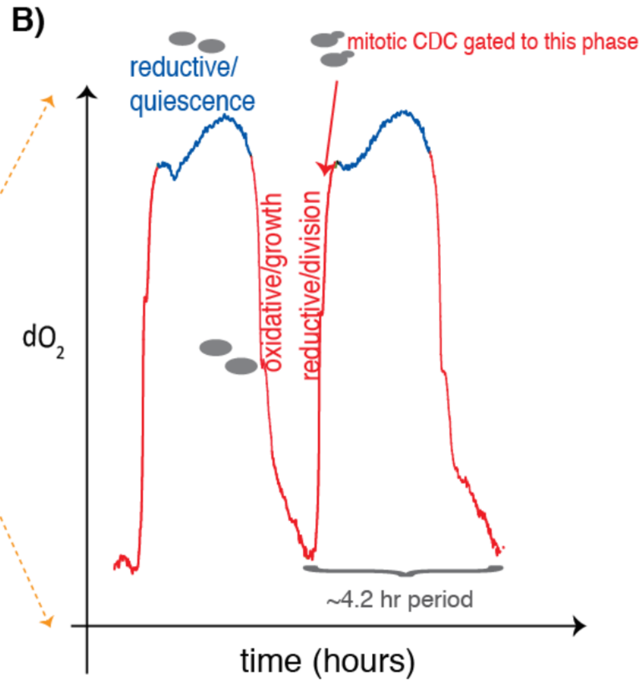
Sandeep Krishna, Sunil Laxman (2018) A minimal "push-pull" bistability model explains oscillations between quiescent and proliferative cell states. **bioRxiv 239897; doi: https://doi.org/10.1101/239897**

Funding: NCBS-TIFR, Simons Foundation, inStem, Dept. of Biotechnology, Wellcome DBT India Alliance

Oscillations in a well-mixed chemostat



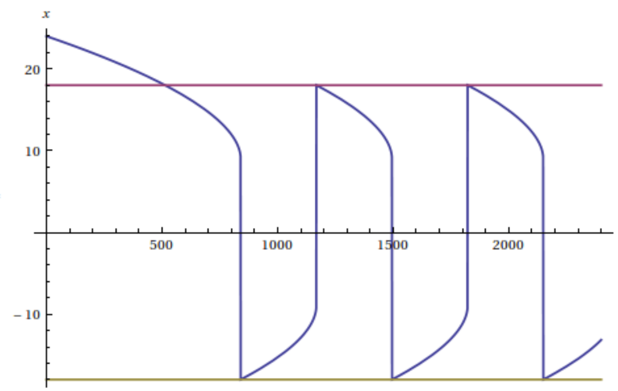




Oscillations in a well-mixed chemostat

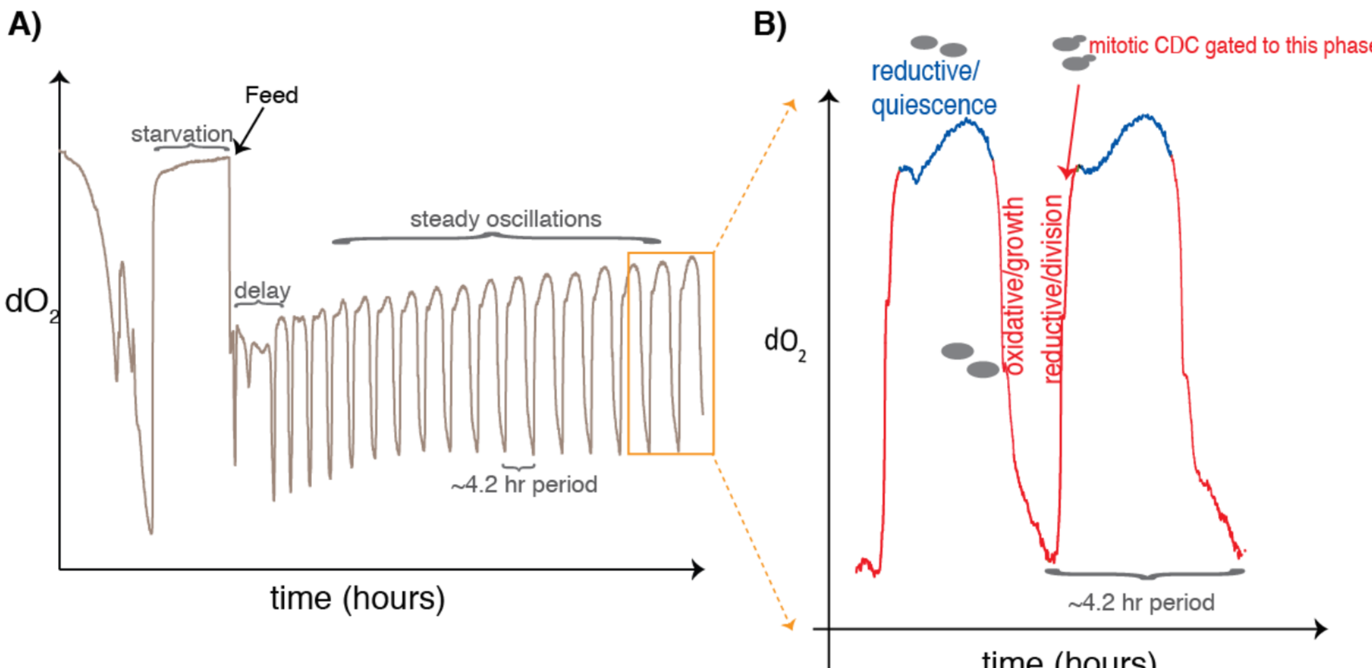
In[16]:=
```
tmax = 2400; M = 5; x0 = 9;
VDP1 = NDSolve[{x''[t] + M (x[t] ^ 2 - x0 ^ 2) x'[t] + x[t] == 0, x[0] == 2 x0 + 6,
    x'[0] == 0}, x, {t, 0, tmax}];
Plot[{Evaluate[{x[t]} /. {VDP1}], 2 x0, -2 x0}, {t, 0, tmax},
 PlotStyle → Thickness[0.004], AxesLabel → {t, x}]
```

Out[18]=

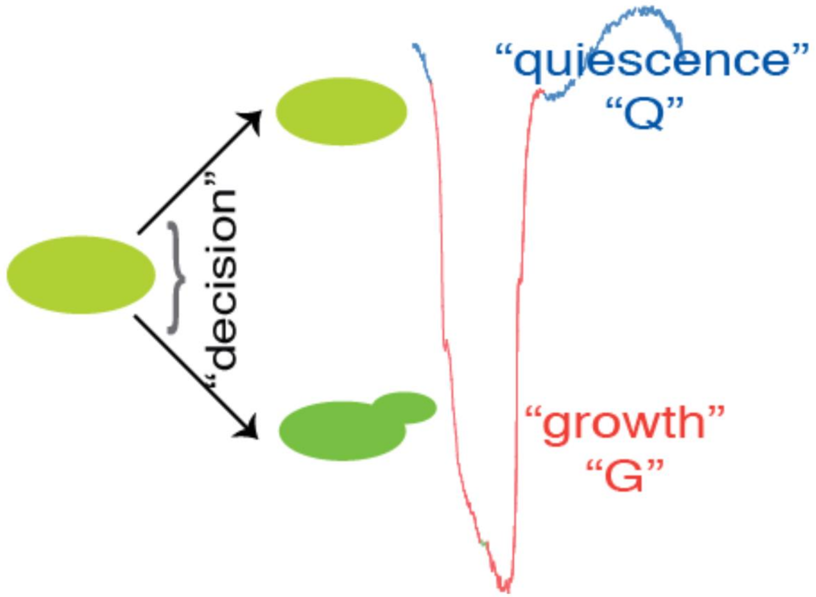


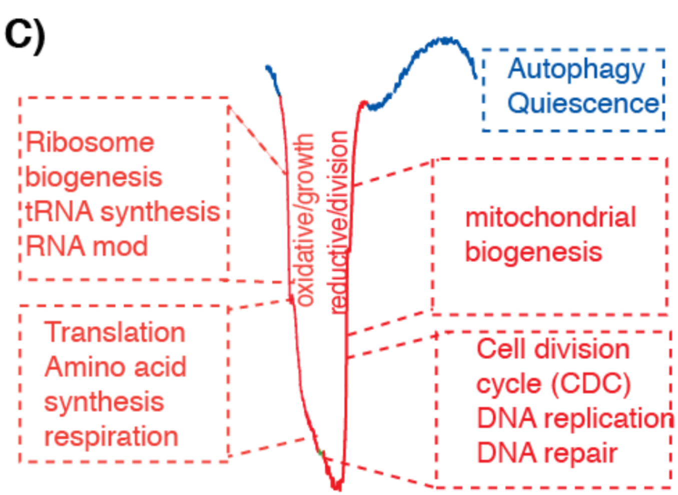
Relaxation oscillator (Van der Pol)

https://physics.stackexchange.com/questions/73118/what-is-the-amplitude-of-the-limit-cycle-of-the-van-der-pol-oscillator

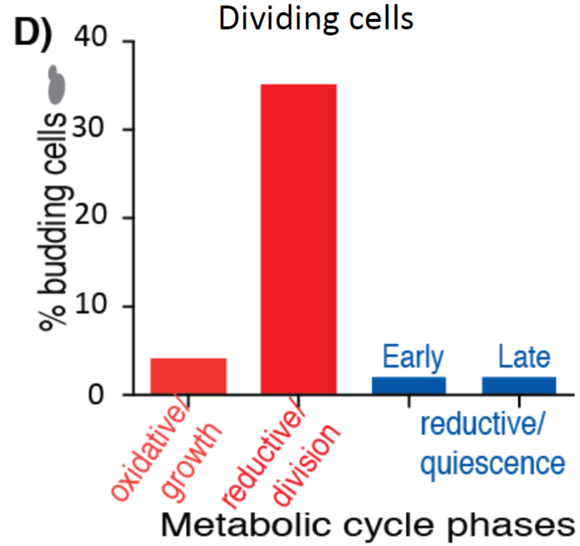


The metabolic oscillation as reflecting a two state (Q and G) oscillation





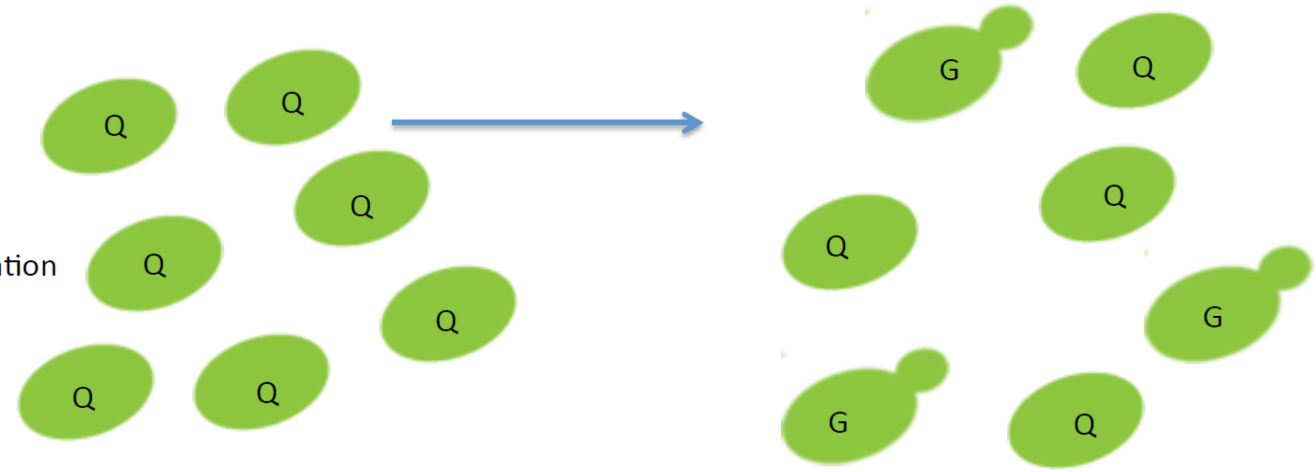
Gene expression data



Proliferation decisions in a population of cells

Q="quiescent"

G=growth/proliferation



Of biological interest:

What makes some cells enter growth/proliferation, while others don't?
How does the metabolic state of a cell regulate different cell fates?

