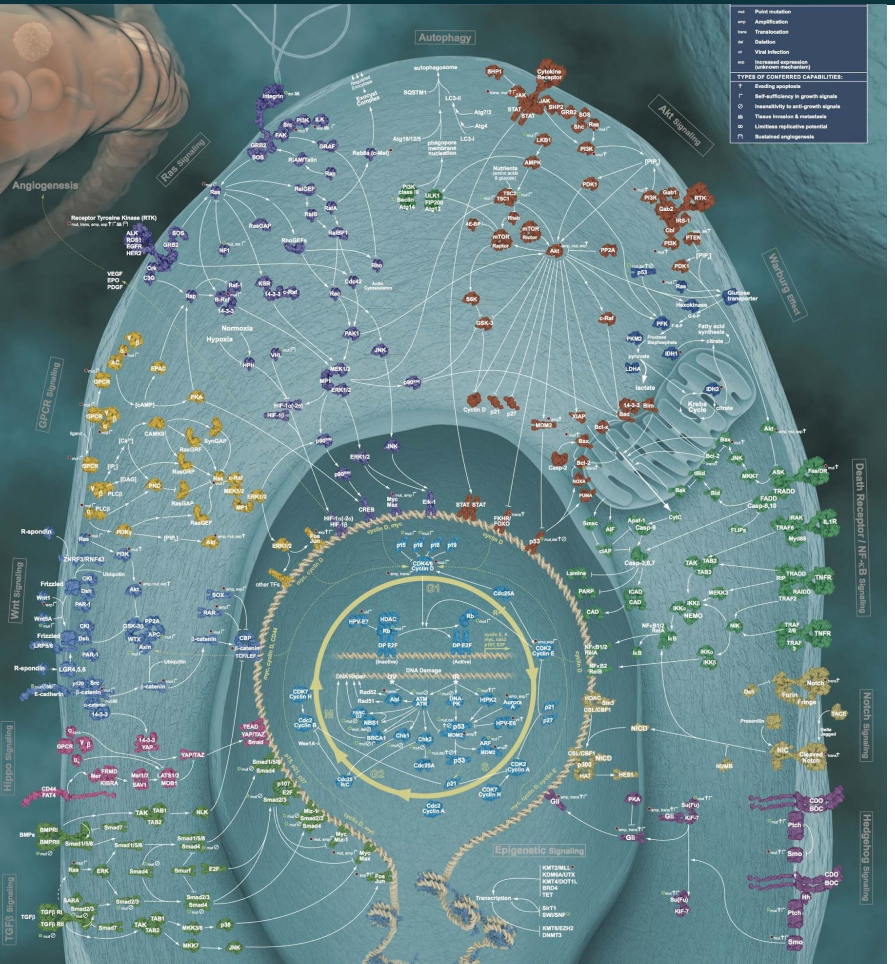
Cellular signaling and regulatory pathways

