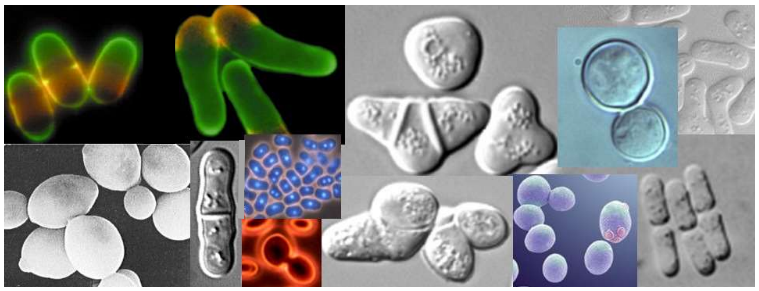
# Information Processing in Living Organisms: Network Dynamics ↔ Cell Physiology

*BIRS Workshop, September 2021*



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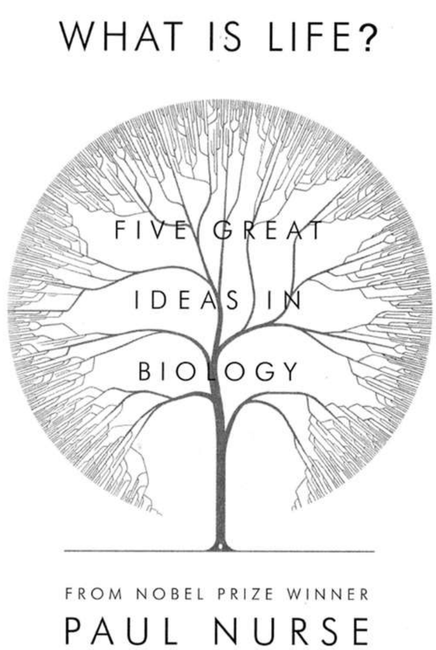
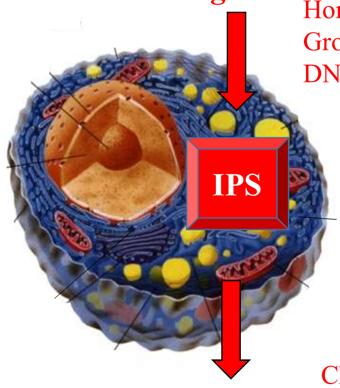



2020

1. **The Cell**: the building blocks of all living organisms.
2. **The Gene**: the purveyor of hereditary identity.
3. **Evolution by Natural Selection**: the engine driving biological diversity.
4. **Life is Chemistry**: all cellular functions are carried out by biochemical (genes, proteins, metabolites).
5. **Life is Information**: how cells make 'sense' of the world.

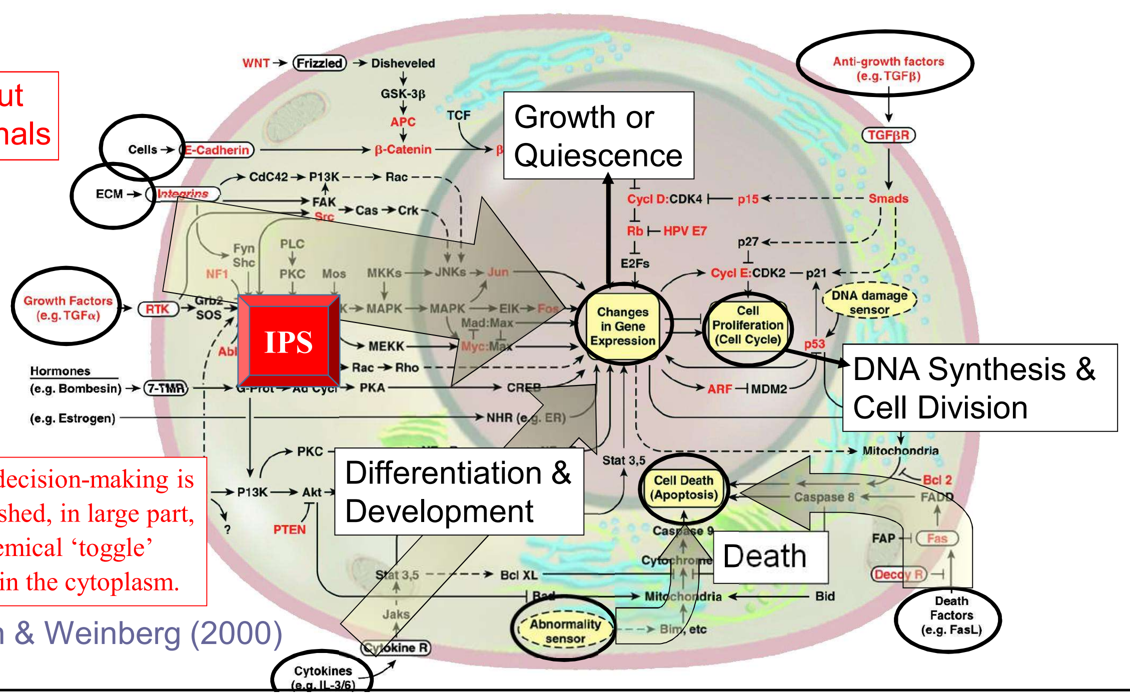
# A cell is an information processing machine!

**Signals:** Nutrients, Hormones, Growth factors, DNA damage




**Responses:** Chemotaxis, Gene expression, Cell differentiation, Cell growth & division, Programmed cell death

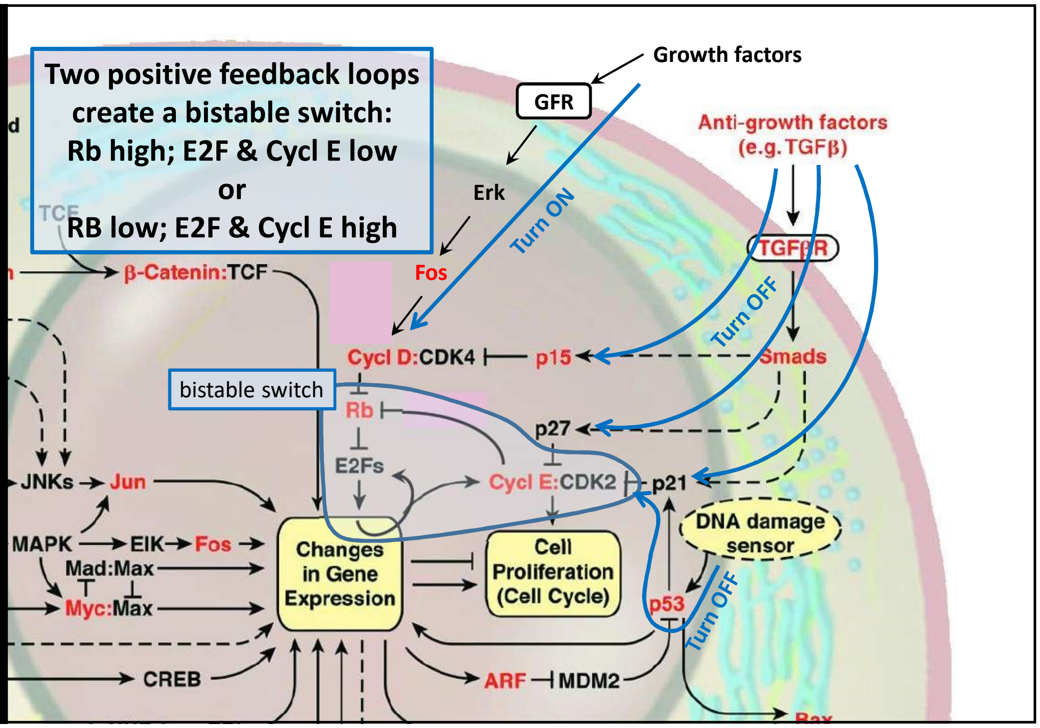
Input signals



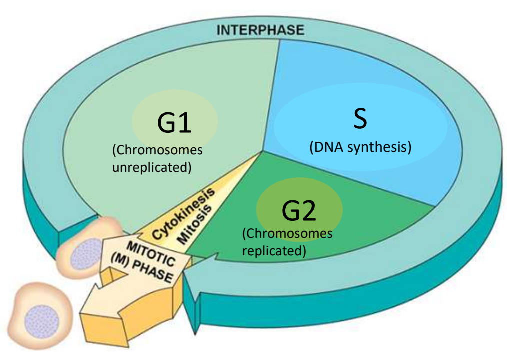

Cellular decision-making is accomplished, in large part, by biochemical 'toggle' switches in the cytoplasm.