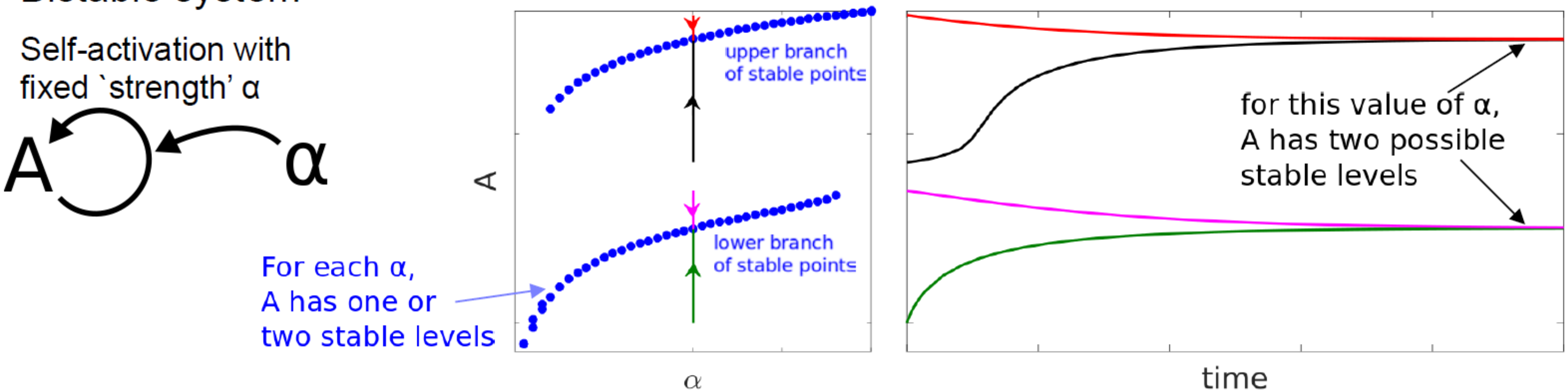
Of mathematical interest:

Can the yeast metabolic oscillations be explained as a two-state relaxation oscillator?
If so, what does this tell us about the above biological questions?

“Frustrated bistability”: a mechanism to engineer oscillations

Bistable system

Self-activation with fixed `strength’ α



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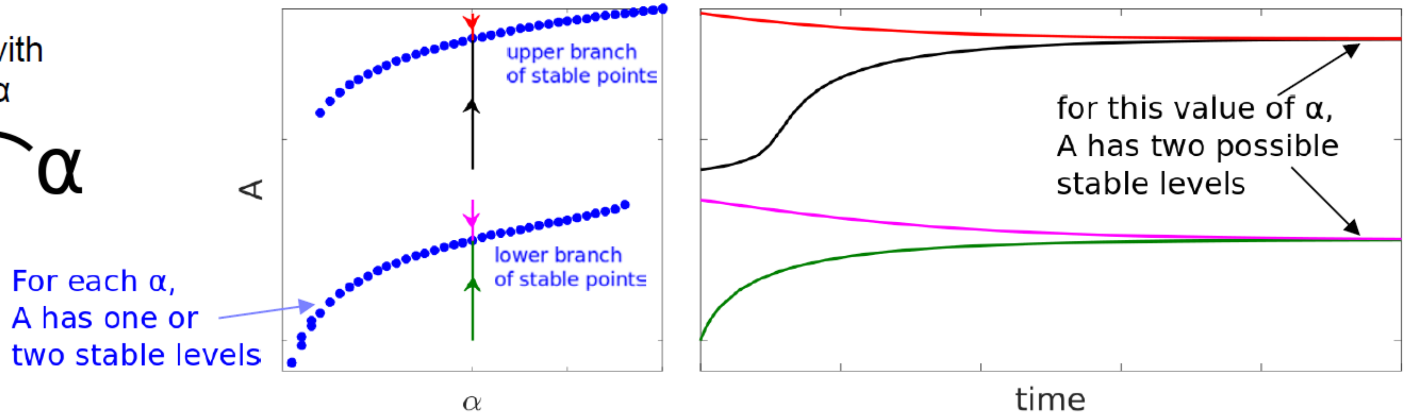
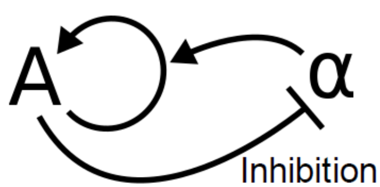
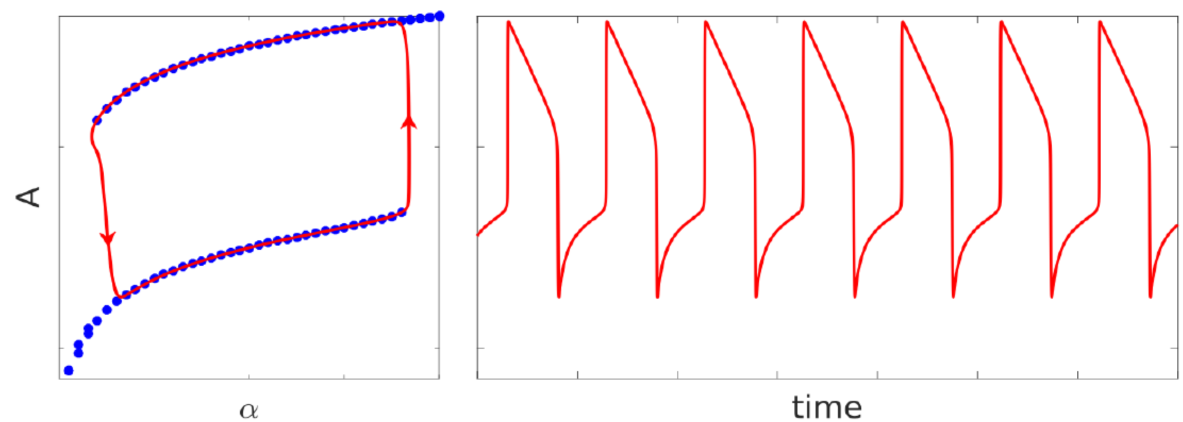


Negative feedback loop so α changes (slowly) with time

Frustrated bistability





This is a sub-class of `relaxation oscillators’

More details: Krishna et al. (2009) Phys. Biol. 6:036009

A frustrated bistability model of yeast oscillations

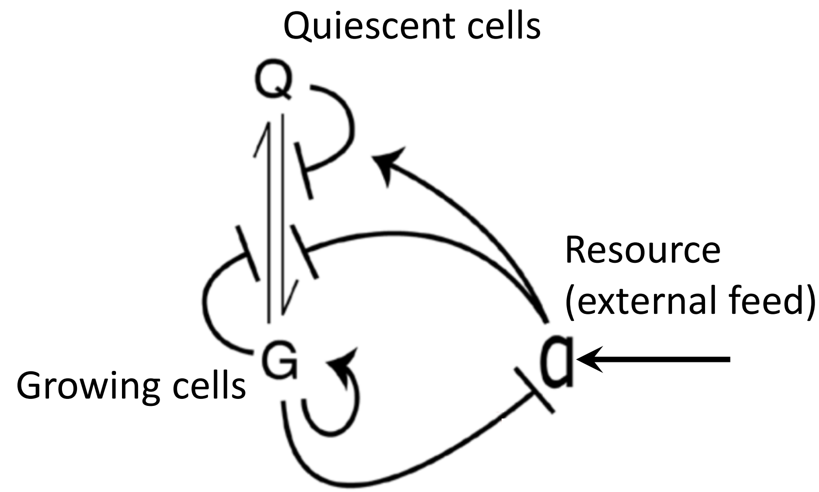
Switching G->Q, Q->G   Growth/Dilution

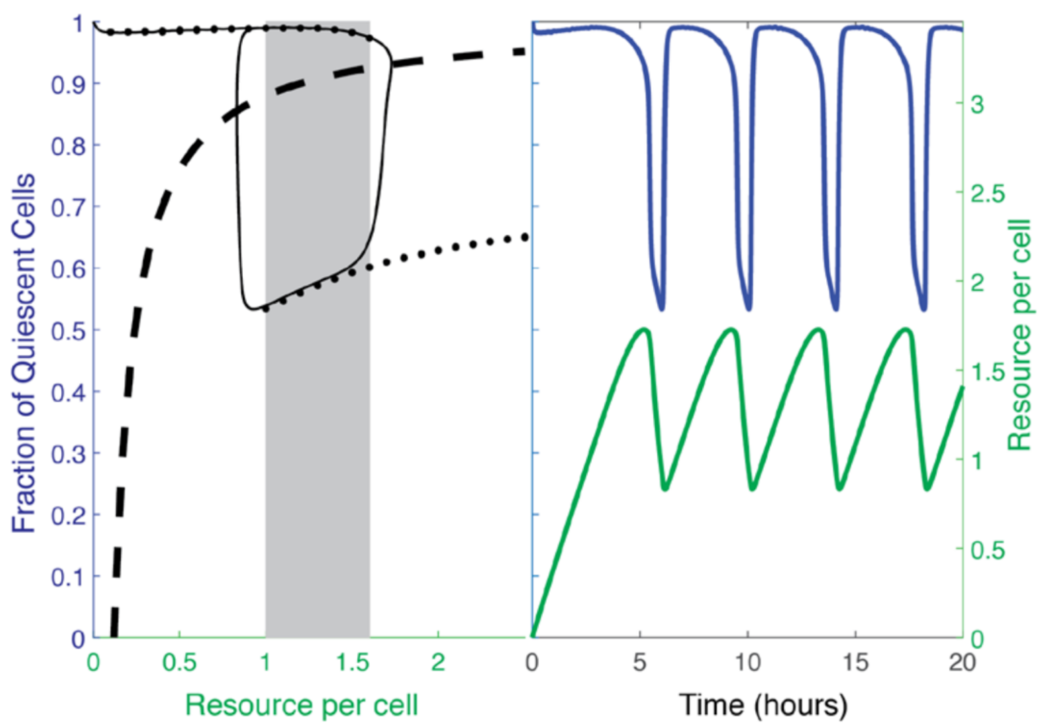
$$\frac{dq}{dt} = \nu_{GQ}(1-q) - \nu_{QG}q - \gamma q(1-q),$$

$q \equiv Q/(G+Q)$ Fraction of quiescent cells

$$\frac{da}{dt} = \sigma - \mu\gamma(1-q)a - \gamma(1-q)a,$$

Resource consumption   Growth/Dilution





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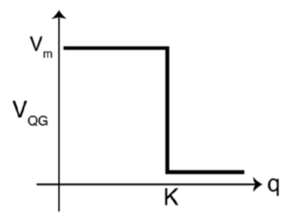
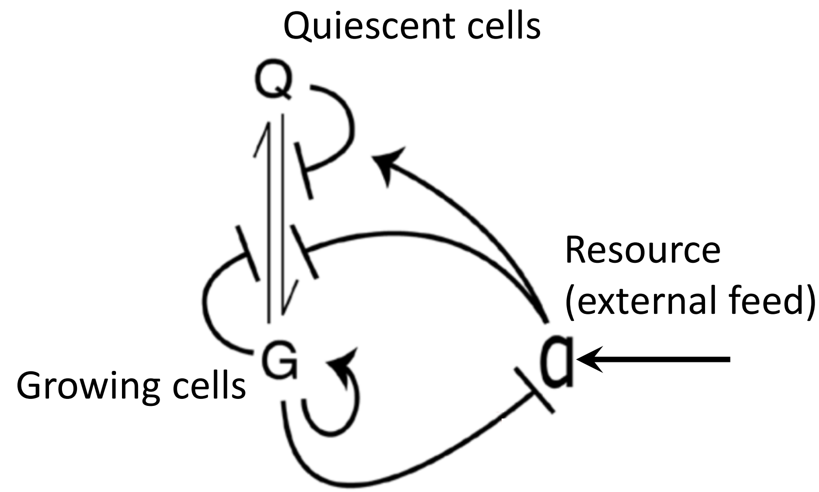
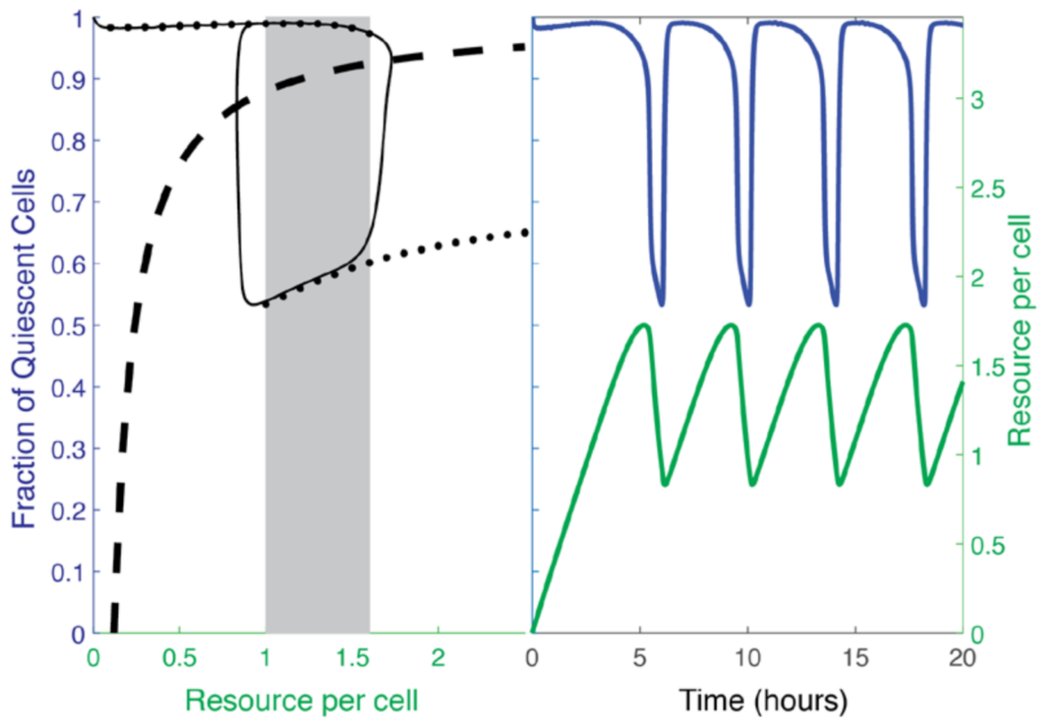
v_{QG} and/or v_{GQ} must be (nonlinear) functions of q