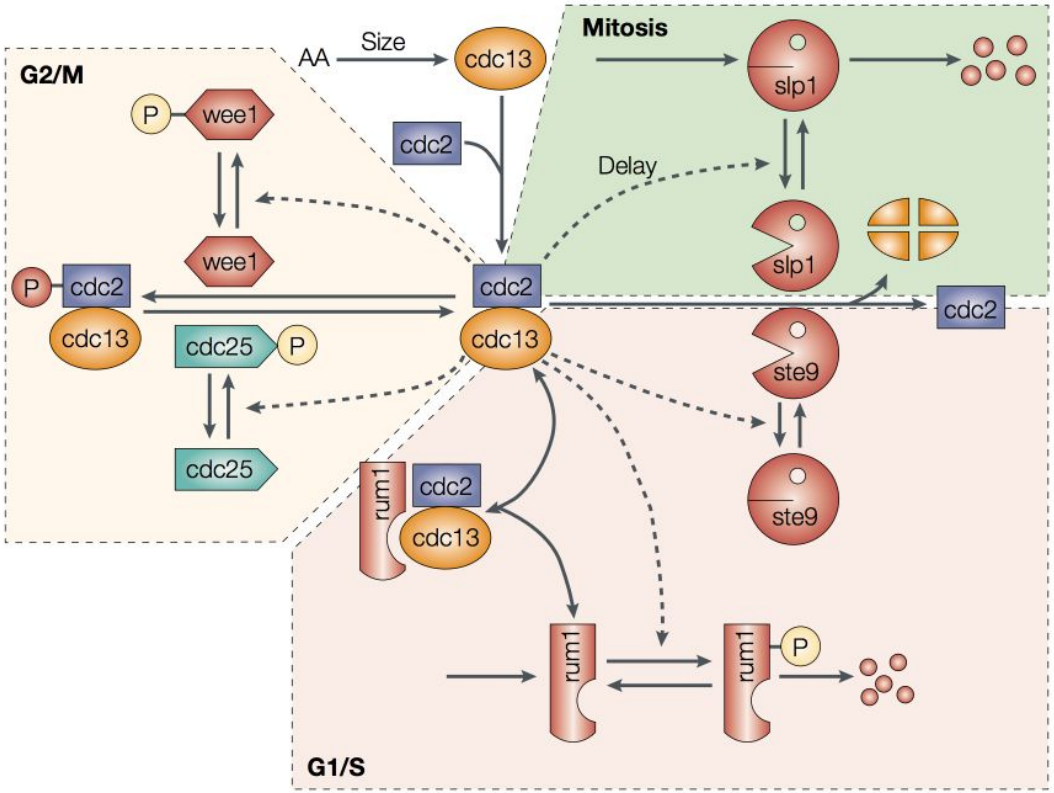


Cell physiology is governed by complex assemblies of interacting proteins carrying out most of the interesting jobs in a cell, such as metabolism, DNA synthesis, movement and information processing.

These processes are orchestrated by signaling and regulatory networks.

media.cellsignal.com

The cell-cycle control system in fission yeast

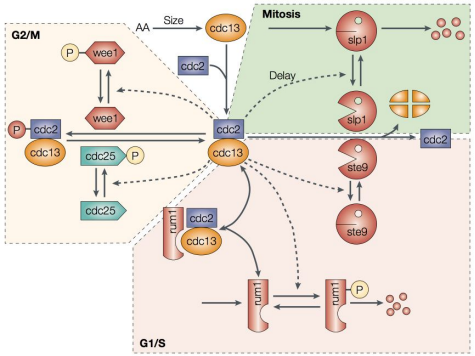


The cell cycle is divided into **phases** brought about by distinct signaling/regulatory interactions.

- **Brief G1 phase**: ste9 is active & rum1 is abundant.
- **Long S/G2 phase**: cdc2 is tyrosine phosphorylated
- Cell enters **M phase**: cdc25 removes the inhibitory phosphate group.
- After some delay, slp1 activates and degrades cdc13. As cdc2–cdc13 activity falls, the cell **exits mitosis**.
- Size decreases twofold at **nuclear division**.

Tyson (2001) Nat. Rev. Mol. Cel. Biol.