Hanahan & Weinberg (2000)

[redacted]

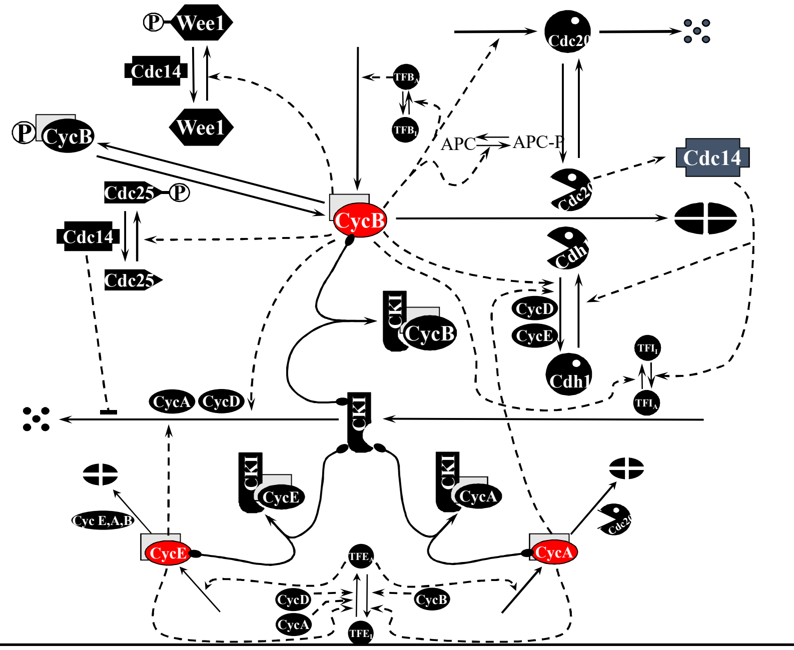



## The Cell Division Cycle




The cell division cycle is the sequence of events by which a growing cell replicates all its components and divides them, more or less evenly, between two daughter cells, so that each daughter receives all the information and machinery necessary to repeat the process.

# Universal control mechanism regulating the eukaryotic cell cycle

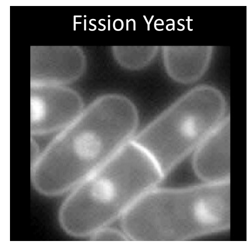



Nurse, *Nature* (1990), *Cell* (2000), *Biosci Rep* (2002)

(1971 – 2001)

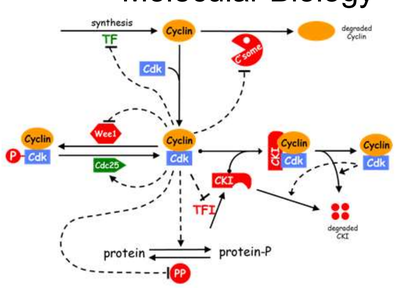
Isolation of first *cdc* genes

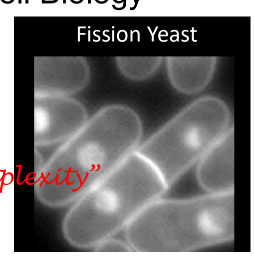
Noble prizes to Hartwell, Nurse & Hunt




# The Dynamical Paradigm for Molecular Cell Biology

Molecular Biology (1989 – 2019) Cell Biology




Molecular Mechanism

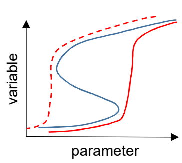
*"The Curse of Complexity"*

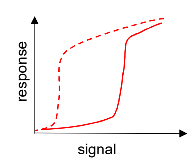
Kinetic Equations

*"The Curse of Parameter Space"*

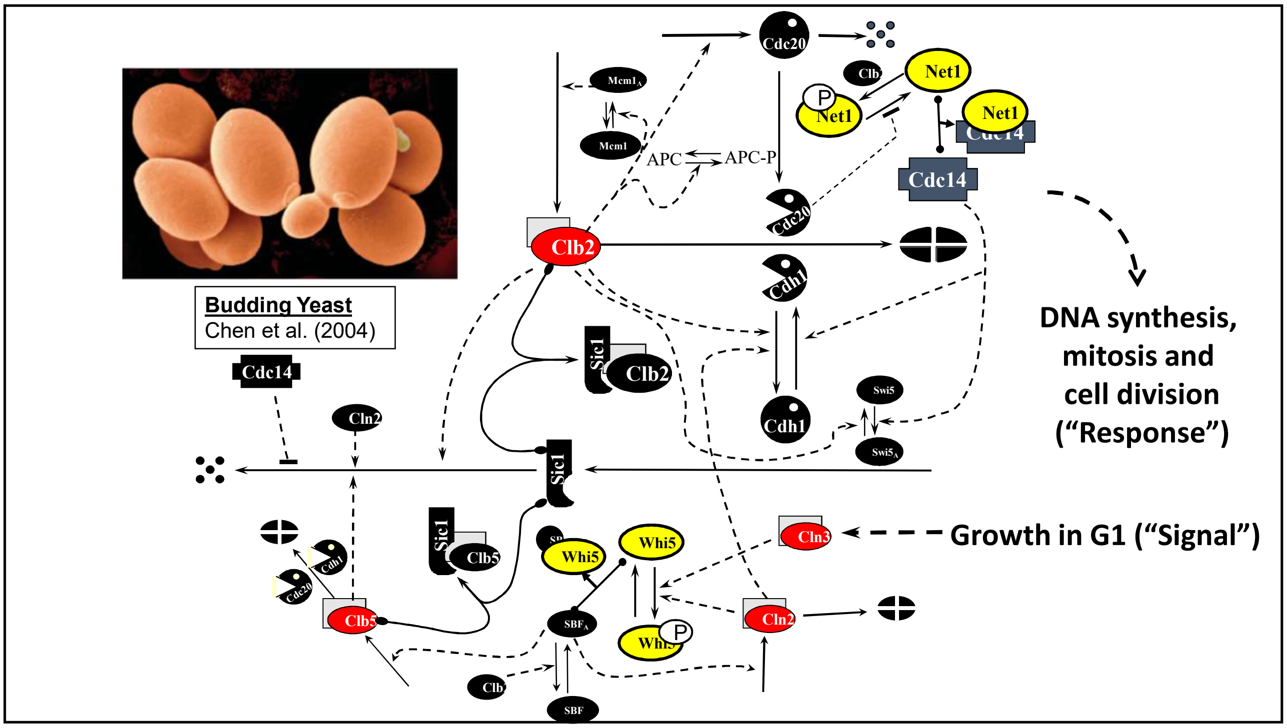
State Space, Vector Field

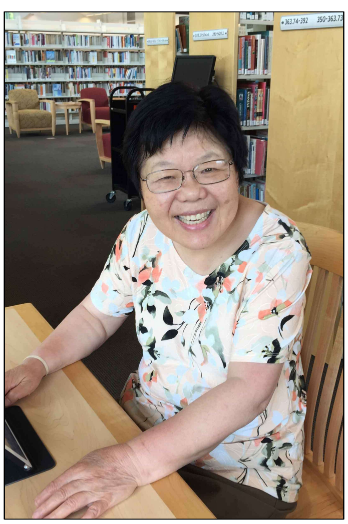
Attractors, Repellors, Transients




Bifurcation Diagrams ⟷ Signal-Response Curves





Kathy Chen


Bela Novak


Attila Csikasz-Nagy


Dorjsuren Battogtokh



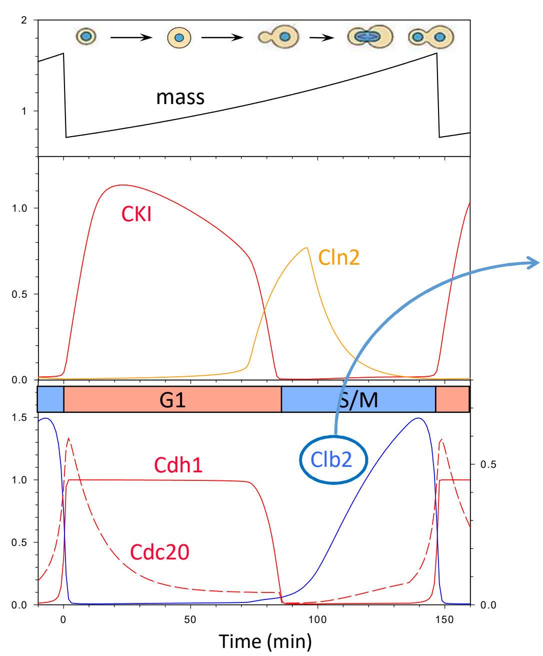
Andrea Ciliberto

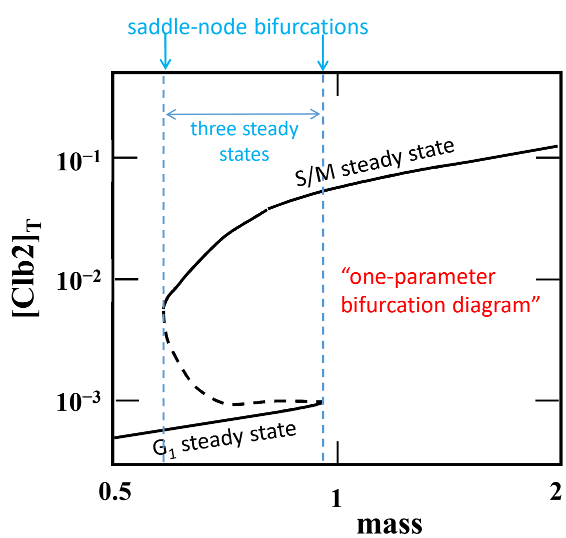
$$\underbrace{\frac{d[\mathrm{Cln2}]}{dt} = k_1 + k_1'[\mathrm{SBF}]}_{\text{synthesis}} - \underbrace{k_2[\mathrm{Cln2}]}_{\text{degradation}}$$

$$\frac{d[\mathrm{Clb2}]}{dt} = \underbrace{k_3 + k_3'[\mathrm{Mcm1}]}_{\text{synthesis}} - \underbrace{\left(k_4 + k_4'[\mathrm{Cdh1}]\right)[\mathrm{Clb2}]}_{\text{degradation}} - \underbrace{k_5[\mathrm{Sic1}][\mathrm{Clb2}]}_{\text{binding}}$$