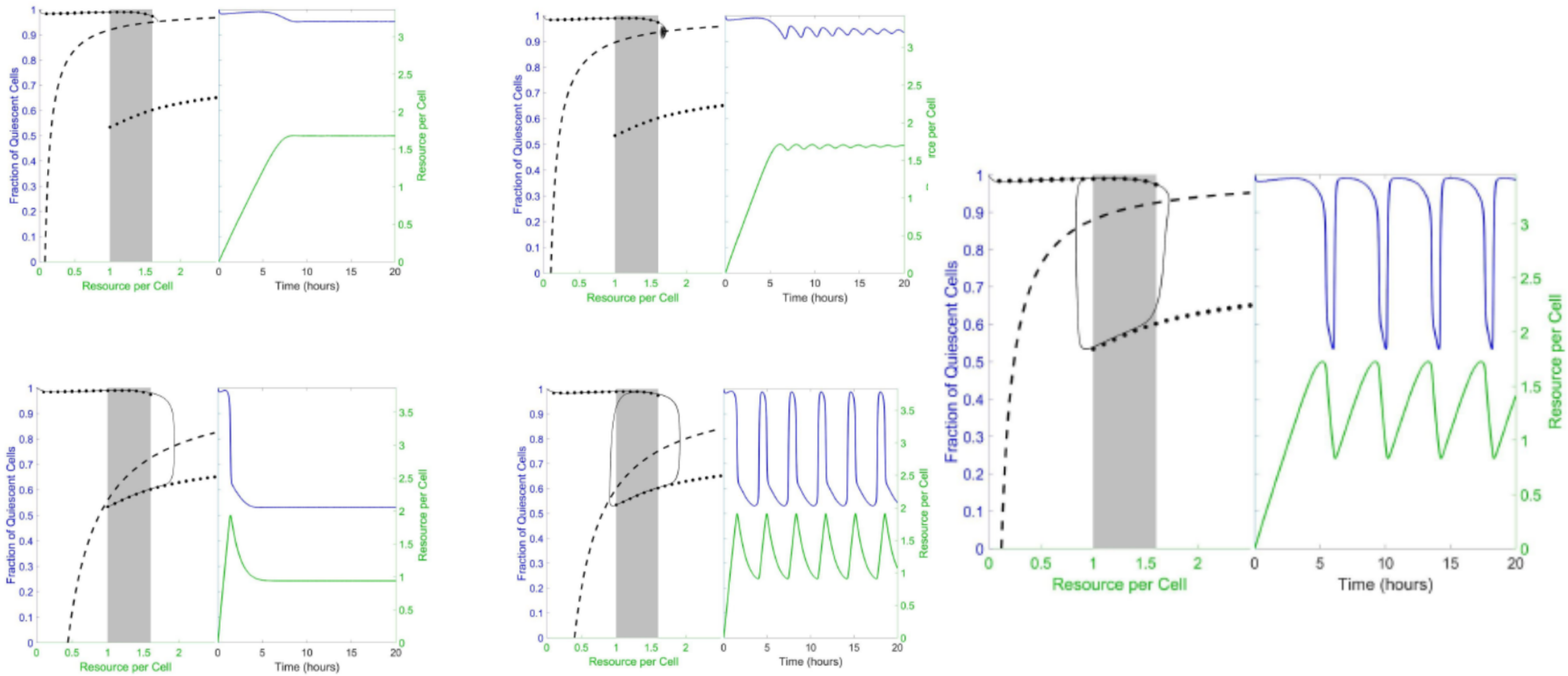
Cell-cell communication is necessary

Sandeep Krishna, Sunil Laxman (2018)
bioRxiv 239897; doi: https://doi.org/10.1101/239897



Predicting what happens to oscillations as we alter resource availability

Decrease σ by > 50%



Increase σ by > 50%

- Prediction: Changing feeding rate changes frequency but not amplitude.
- Oscillation disappears when feeding rate is increased or decreased ~2-fold.

Sandeep Krishna, Sunil Laxman (2018) A minimal "push-pull" bistability model explains oscillations between quiescent and proliferative cell states. **bioRxiv 239897; doi: https://doi.org/10.1101/239897**

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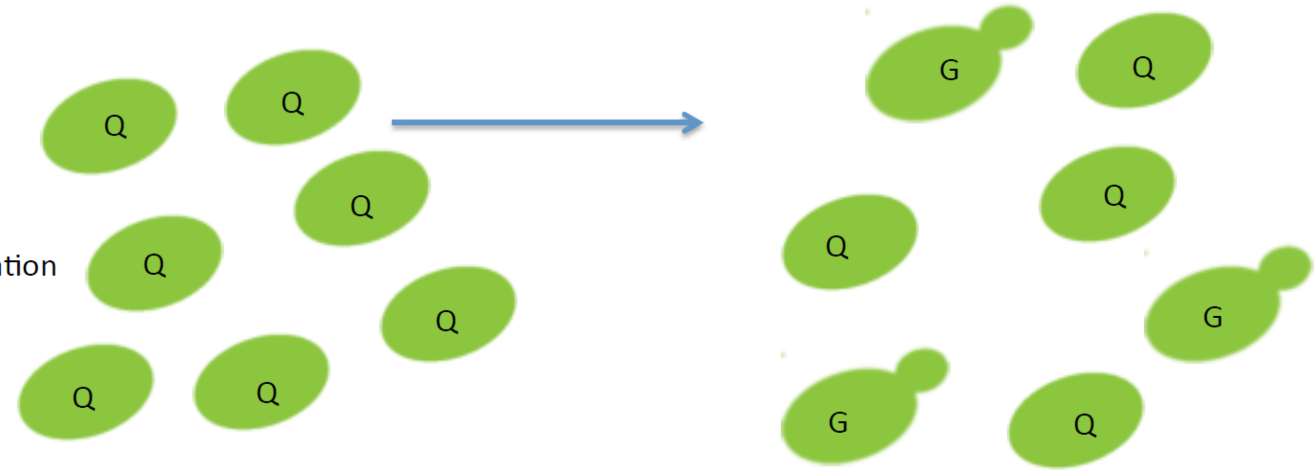