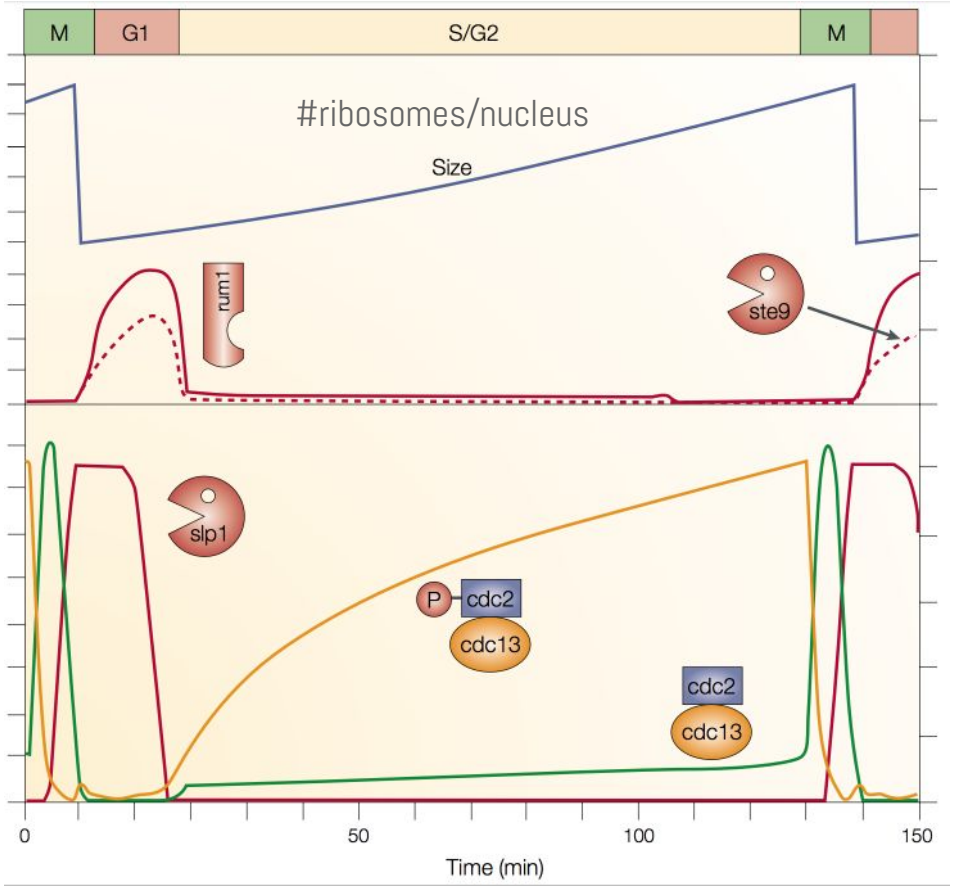
The cell-cycle control system is highly conserved



Fission yeast	Budding yeast	Frog egg	Mammal	Generic role
cdc2	Cdc28	Cdk1,2	Cdk1,2	Cyclin-dependent kinase
cdc13	Clb1–6	Cyclin A,B,E	Cyclin A,B,E	Cyclins
rum1	Sic1	Xic1	$p27^{Kip1}$	Stoichiometric inhibitor
ste9	Cdh1	Fizzy-related	Cdh1	APC auxiliary
slp1	Cdc20	Fizzy	$p55^{cdc}$	APC auxiliary
wee1	Swe1	Wee1	Wee1	Tyrosine kinase
cdc25	Mih1	Cdc25C	Cdc25C	Tyrosine phosphatase

Tyson (2001) Nat. Rev. Mol. Cel. Biol.

Modeling the cell-cycle control system in fission yeast



Write the full set of differential equations that describe the wiring diagram.

Perform numerical integration of these equations to get time courses.

- Brief G1 phase: ste9 is active & rum1 is abundant.
- Long S/G2 phase: cdc2 is tyrosine phosphorylated
- Cell enters M phase: cdc25 removes the inhibitory phosphate group.
- After some delay, slp1 activates and degrades cdc13. As cdc2–cdc13 activity falls, the cell exits mitosis.
- Size decreases twofold at nuclear division.