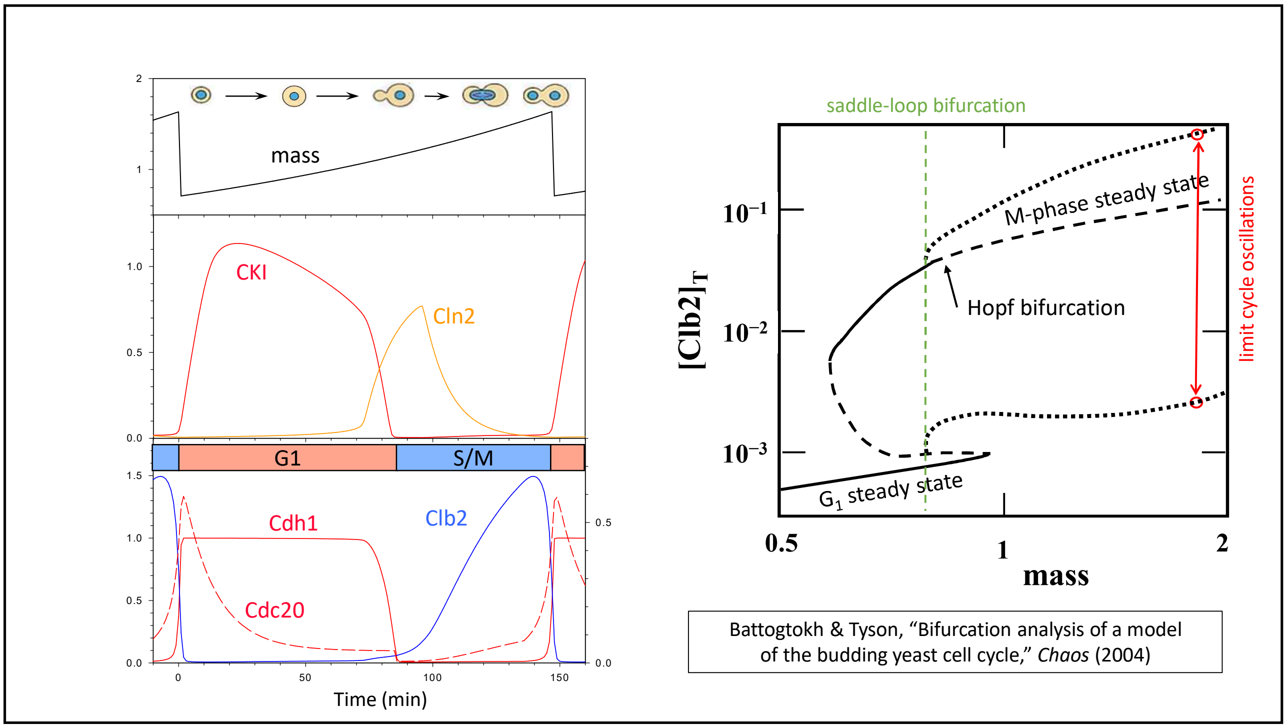
$$\frac{d[\mathrm{Cdh1}]}{dt} = \underbrace{\frac{\left(k_6 + k_6'[\mathrm{Cdc20}]\right)\left([\mathrm{Cdh1}]_T - [\mathrm{Cdh1}]\right)}{J_6 + [\mathrm{Cdh1}]_T - [\mathrm{Cdh1}]}}_{\text{activation}} - \underbrace{\frac{\left(k_7 + k_7'[\mathrm{Clb5}]\right)[\mathrm{Cdh1}]}{J_7 + [\mathrm{Cdh1}]}}_{\text{inactivation}}$$

et cetera…

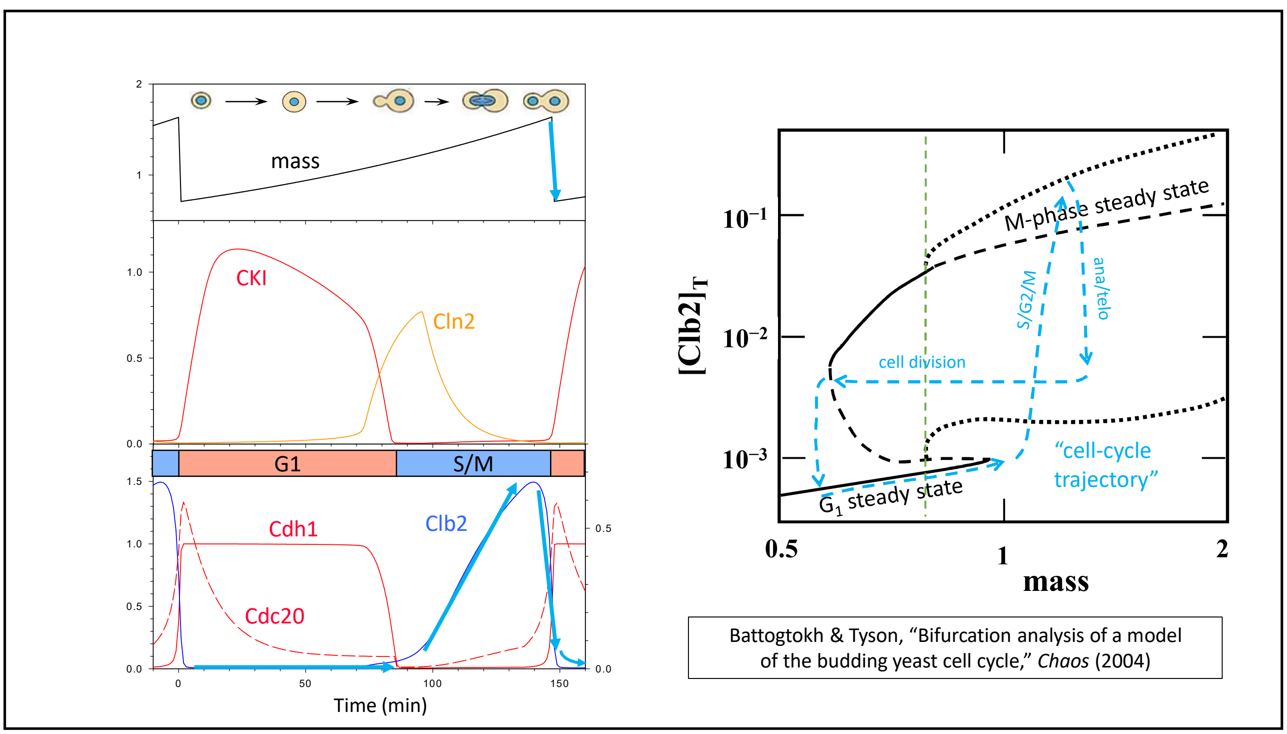


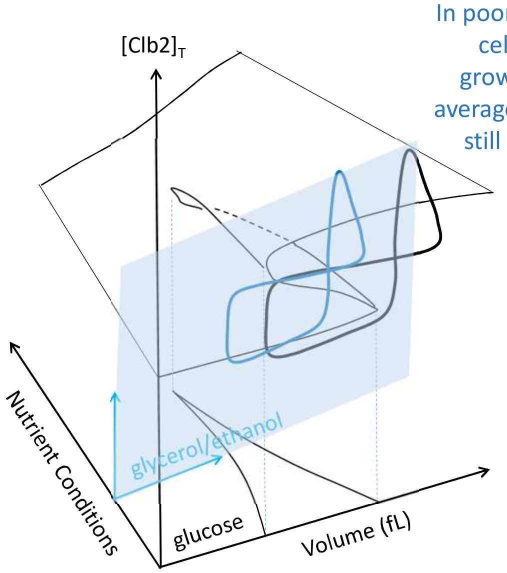

Battogtokh & Tyson, "Bifurcation analysis of a model of the budding yeast cell cycle," *Chaos* (2004)