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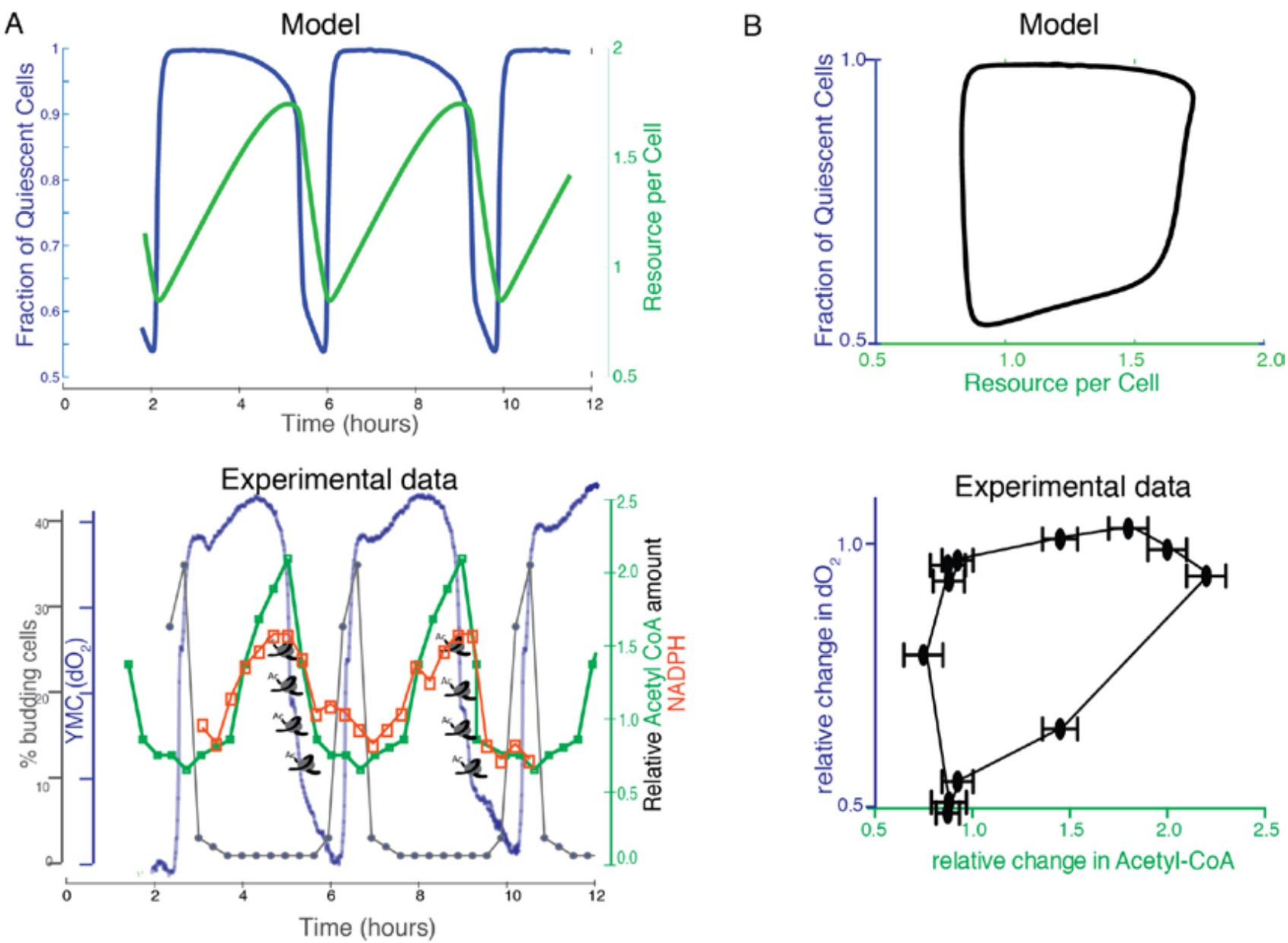
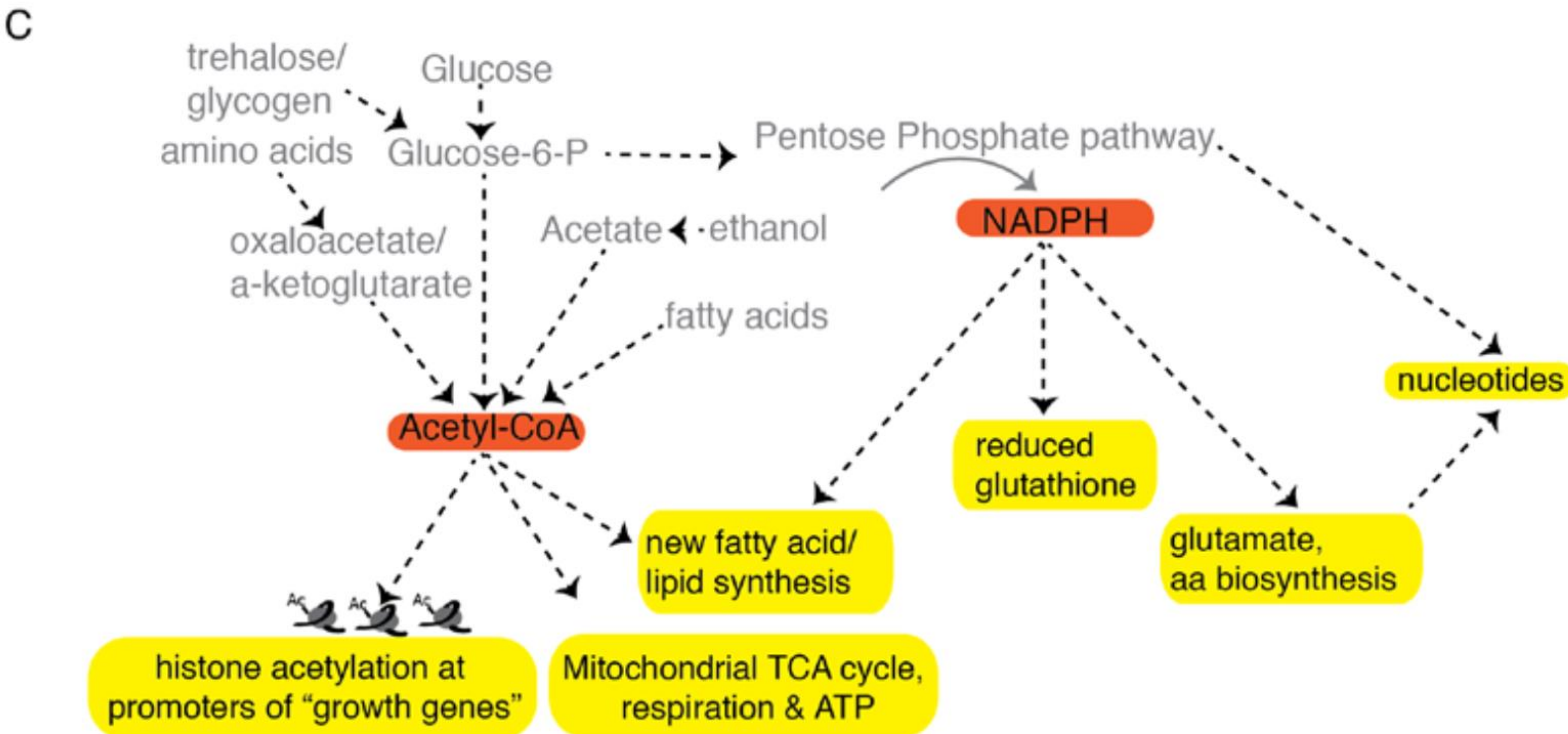
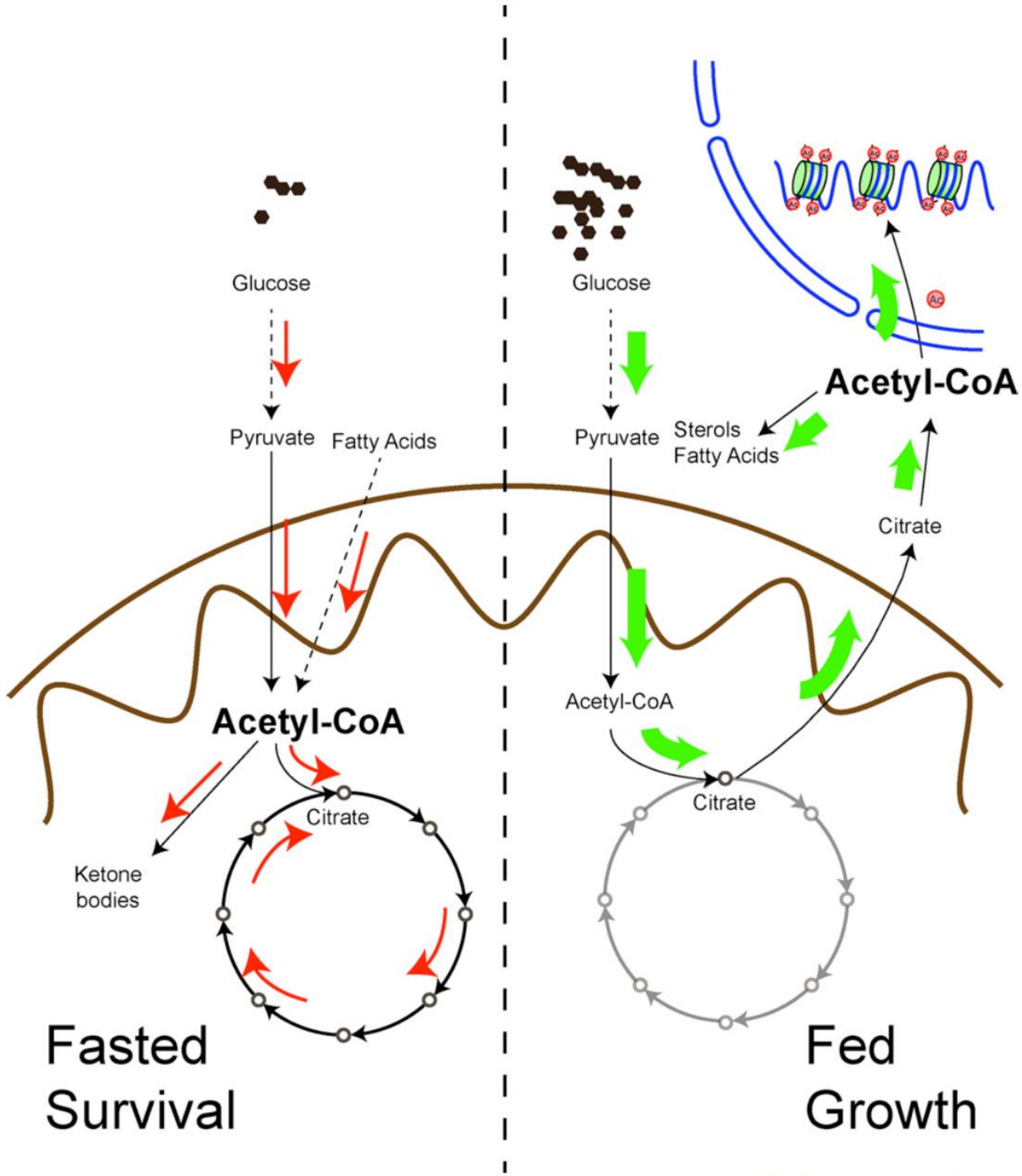
Identifying the metabolic driver



Identifying the metabolic driver

Our best guess: Acetyl-CoA





Shi & Tu, Curr Op Cell Bio 2015

Summary / Future directions

Theory:

Can the yeast metabolic oscillations be explained as a two-state relaxation oscillator? Yes
If so, what does this tell us about the above biological questions? Acetyl-CoA

>Some counter-intuitive elements in the model that need explanation
>Need a more detailed model where the internal resource amount varies from cell to cell

Experiment:

How does the metabolic state (Acetyl-CoA) of a cell regulate different cell fates?
How do cells communicate their metabolic state to each other?

>Experiments that manipulate Acetyl-Coa
>Experiments that manipulate the external environment of the population

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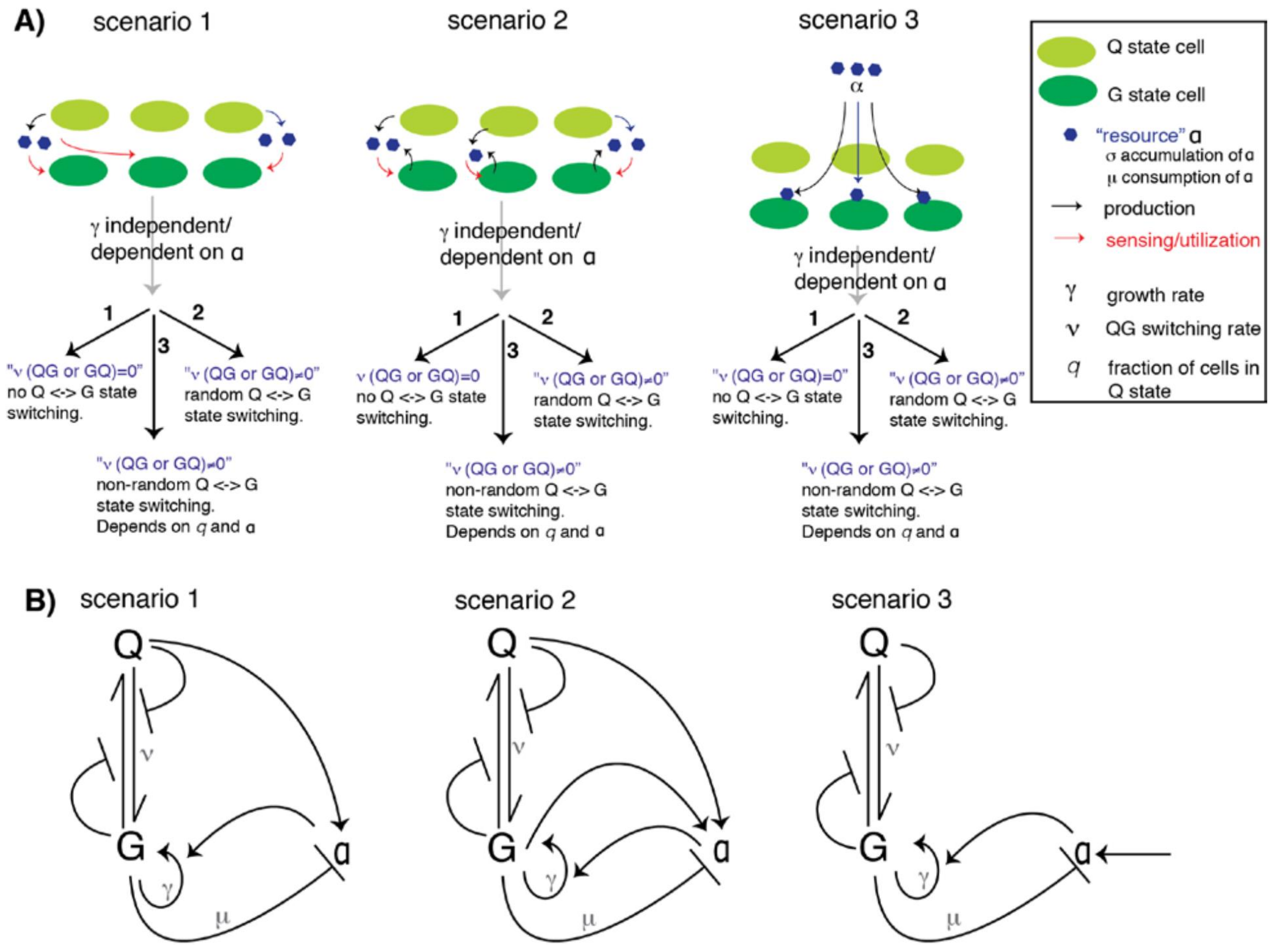
$$\frac{dQ}{dt} = \nu_{GQ}G - \nu_{QG}Q - \phi(t)Q,$$