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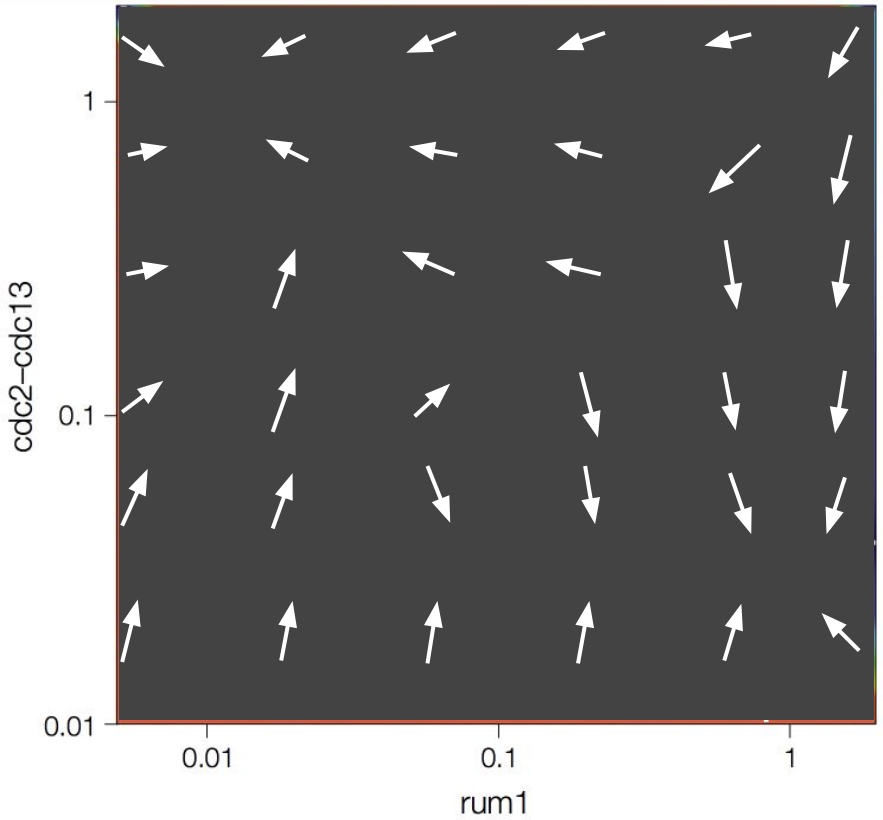
State spaces and vector fields

At any given point, the differential equations determine how fast the state of the system is changing.

Let's consider the rates of change of `[cdc2-cdc13]` and `[rum1]`.

- Plot `[rum1]` vs. `[cdc2-cdc13]`.
- We know the equations `d[rum1]/dt` and `d[cdc2-cdc13]/dt`.
- Each point in this space is associated with an arrow, which indicates the direction and magnitude of the rates of change of `[cdc2-cdc13]` and `[rum1]`.

The collection of arrows at every point in **state space** defines the **vector field** of the dynamical system.

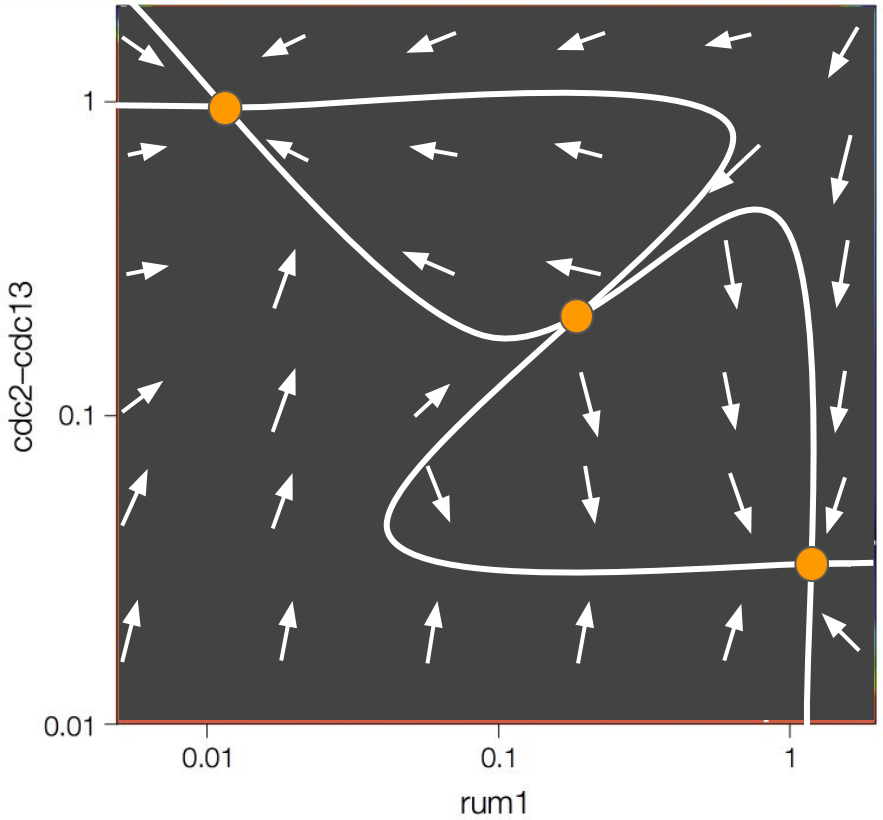


Tyson (2001) Nat. Rev. Mol. Cel. Biol.