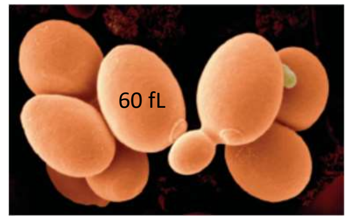
mass
CKI
Cln2
G1
S/M
Cdh1
Clb2
Cdc20
Time (min)
saddle-loop bifurcation
M-phase steady state
Hopf bifurcation
limit cycle oscillations
$G_1$ steady state
$[Clb2]_T$
mass
Battogtokh & Tyson, "Bifurcation analysis of a model of the budding yeast cell cycle," *Chaos* (2004)

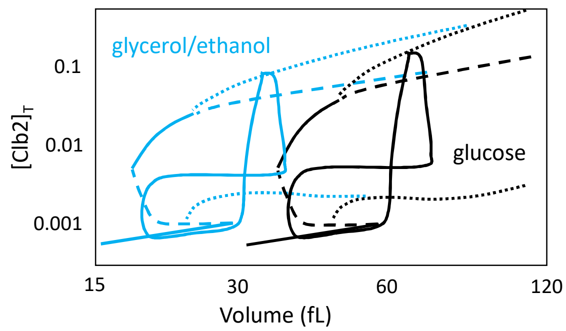
mass
CKI
Cln2
G1
S/M
Cdh1
Clb2
Cdc20
Time (min)
M-phase steady state
S/G2/M
ana/telo
cell division
"cell-cycle trajectory"
$G_1$ steady state
$[Clb2]_T$
mass
Battogtokh & Tyson, "Bifurcation analysis of a model of the budding yeast cell cycle," *Chaos* (2004)

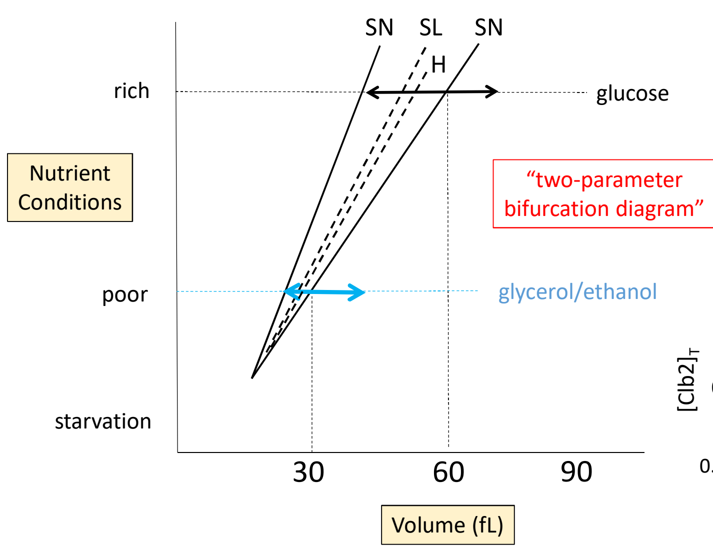


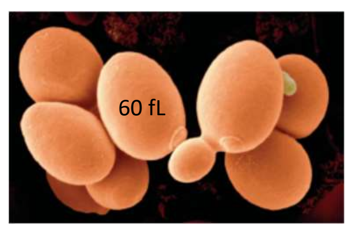

In poor growth medium, cells are smaller and grow more slowly, but average cell cycle time is still equal to the mass doubling time!



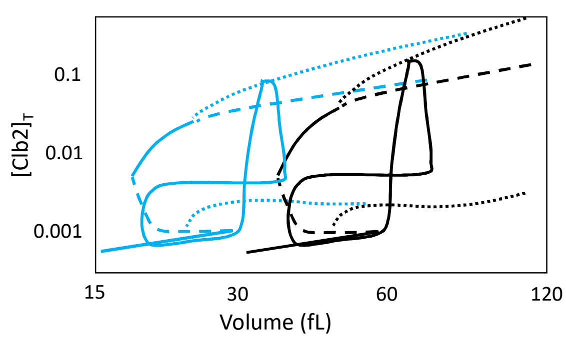

Saccharomyces cerevisiae



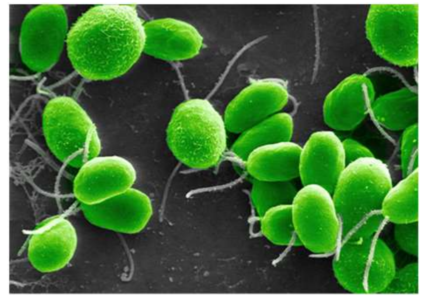




Saccharomyces cerevisiae



## Cell growth and division of the algal cell, *Chlamydomonas reinhardtii*

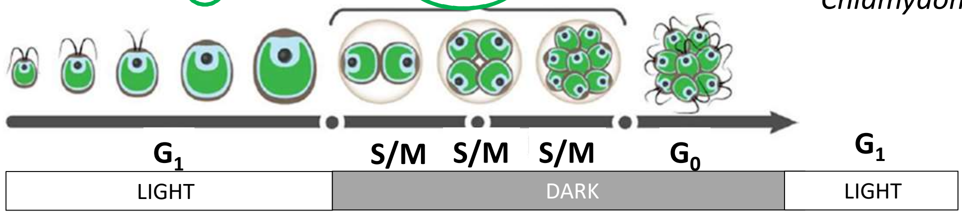
Grow in the light (without dividing)
Synthesize DNA and divide in dark (without growing)
Rapid S-M cycles in the dark (very short G1 and G2 phases)
Balanced growth and division over the course of 24 h