$$\frac{dG}{dt} = \gamma G - \nu_{GQ}G + \nu_{QG}Q - \phi(t)G,$$

$$\Big\downarrow \; q \equiv Q/(G+Q)$$

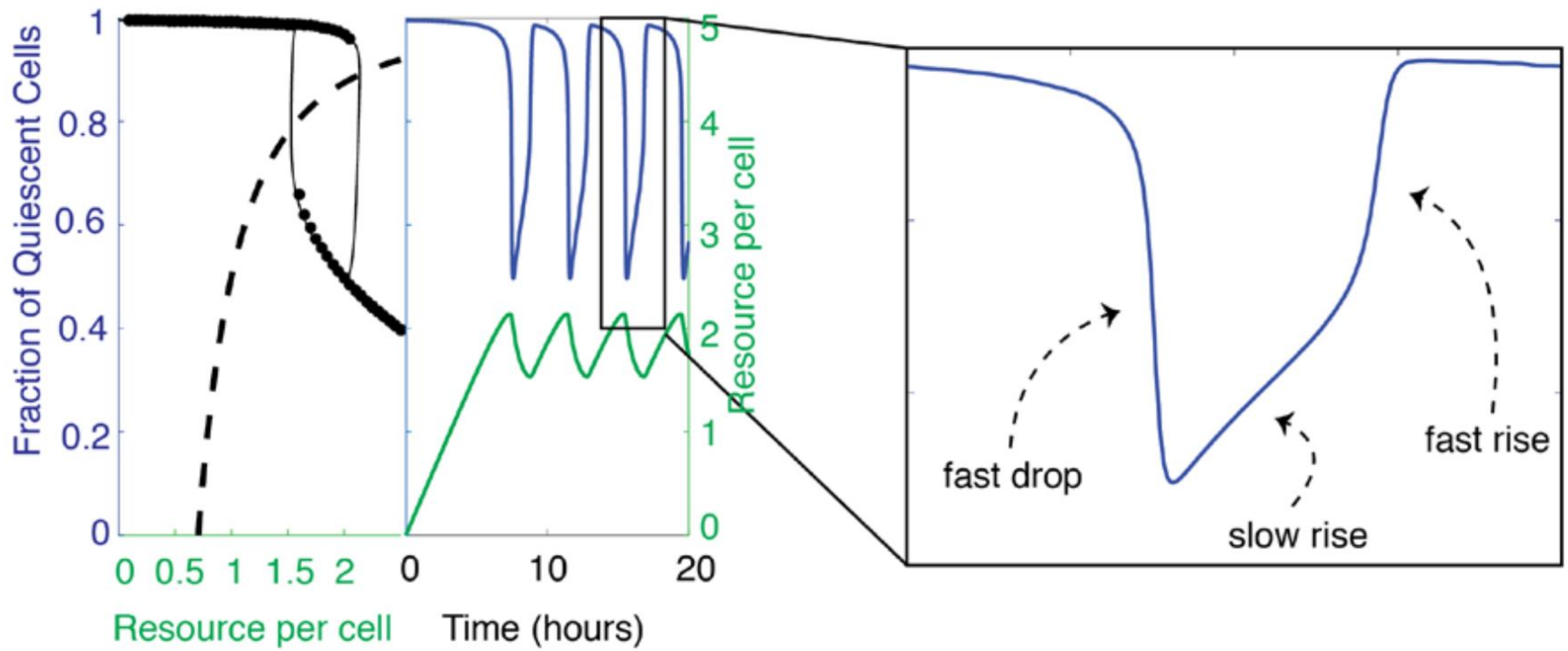
$$\frac{dq}{dt} = \nu_{GQ}(1-q) - \nu_{QG}q - \gamma q(1-q),$$

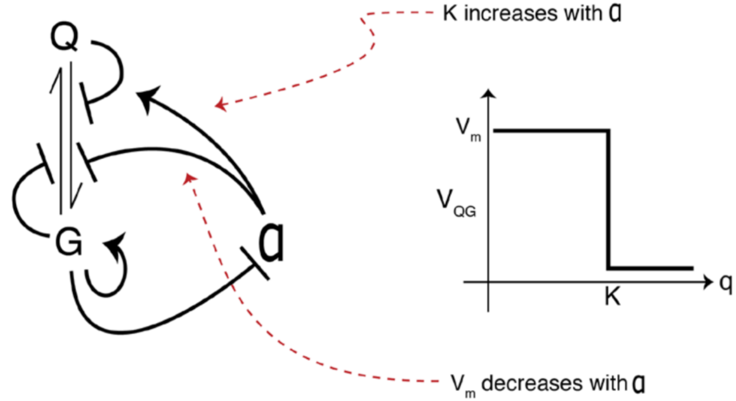

A)
scenario 1
scenario 2
scenario 3
Q state cell
G state cell
"resource" α
σ accumulation of α
μ consumption of α
production
sensing/utilization
γ growth rate
ν QG switching rate
q fraction of cells in Q state
γ independent/ dependent on α
"ν (QG or GQ)=0" no Q <-> G state switching.
"ν (QG or GQ)≠0" random Q <-> G state switching.
"ν (QG or GQ)≠0" non-random Q <-> G state switching. Depends on q and α
B)
scenario 1
scenario 2
scenario 3

$$\frac{dq}{dt} = \nu_{GQ}(1-q) - \nu_{QG}q - \gamma q(1-q),\ \frac{da}{dt} = \sigma - \mu\gamma(1-q)a - \gamma(1-q)a,$$

$$\gamma = 0.32 \times a\ hr^{-1},\ \sigma = 0.32\ hr^{-1},\ \mu = 1, \nu_{QG} = 0.32\ hr^{-1},\ \nu_{GQ} = [1 + 1.8 \times \theta(q-0.9)] \times 32\ hr^{-1},$$

C)

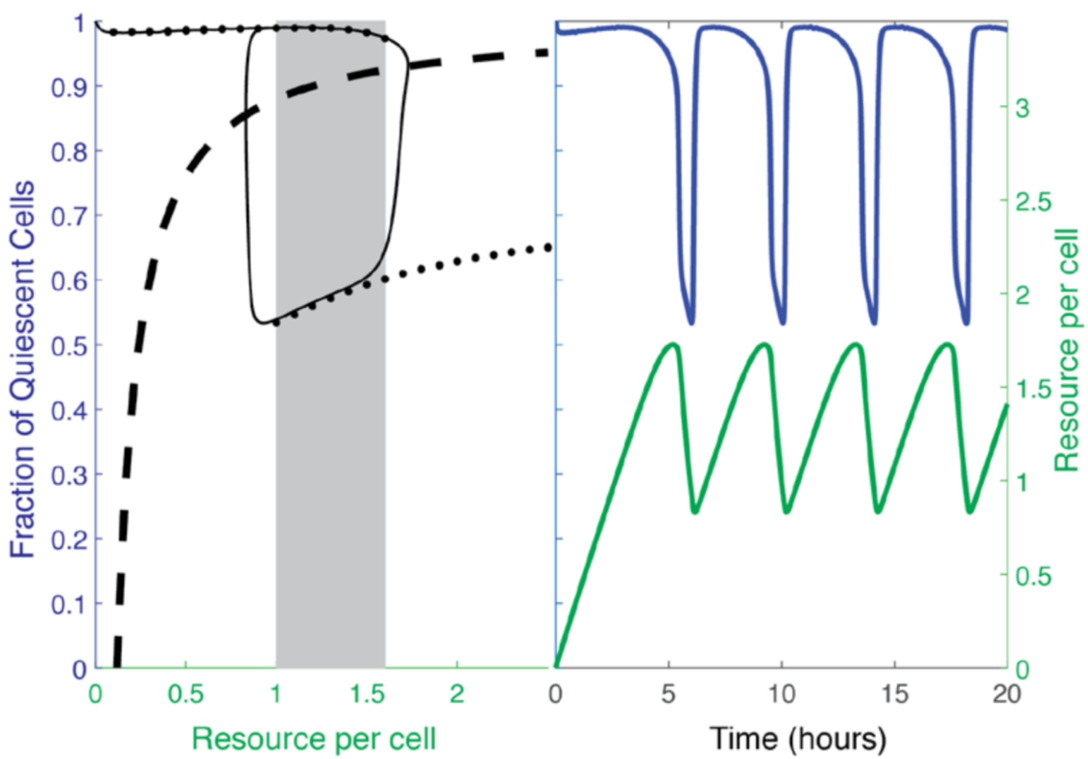




$$\frac{dq}{dt} = \nu_{GQ}(1-q) - \nu_{QG}q - \gamma q(1-q),\ \frac{da}{dt} = \sigma - \mu\gamma(1-q)a - \gamma(1-q)a,$$

$$\gamma = 1.665\ hr^{-1},\ \sigma = 0.3996\ hr^{-1},\ \mu = 1, \nu_{QG} = v[1-0.99\times\theta(q-K)],\ \ K = a^2/(0.75^2 + a^2),$$