State spaces and vector fields

We know the eqs `d[rum1]/dt` & `d[cdc2-cdc13]/dt`.

- Solve `d[rum1]/dt = 0`.
  - Returns a curve that represents all the points in the state space where `[rum1]` does not change (steady state).
  - All vectors on this curve are vertical.
- Solve `d[cdc2-cdc13]/dt = 0`.
  - Returns a curve that represents all the points in the state space where `[cdc2-cdc13]` does not change.
  - All vectors on this curve are horizontal.
- These two curves are called the **nullclines**.



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State spaces and vector fields

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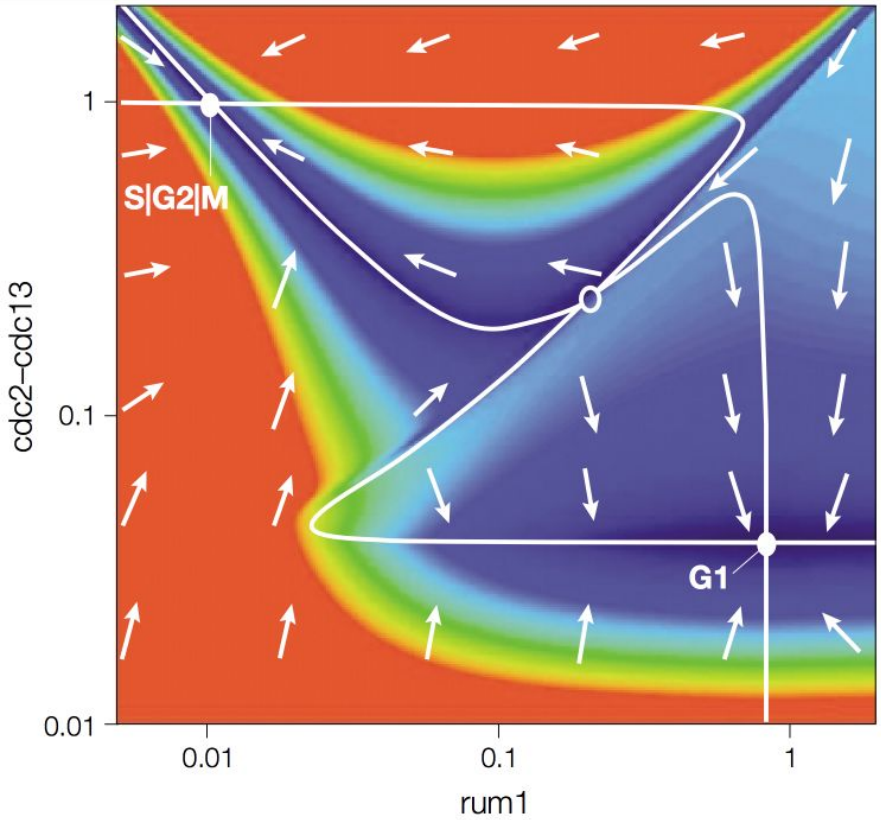
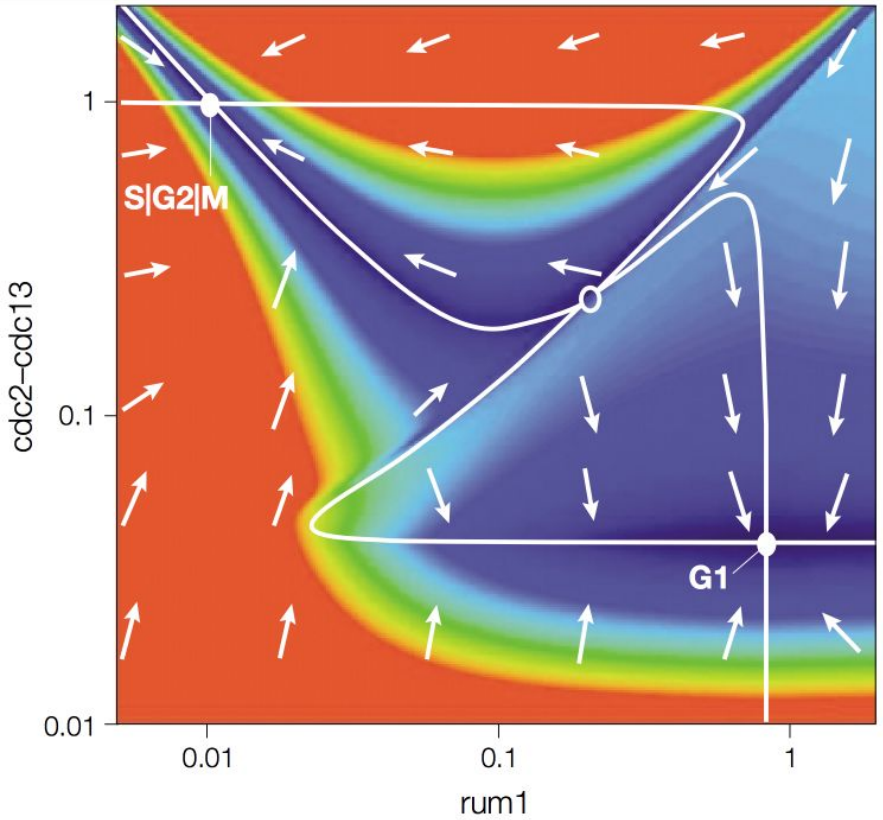