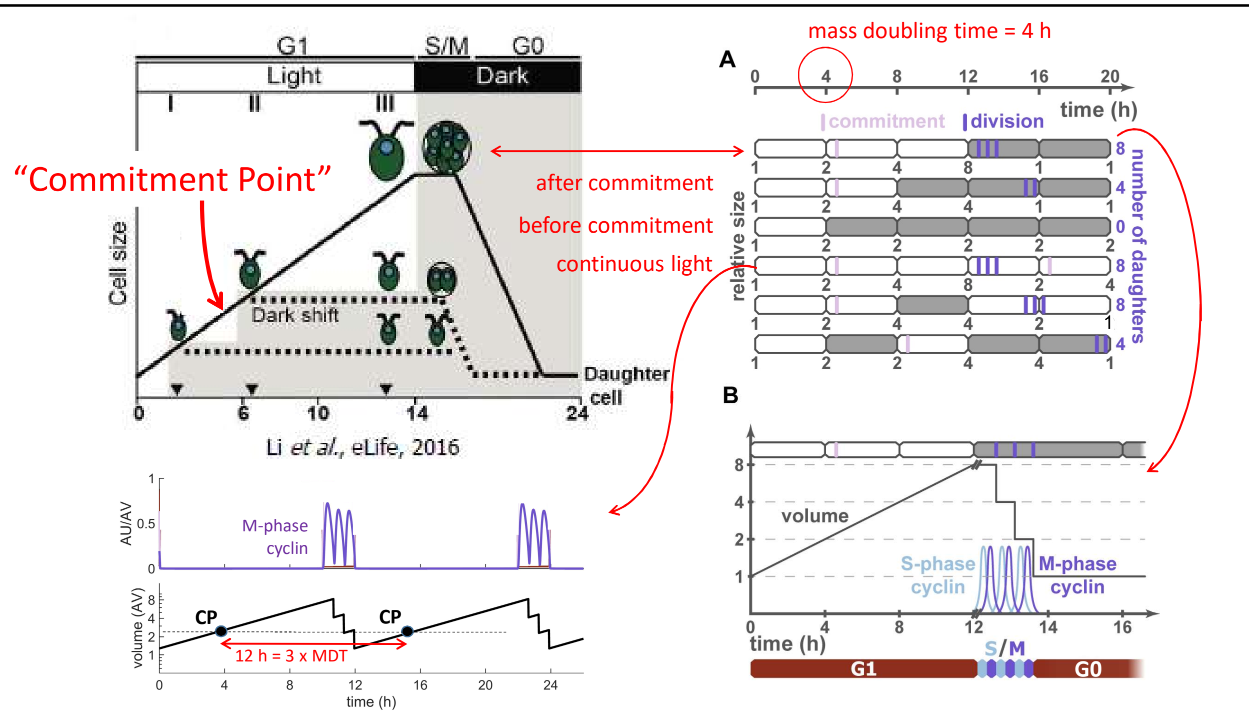


Chlamydomonas

### "Multiple Fission Cycles"

grow by factor $2^n$ in light, divide $n$ times in dark



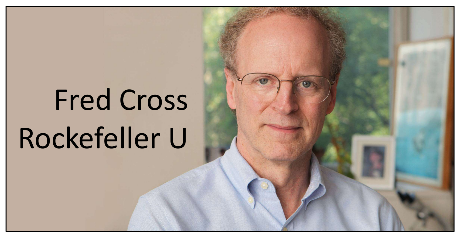



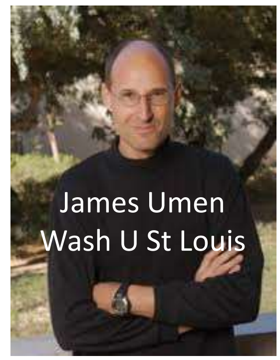
**Bela Novak**

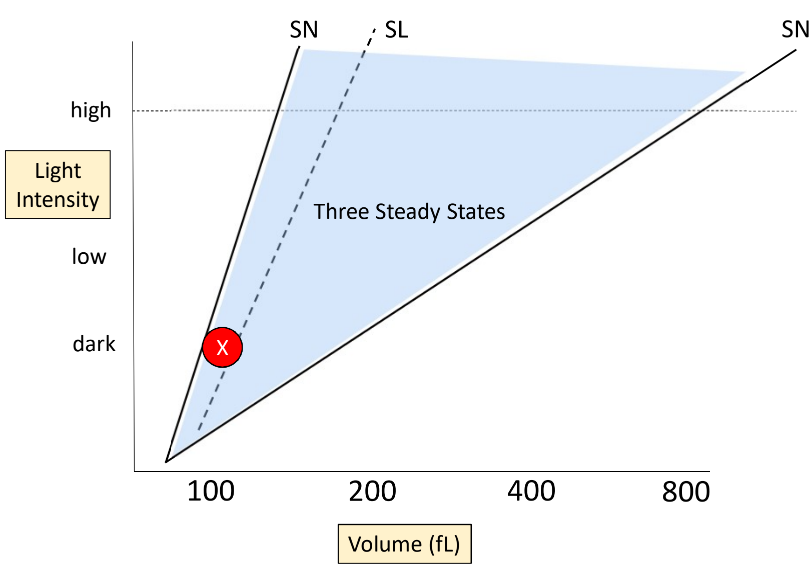
**Stefan Heldt**

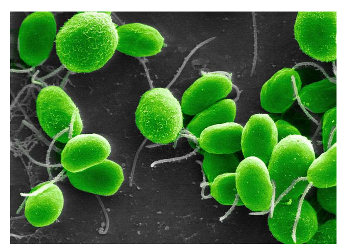
Heldt, Tyson, Cross & Novak
"A single light-responsive sizer can control multiple-fission cycles in *Chlamydomonas*"
*Current Biology* (2020)

Cross & Umen
"The *Chlamydomonas* cell cycle"
*The Plant Journal* (2015)