$$v = (0.165 - 0.125K)\ hr^{-1},\ \nu_{GQ} = 16.65\ hr^{-1}$$



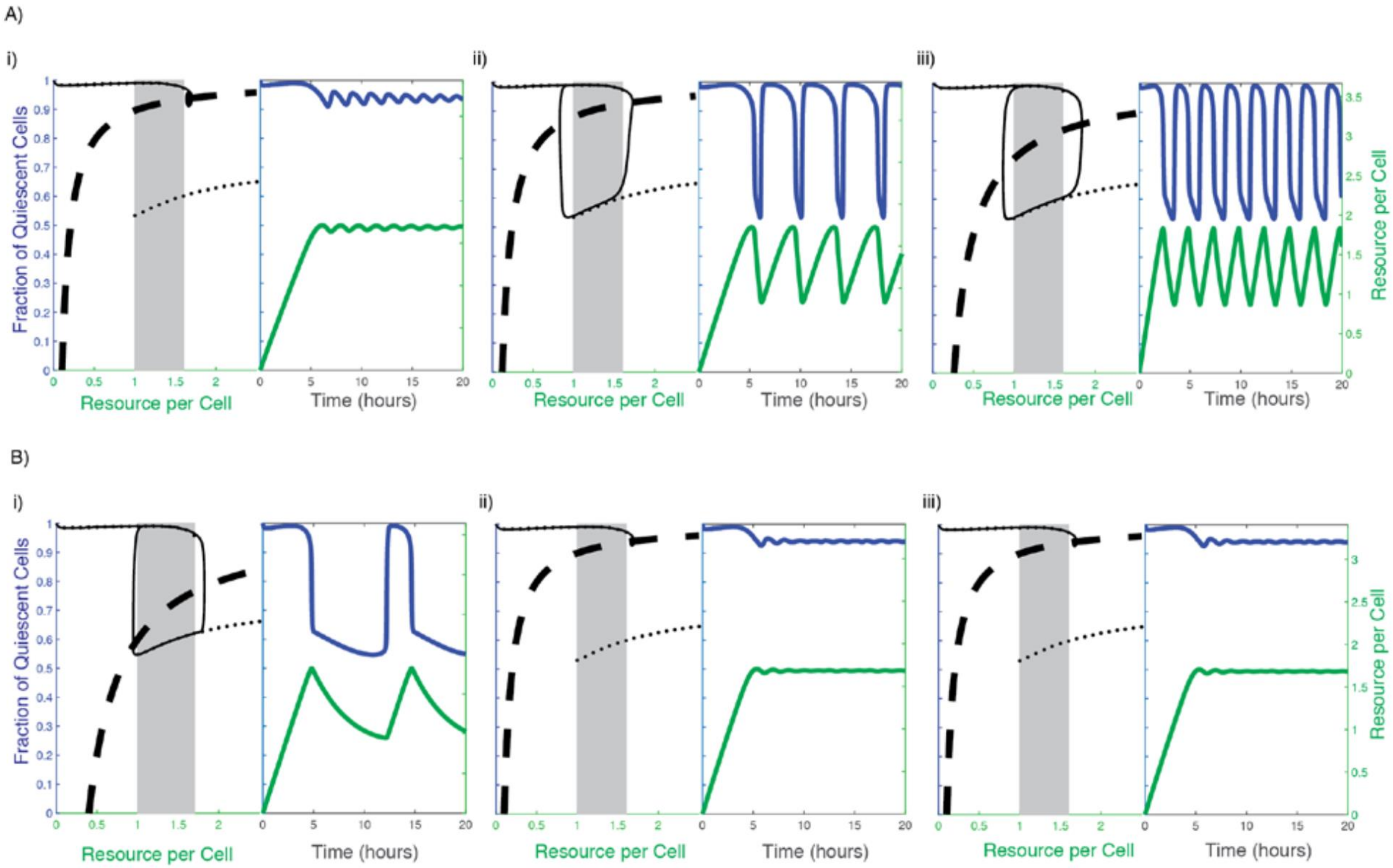
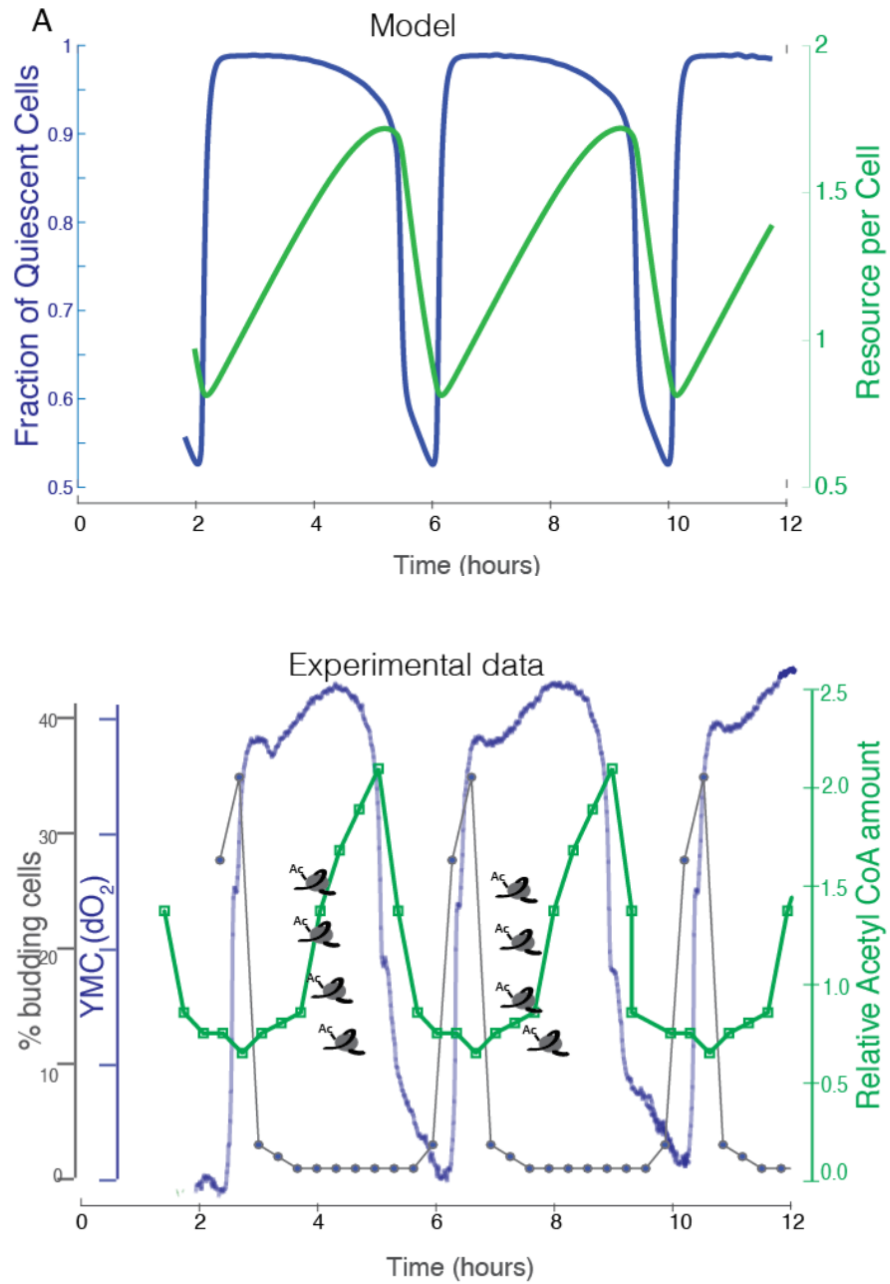
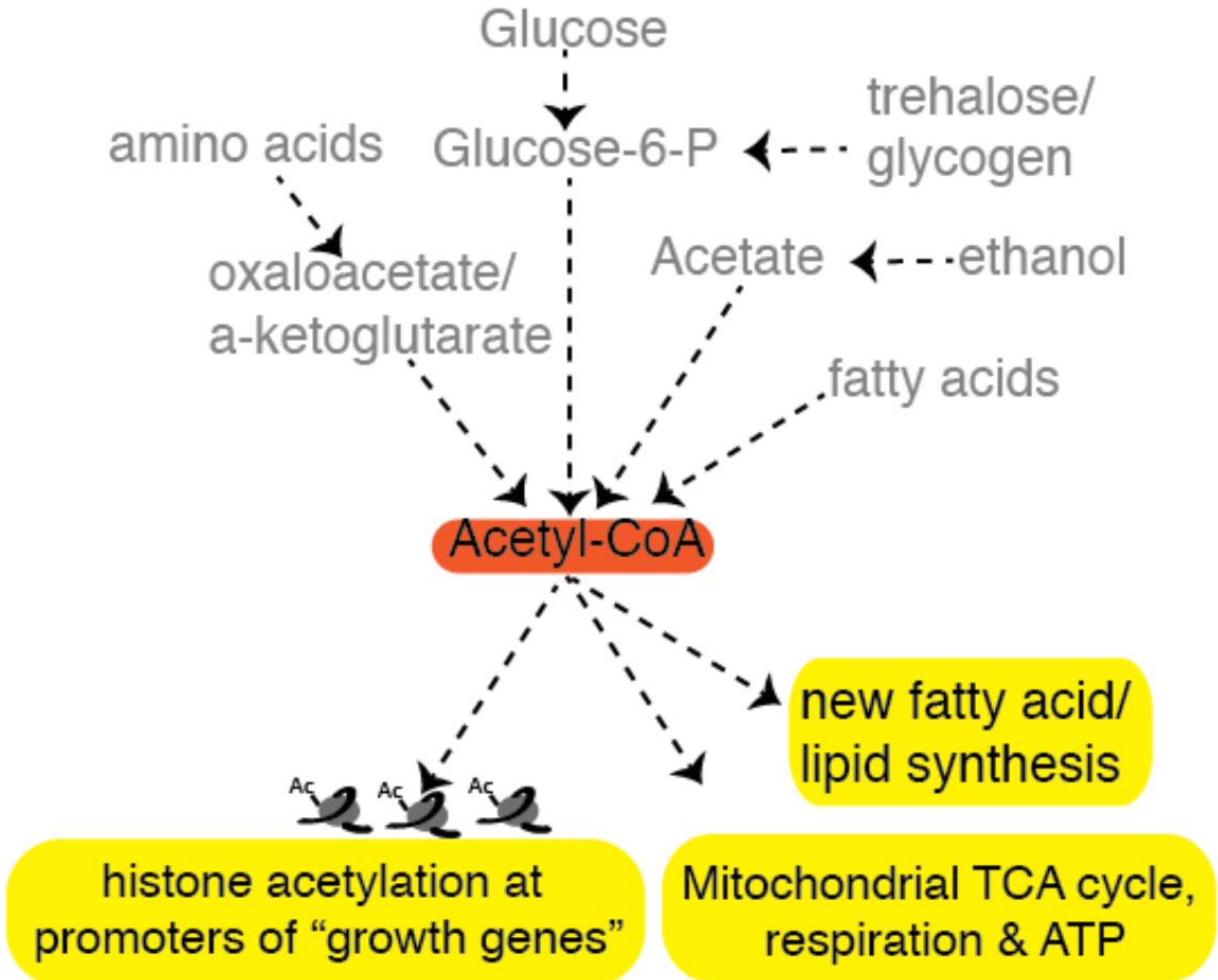


Figure 4: Breakdown of oscillations.
A) Varying the rate of production of resource σ. (i) σ = 0.346/hr, (ii) σ = 0.400/hr (default parameters, same as Fig 3), (iii) σ = 0.866/hr.
B) Varying the growth rate of cells γ. (i) γ = 0.500/hr, (ii) γ = 1.665/hr (default parameters, same as Fig 3), (iii) γ = 2.000/hr.

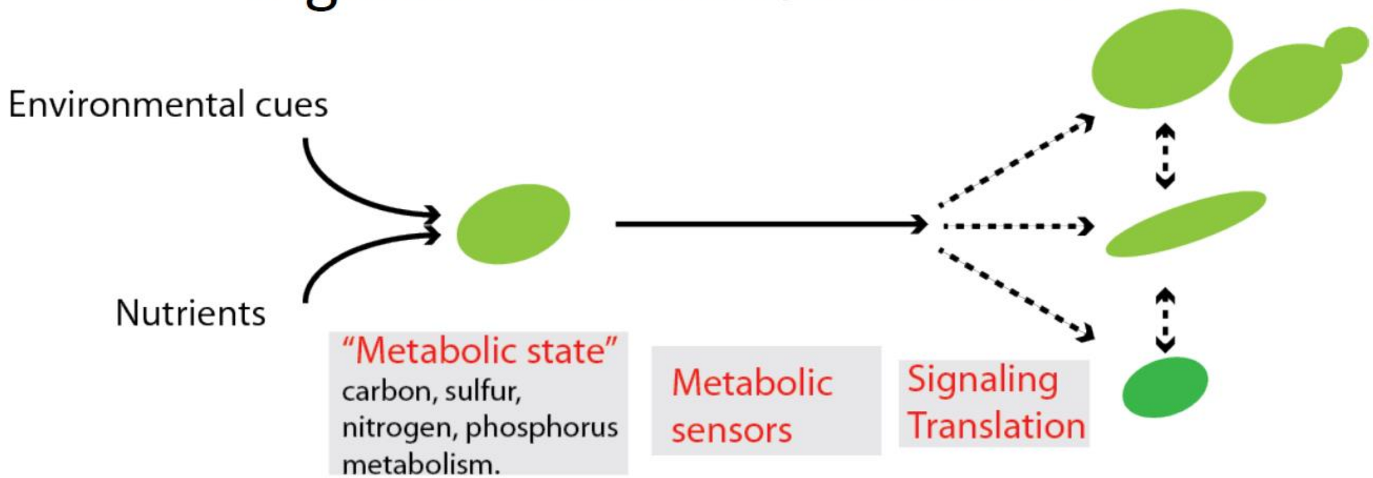
A metabolic resource, acetyl CoA satisfies criteria to be the controller of this Q ←→ G bistability



Why Acetyl-CoA?



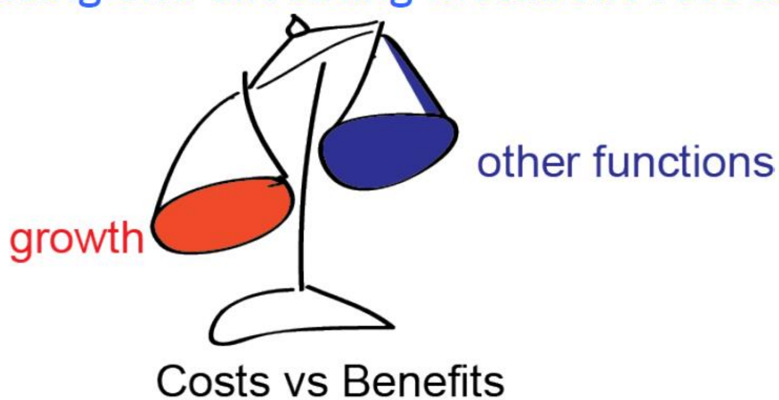
Our interest: How does the metabolic state of a cell regulate different cell fates?



Metabolic phenotype → How? Why? What? → Mechanism & cell biology

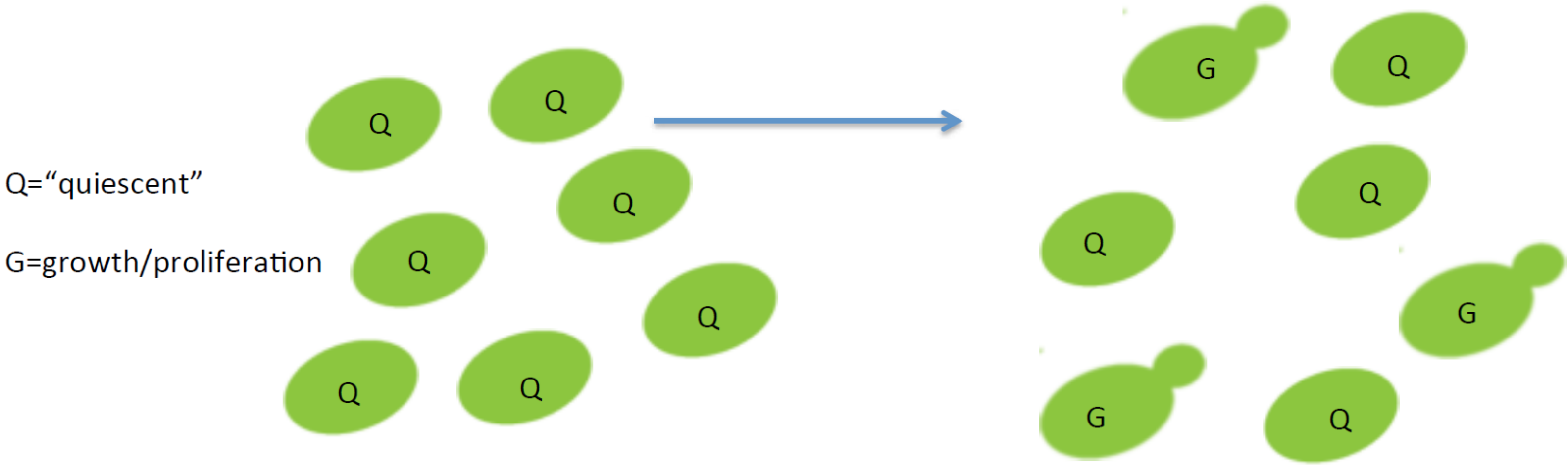
Balancing and allocating metabolic resources