Tyson (2001) Nat. Rev. Mol. Cel. Biol.

State spaces and vector fields

- The collection of arrows at every point in **state space** defines the **vector field** of the dynamical system.
- A plot of two variables displaying the vector field and the nullclines is called the **phase plane**.
  - **Direction** of the vectors: arrow
  - **Magnitude** of the vectors: color (red, fast; blue, slow).
  - **Curves**: nullclines with horizontal/vertical vectors.
  - Within the regions bounded by these curves, all arrows lie in the same quadrant of compass directions.



Tyson (2001) Nat. Rev. Mol. Cel. Biol.

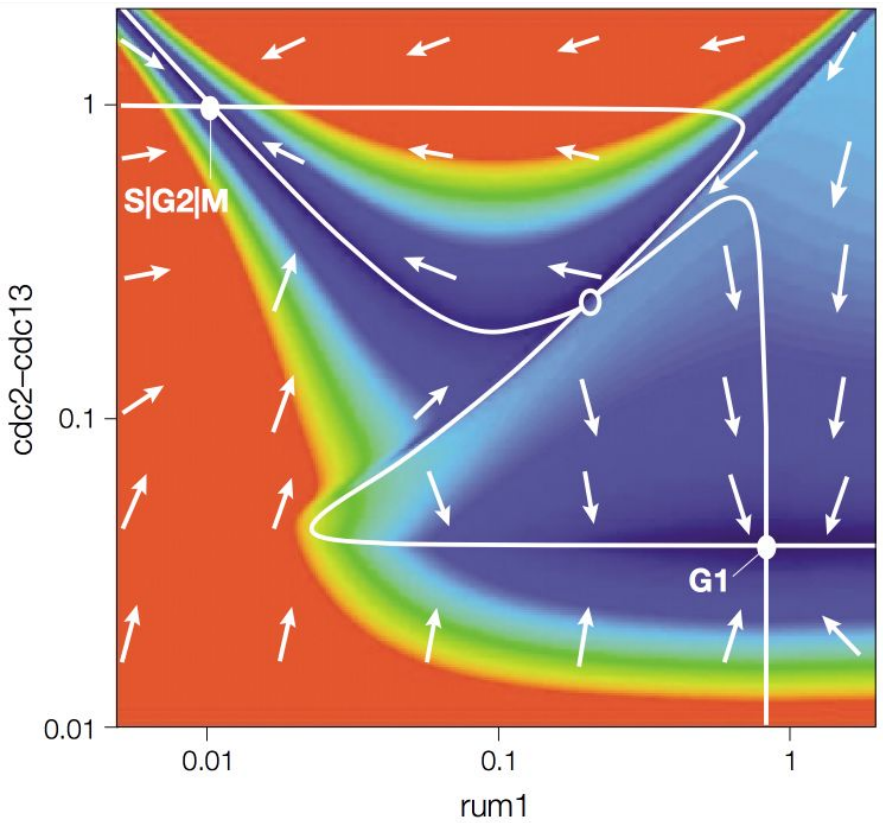
State spaces and vector fields

Knowing the vector field, one can predict the response of the control system to any initial condition - simply pick a starting point and follow the arrows.