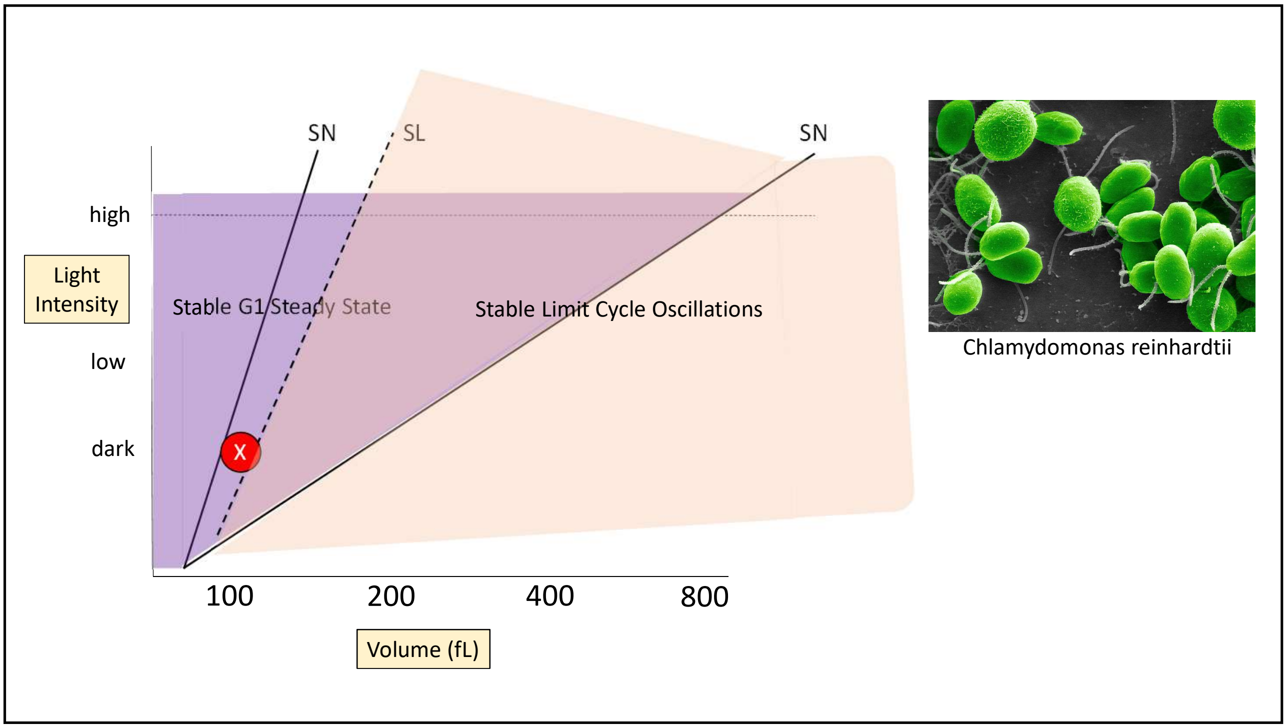


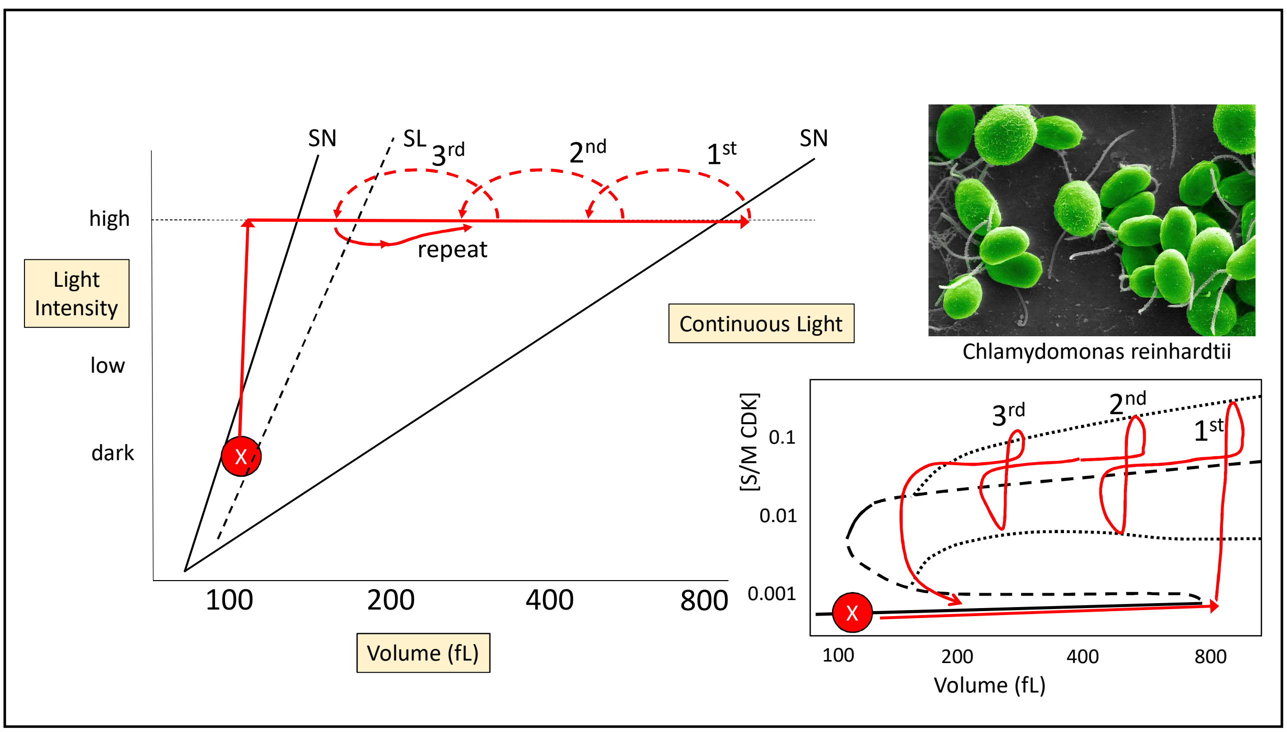



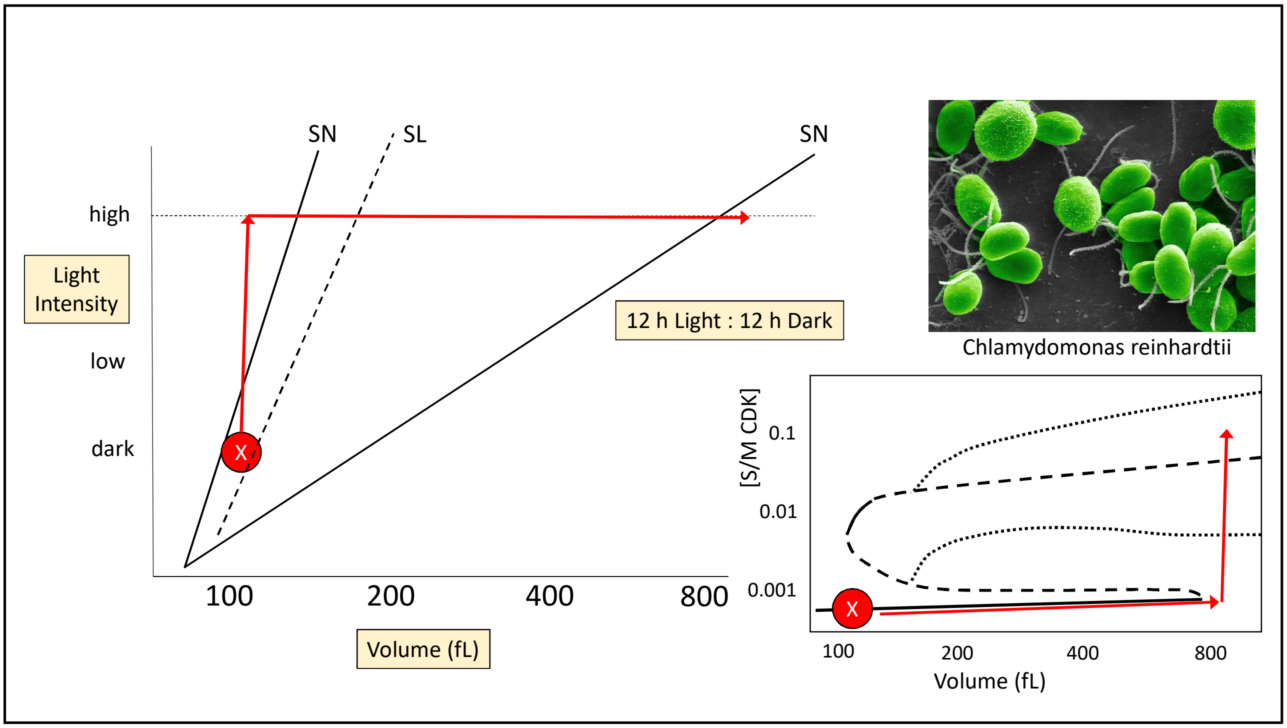



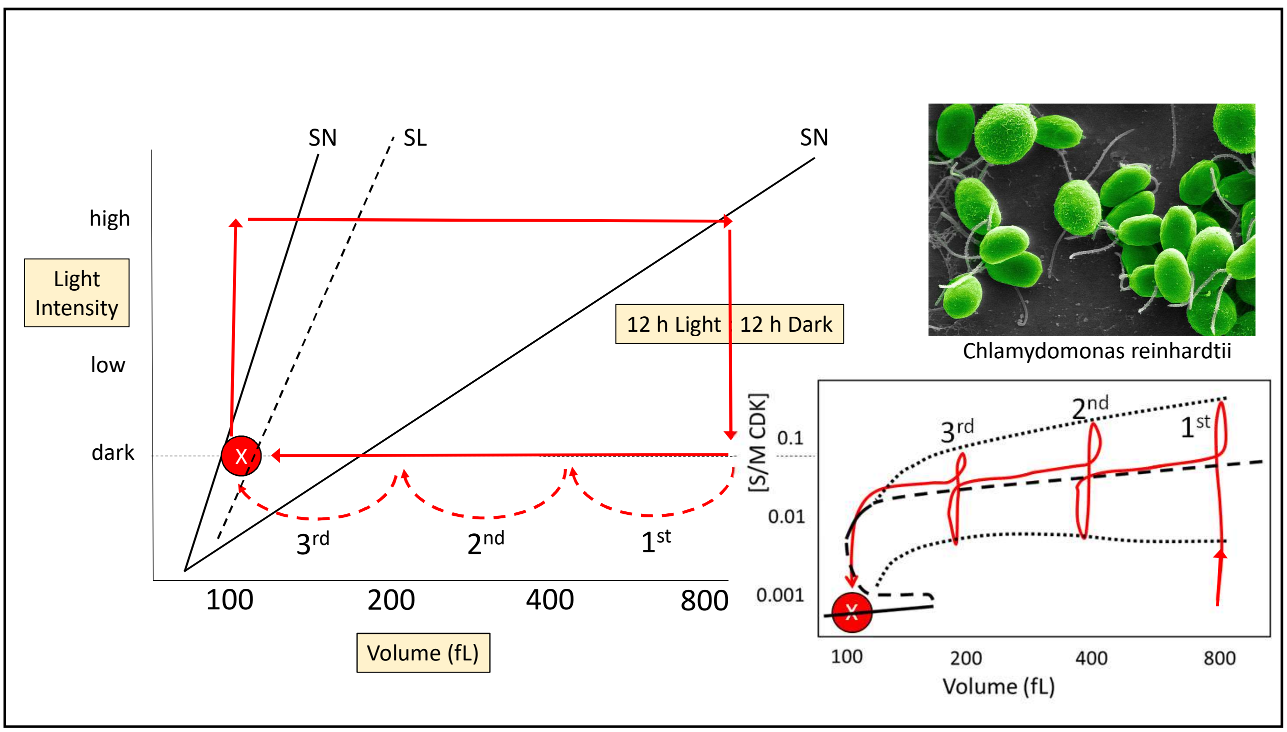



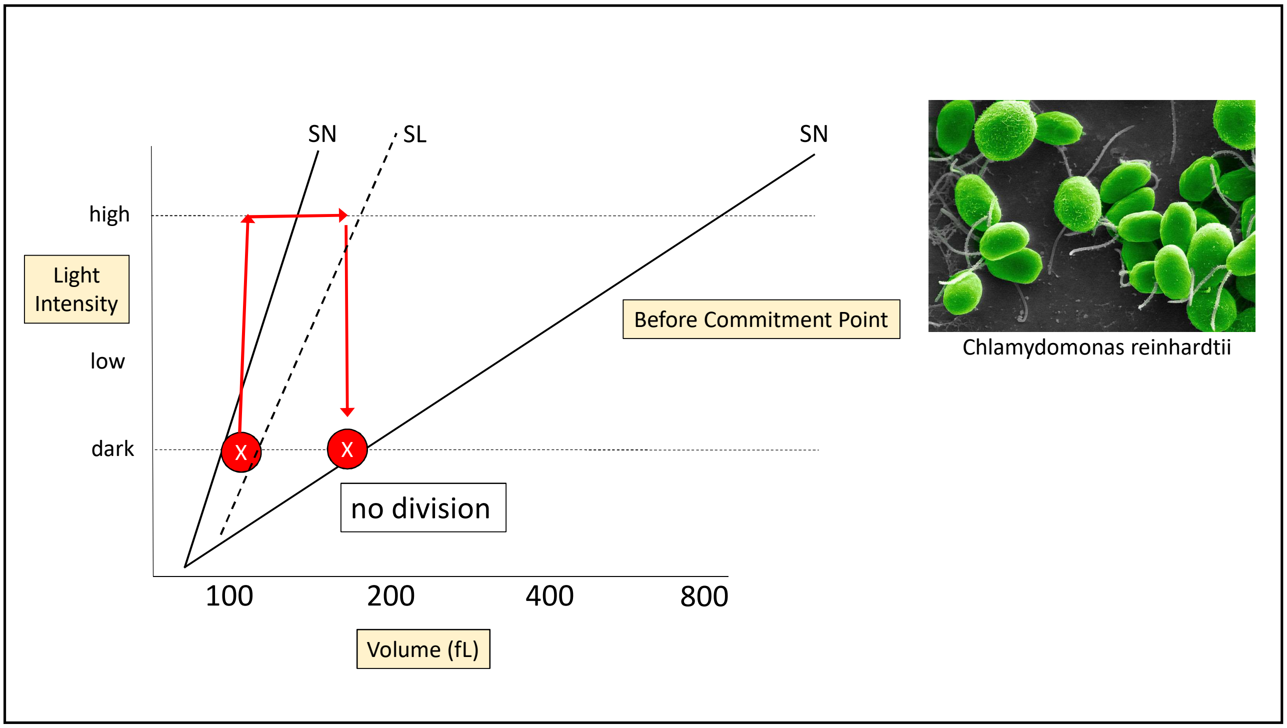
Chlamydomonas reinhardtii

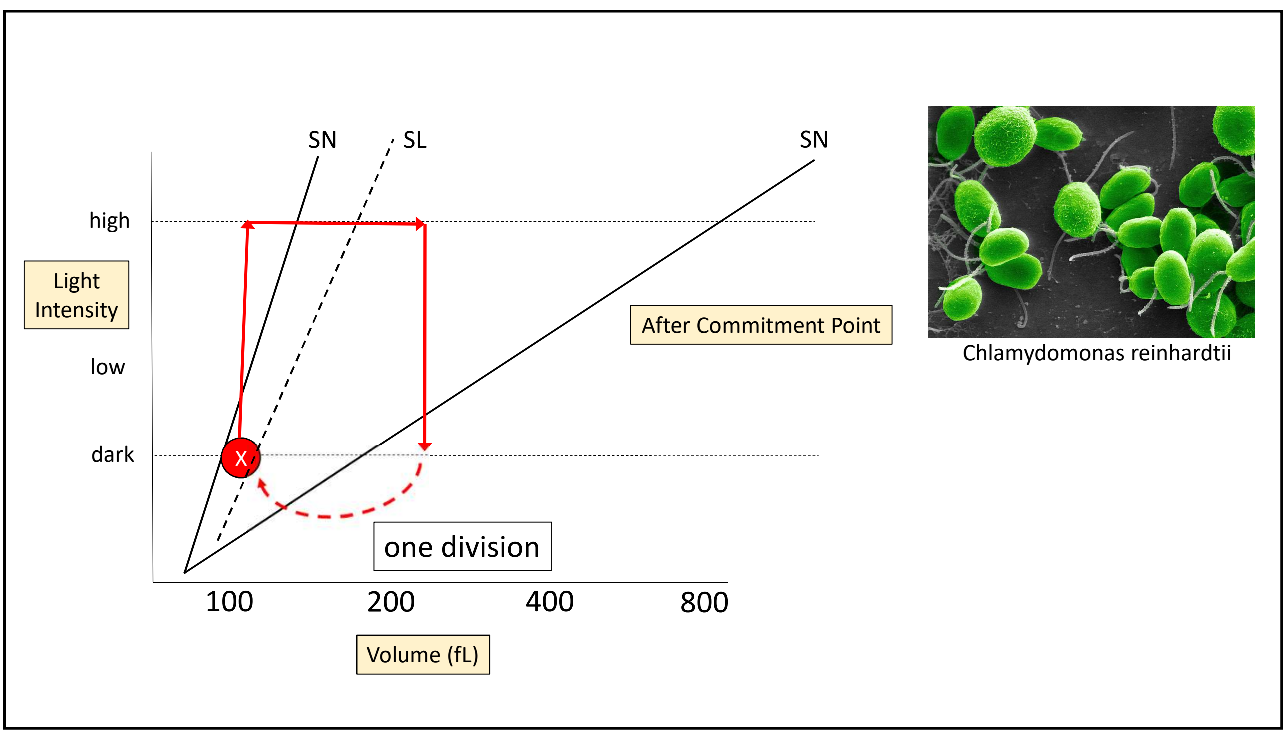

SN
SL
SN
high
Light Intensity
low
dark
Stable G1 Steady State
Stable Limit Cycle Oscillations
X
100
200
400
800
Volume (fL)
Chlamydomonas reinhardtii