ATP
Nucleotides
Proteins
Membranes

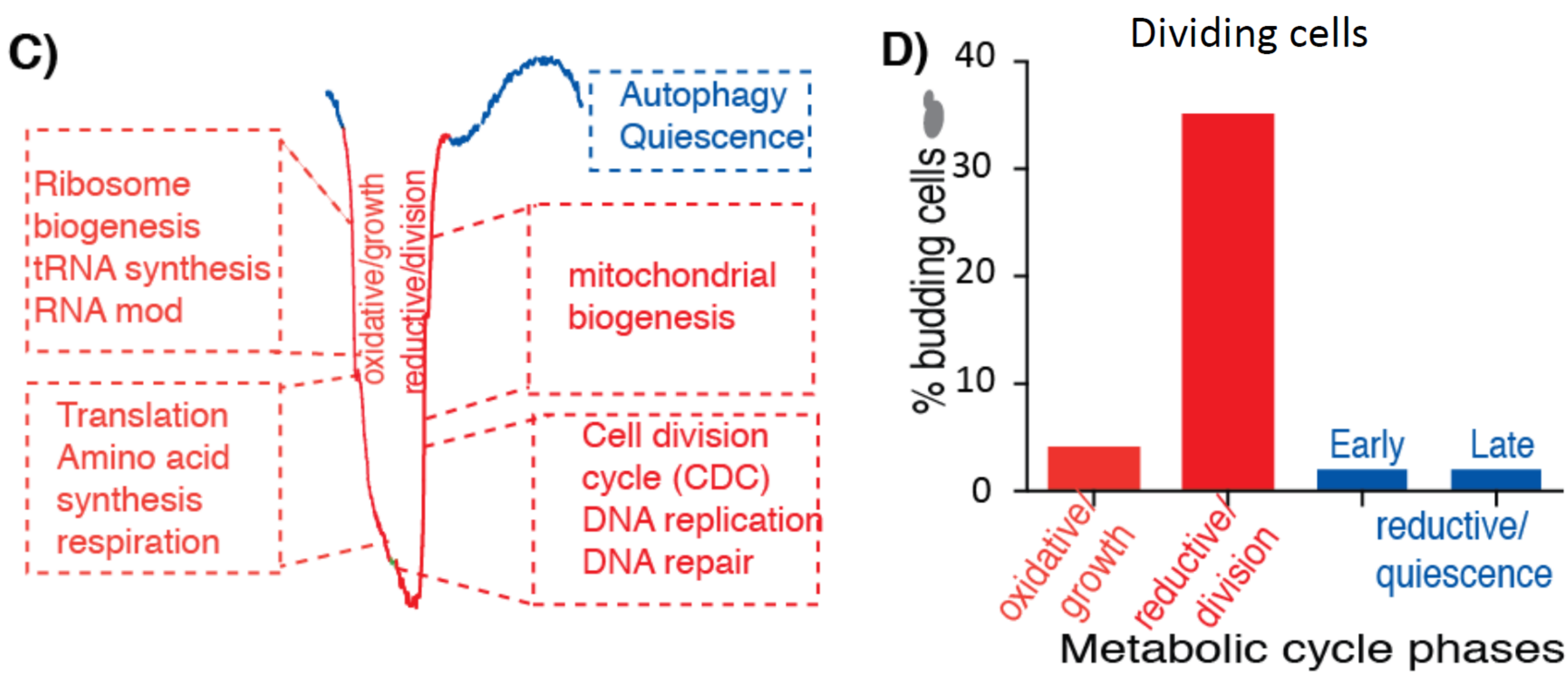


Survival/autophagy
Differentiation
Quiescence
Dehydration/freezing.

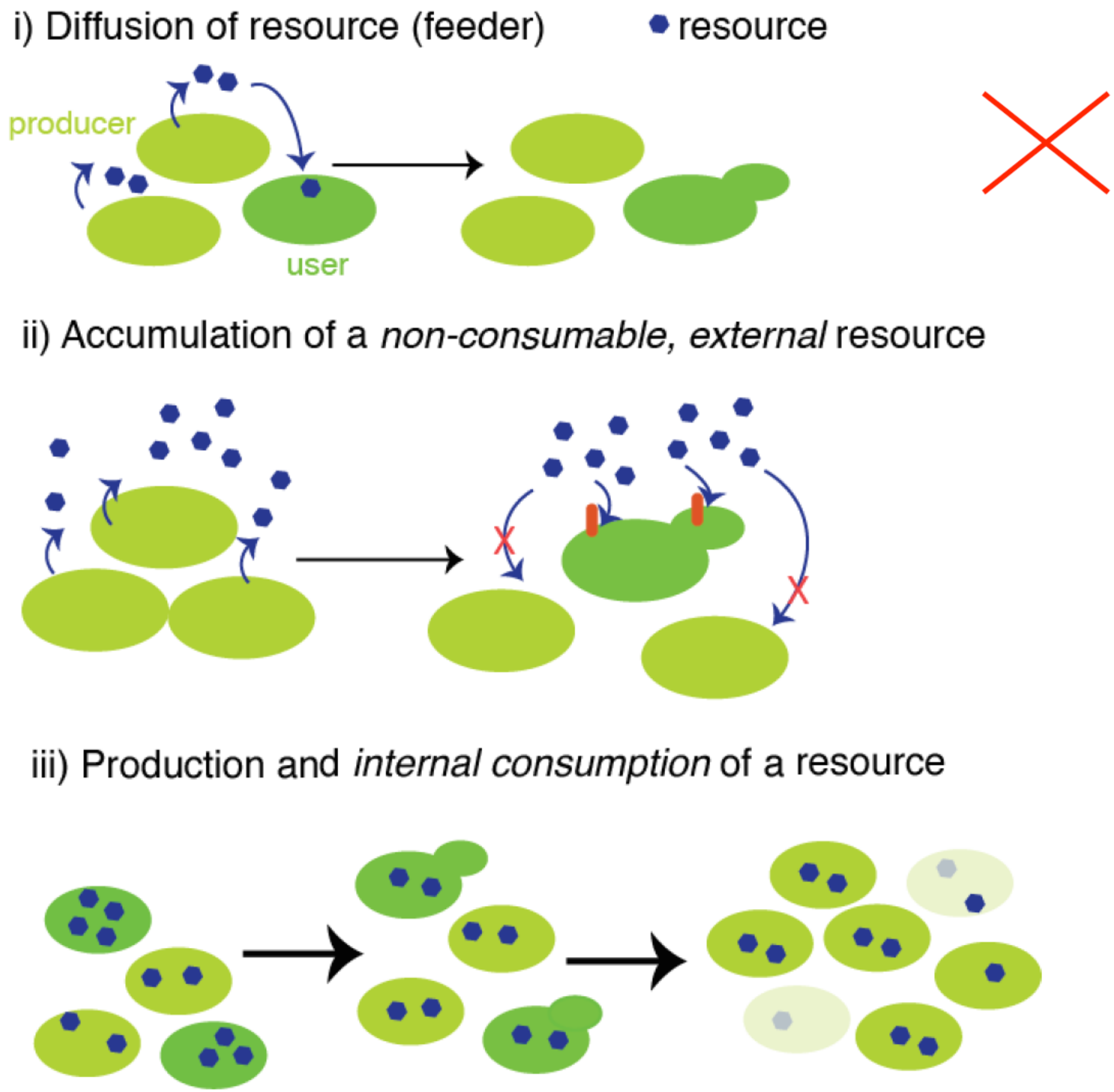
Proliferation decisions in a population of cells



- <u>The question:</u> What makes some cells enter growth/proliferation, while the others don't?
- <u>Important driver of such behavior:</u> the availability and use of a metabolic resource.
- <u>Our goal:</u> can you use theoretical/mathematical models to explain such phenomena?


C)
Ribosome
biogenesis
tRNA synthesis
RNA mod
Translation
Amino acid
synthesis
respiration
oxidative/growth
reductive/division
Autophagy
Quiescence
mitochondrial
biogenesis
Cell division
cycle (CDC)
DNA replication
DNA repair
D)
Dividing cells
% budding cells
40
30
20
10
0
Early
Late
oxidative/
growth
reductive/
division
reductive/
quiescence
Metabolic cycle phases

Plausible scenarios leading to a two-state Q & G oscillation.



A “tug-of-war” between Q and G is necessary for oscillations between the two states.

$$\frac{dq}{dt} = \nu_{GQ}(1-q) - \nu_{QG}q - \gamma q(1-q),$$

$$q \equiv Q/(G+Q)$$

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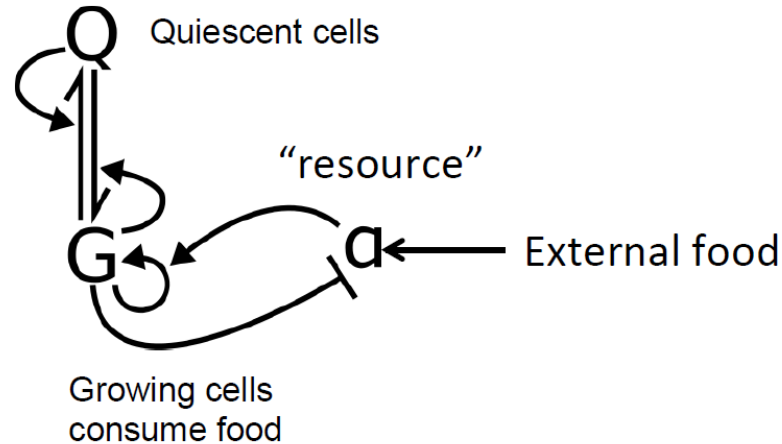
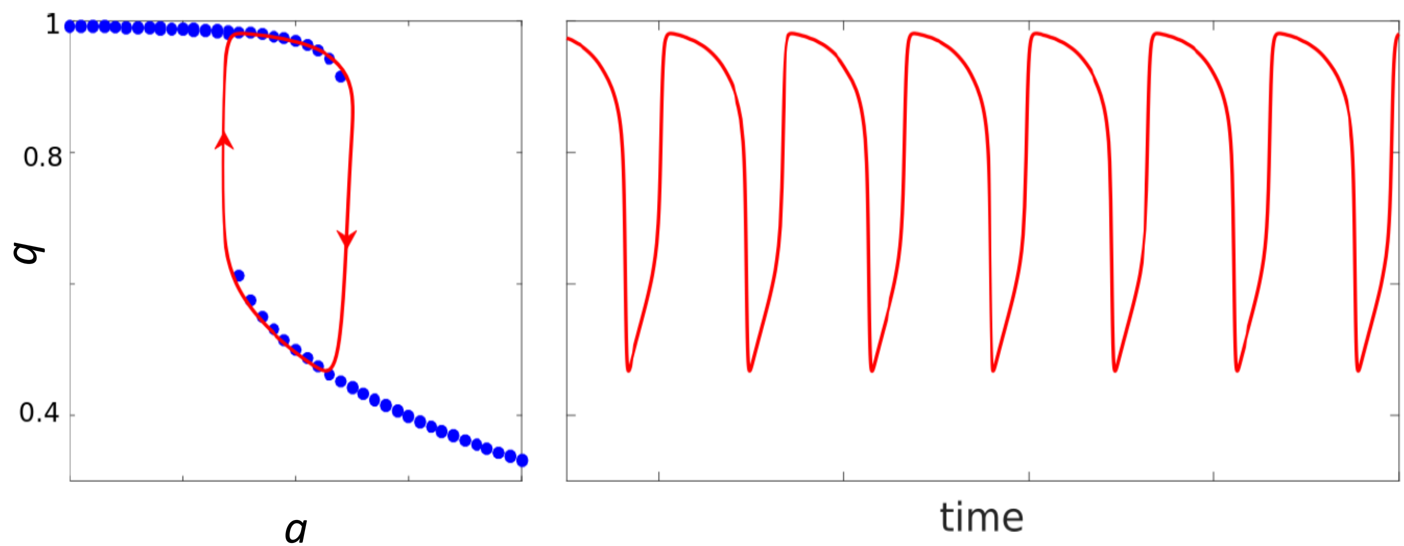
\`Tug-of-war’ between quiescent and growing cells





$$\gamma = 0.32\times a\ hr^{-1},\ \sigma = 0.32\ hr^{-1},\ \mu = 1, \nu_{QG} = 0.32\ hr^{-1},\ \nu_{GQ} = [1 + 1.8\times\theta(q - 0.9)]\times 32\ hr^{-1},$$