In this case, the dynamical system has two attractors (●); in the vicinity of a stable steady state, all arrows point towards the steady state.

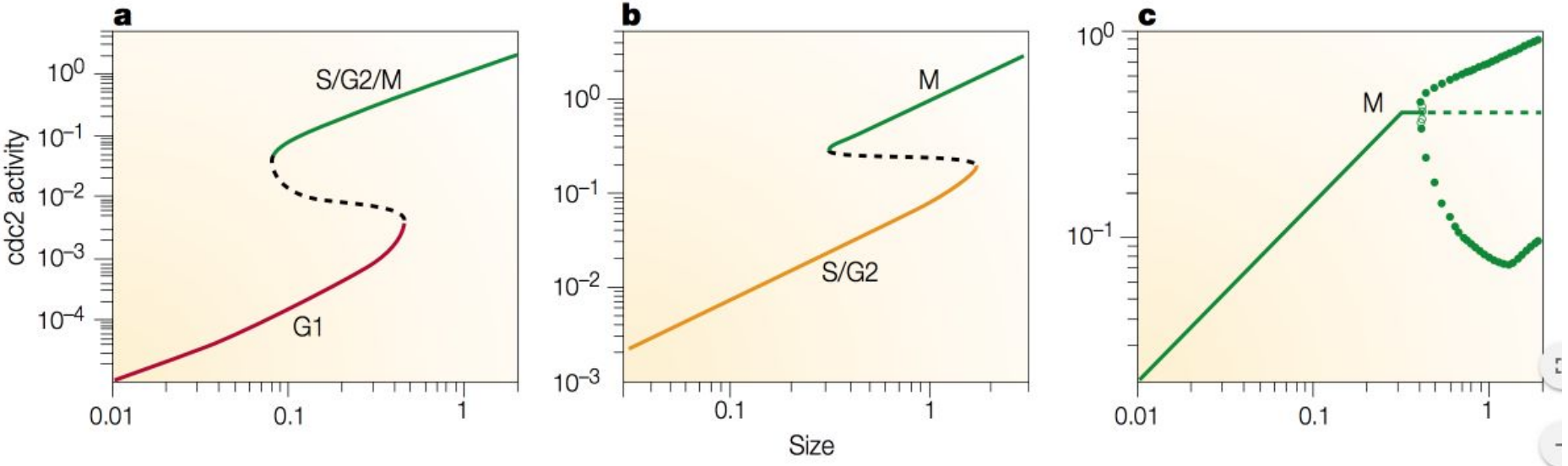
The intermediate steady state (o) is an unstable saddle point (attractive in two directions and repelling in all others).

The 'state-space' idea is readily generalized to any number of dynamical variables, but the vector field is hard to visualize in 3 or more dimensional state space.



Tyson (2001) Nat. Rev. Mol. Cel. Biol.