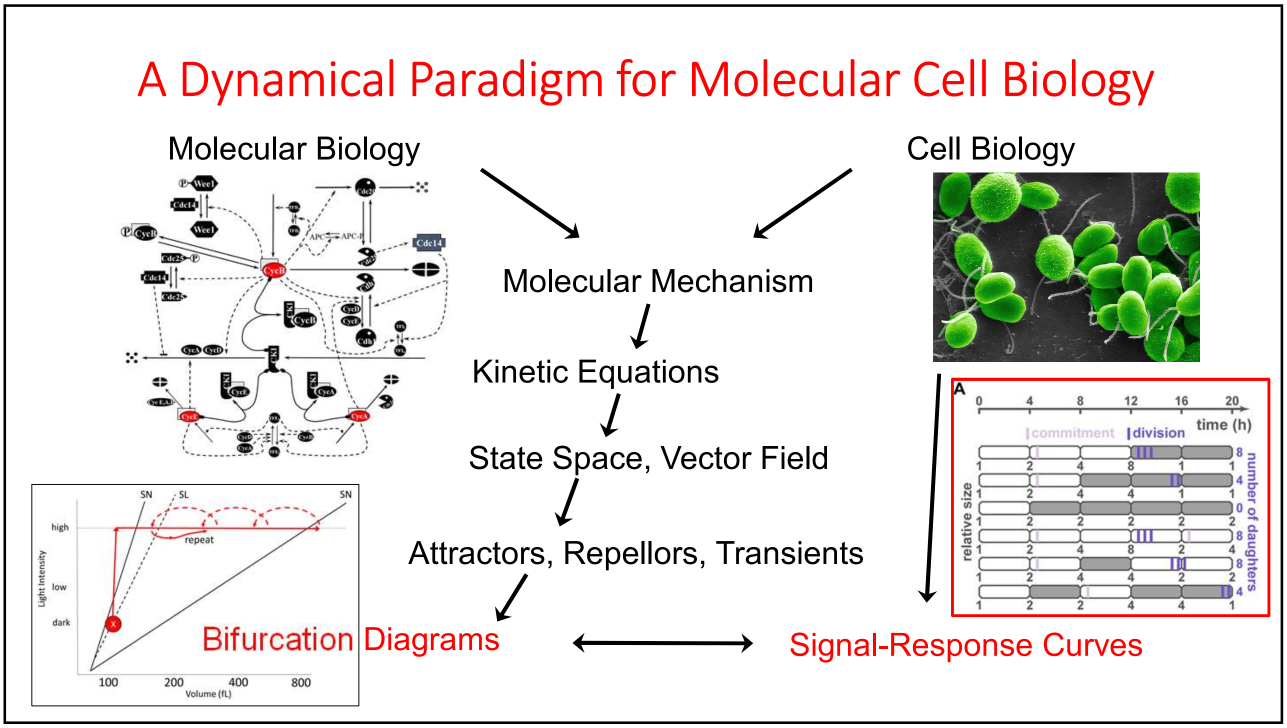

SN
SL
3rd
2nd
1st
SN
high
repeat
Light Intensity
low
dark
X
Continuous Light
100
200
400
800
Volume (fL)
Chlamydomonas reinhardtii
[S/M CDK]
0.1
0.01
0.001
3rd
2nd
1st
X
100
200
400
800
Volume (fL)

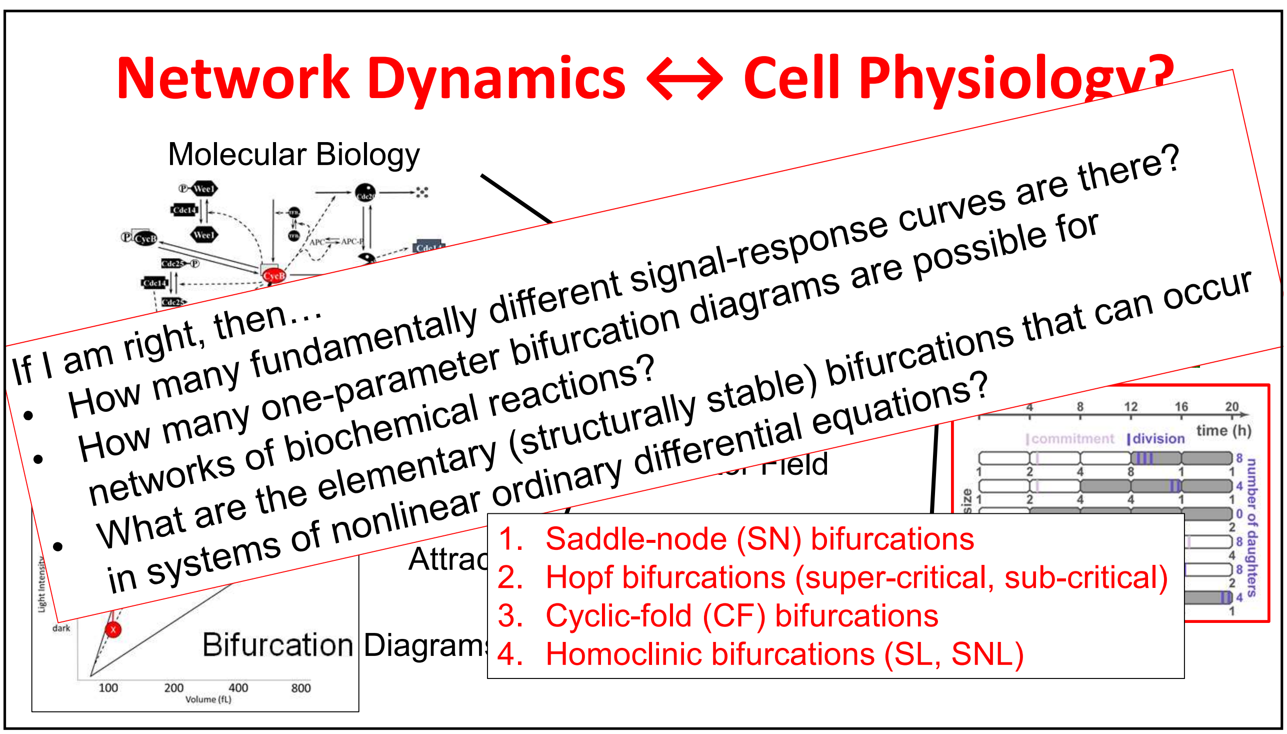

SN
SL
SN
high
Light Intensity
low
dark
X
100
200
400
800
Volume (fL)
12 h Light : 12 h Dark
Chlamydomonas reinhardtii
[S/M CDK]
0.1
0.01
0.001
X
100
200
400
800
Volume (fL)