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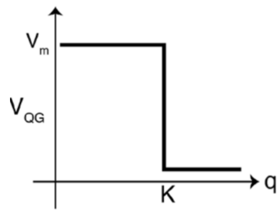
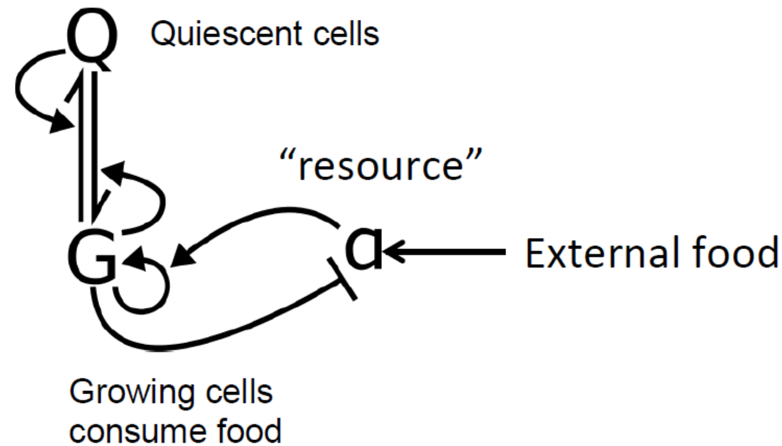
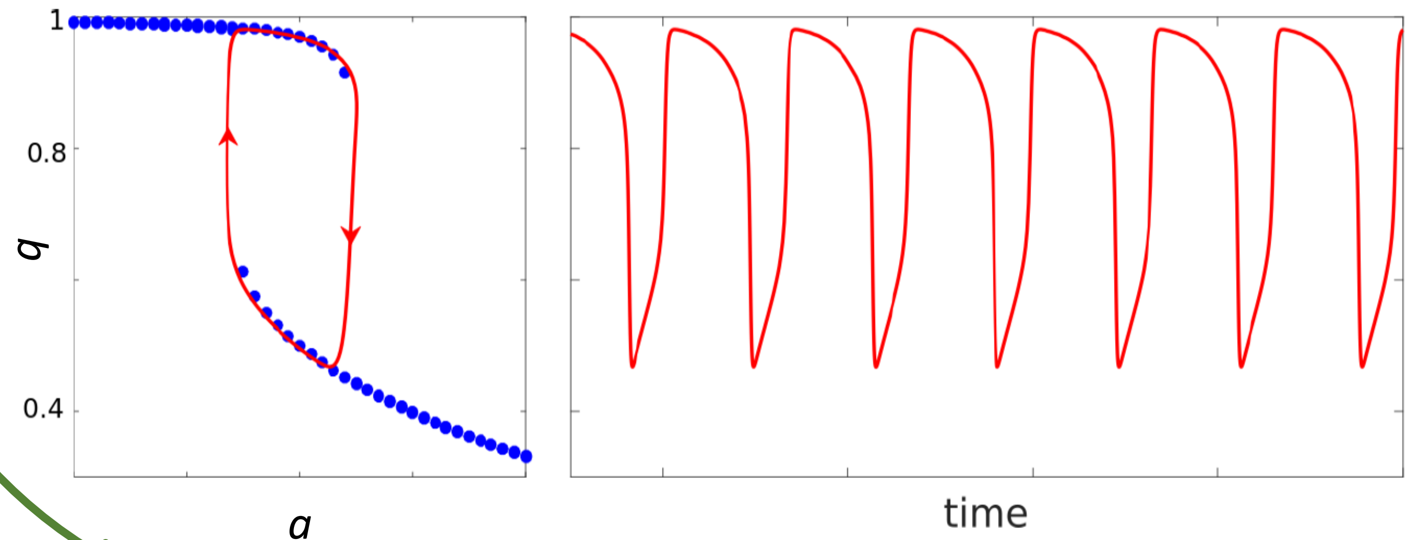


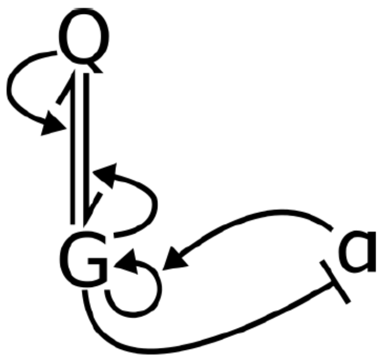
`Tug-of-war' between quiescent and growing cells

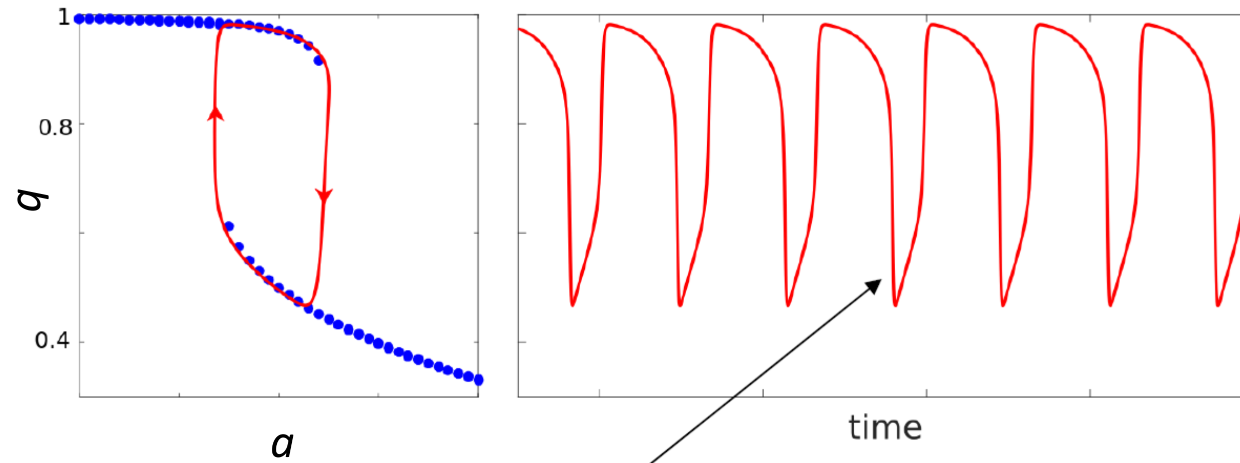




Communication- “push-pull” between the two states is essential for the oscillation.

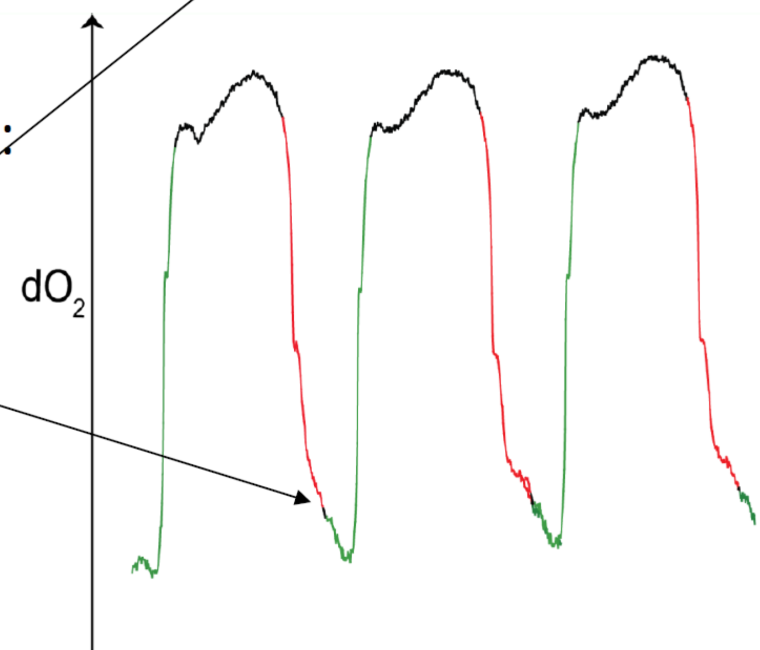
But………..



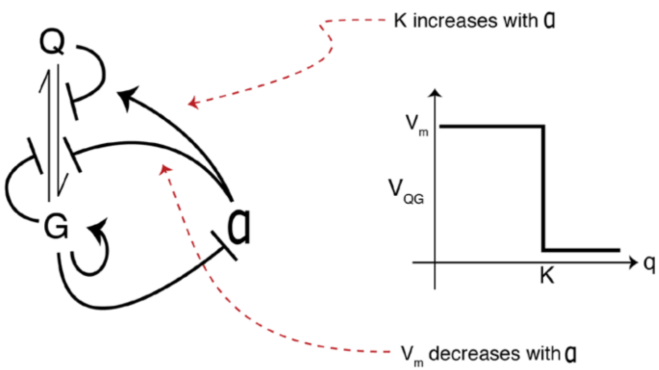


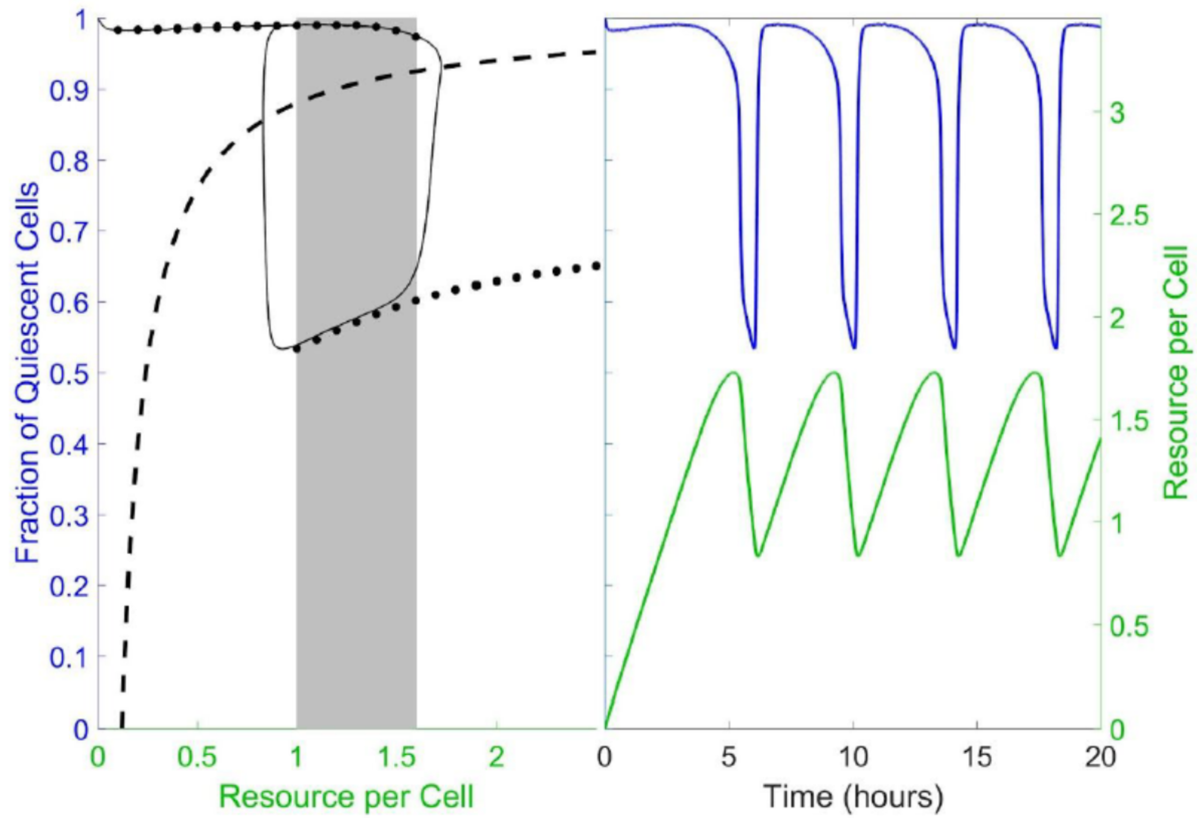
Discrepancy between model and data:

- Model exhibits fast drop and slow rise
- Data has slow drop and fast rise



Counterintuitive model, with the "resource" influencing both Q and G states





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