SN
SL
SN
high
Light Intensity
low
dark
X
3rd
2nd
1st
100
200
400
800
Volume (fL)
12 h Light 12 h Dark
Chlamydomonas reinhardtii
[S/M CDK]
3rd
2nd
1st
0.1
0.01
0.001
X
100
200
400
800
Volume (fL)

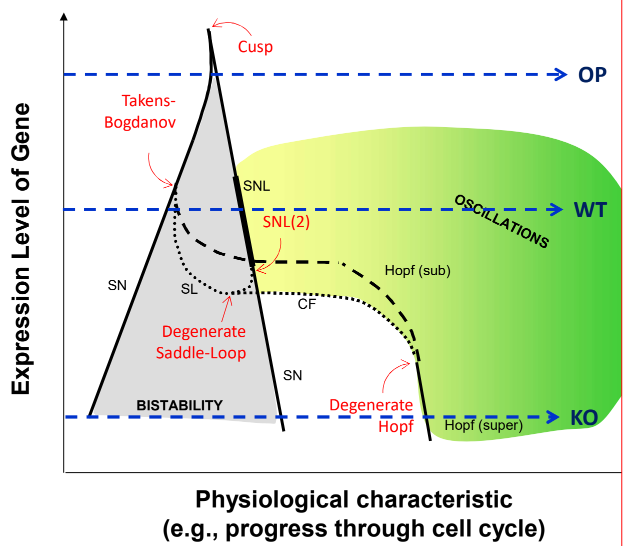

SN
SL
SN
high
Light Intensity
low
dark
X
X
no division
Before Commitment Point
100
200
400
800
Volume (fL)
Chlamydomonas reinhardtii


SN
SL
SN
high
Light Intensity
low
dark
X
one division
After Commitment Point
100
200
400
800
Volume (fL)
Chlamydomonas reinhardtii


A Dynamical Paradigm for Molecular Cell Biology
Molecular Biology
Cell Biology
Molecular Mechanism
Kinetic Equations
State Space, Vector Field
Attractors, Repellors, Transients
Bifurcation Diagrams
Signal-Response Curves
high
low
dark
repeat
SN
SL
Light Intensity
100
200
400
800
Volume (fL)
commitment
division
time (h)
relative size
number of daughters


Network Dynamics ↔ Cell Physiology?
Molecular Biology
If I am right, then…
How many fundamentally different signal-response curves are there?
How many one-parameter bifurcation diagrams are possible for networks of biochemical reactions?
What are the elementary (structurally stable) bifurcations that can occur in systems of nonlinear ordinary differential equations?
1. Saddle-node (SN) bifurcations
2. Hopf bifurcations (super-critical, sub-critical)
3. Cyclic-fold (CF) bifurcations
4. Homoclinic bifurcations (SL, SNL)
Bifurcation Diagrams
100
200
400
800
Volume (fL)
commitment
division
time (h)

## Two-parameter bifurcation diagrams connect cell physiology to levels of gene expression!




If I am right, what are the rules relating cell physiology to "nature and nurture"?

- How many fundamentally different two-parameter bifurcation diagrams are possible for networks of biochemical reactions?
- What are the elementary codimension-two bifurcations that can occur in systems of nonlinear ordinary differential equations?

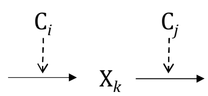
## What mathematical methodologies are needed to move the field forward?

If one- and two-parameter bifurcation diagrams are so informative, what might three-parameter bifurcation diagrams reveal?

Dynamic modeling with nonlinear ODEs is difficult.
We need flexible modeling tools.

## Standard Component Modeling

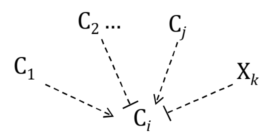
Tyson, Laomettachit & Kraikivski
"Modeling the dynamic behavior of biochemical regulatory networks"
*J Theor Biol* (2019)




$$\frac{dX_k}{dt} = k_{syn}F_k(C_i, X_l) - k_{deg}G_k(C_j, X_l)X_k$$

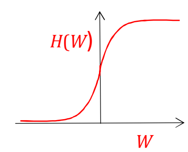
$$X_m + X_n \rightleftarrows X_{mn}$$

$$X_{mn} = \min(X_m^{tot}, X_n^{tot})$$

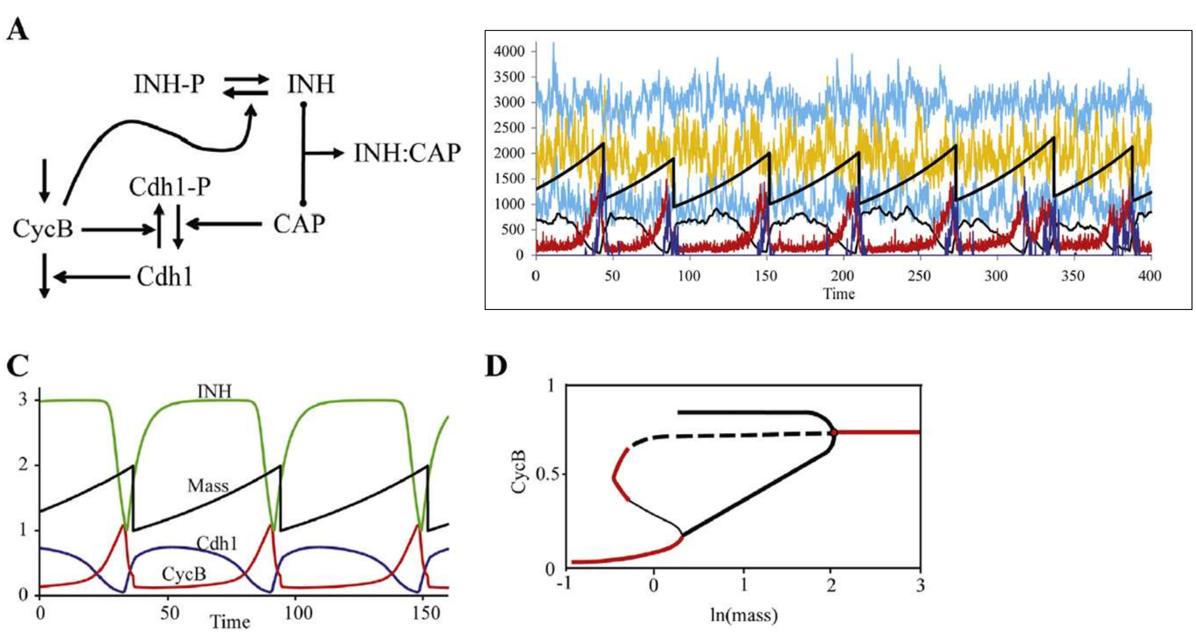



$$\frac{dC_i}{dt} = \gamma_i\left[H\left(W_i(C_j, X_l)\right) - C_i\right]$$

$$H(W) = \frac{1}{1 + e^{-\sigma W}}$$




$$W_i = \alpha_{i0} + \sum_{j=1} \alpha_{ij}C_j + \sum_{k=1} \beta_{ik}X_k$$



## What mathematical methodologies are needed to move the field forward?

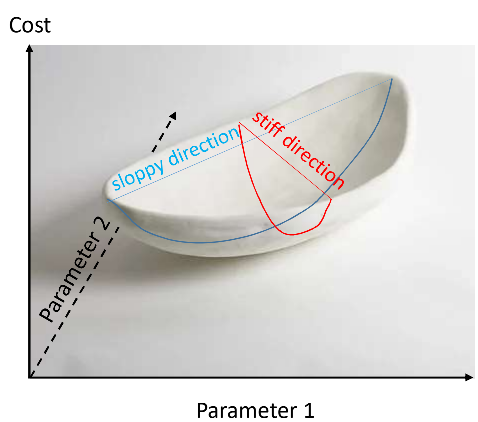
If one- and two-parameter bifurcation diagrams are so informative, what might three-parameter bifurcation diagrams reveal?

Dynamic modeling with nonlinear ODEs is difficult. We need flexible modeling tools.

Once judicious use of bifurcation theory puts us in the 'right' region of parameter space, there remains the problem of estimating dozens of kinetic parameters by fitting experimental data. We need efficient and effective ways to search parameter space.

## Stiff / Sloppy Search

Tavassoly et al. (2015) *CPT Pharmacometrics Syst Pharmacol*




$$\mathbf{p}_{i+1} = \mathbf{p}_i + \boldsymbol{\delta}_i$$

where $\boldsymbol{\delta}_i$ changes are small in stiff directions and large in sloppy directions

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