Bifurcation diagrams for the three control modules of the cell cycle



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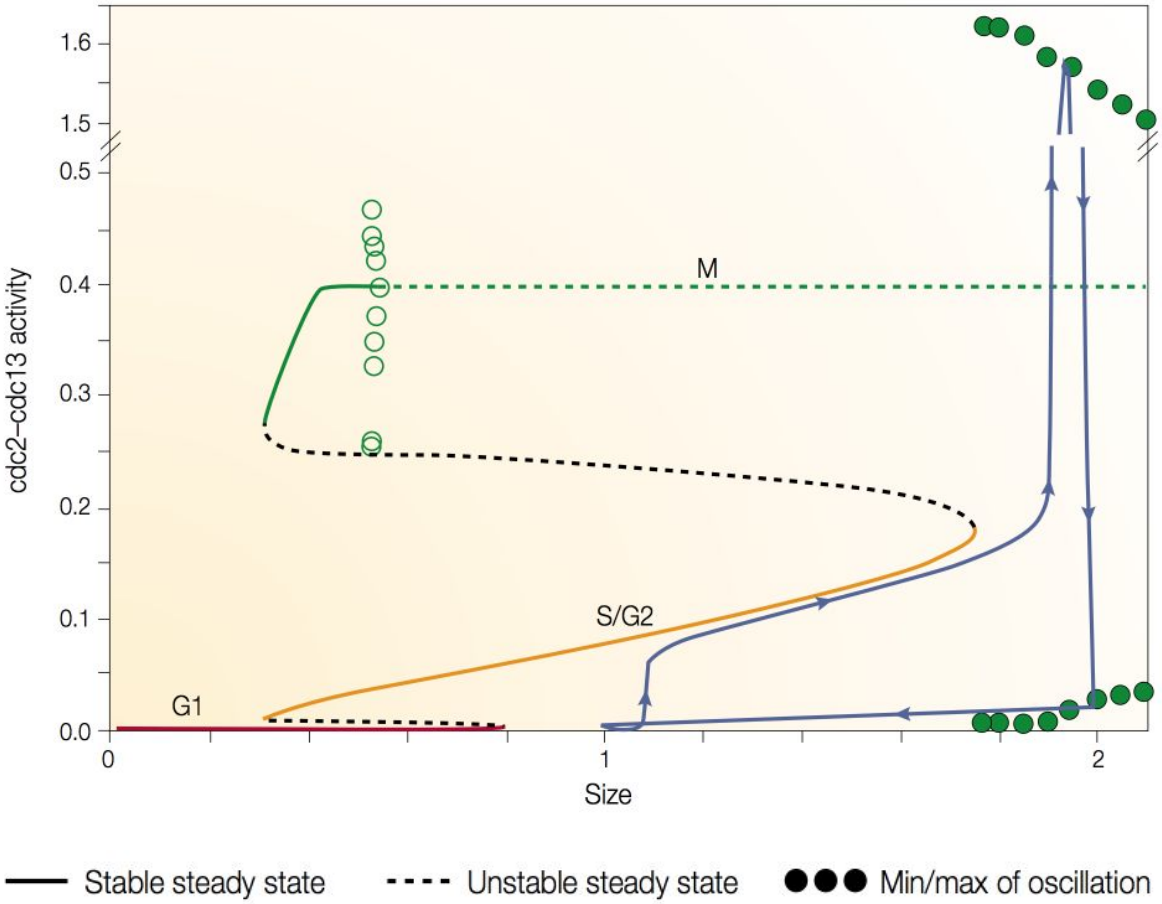
Bifurcation diagram for the full cell-cycle control network



Composite of the 3 diagrams: not a simple sum of the bifurcation diagrams of modules. (e.g. oscillations around the M state)

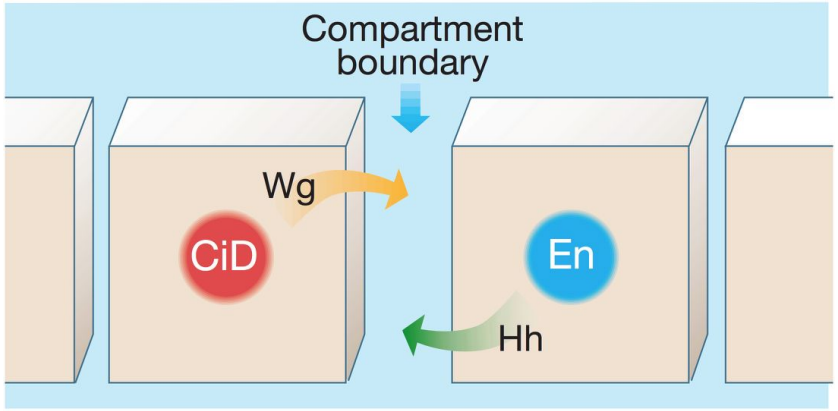
Blue line: Cell-cycle orbit from time course data.

At small cell size, all three modules support stable steady states.

The cell-cycle orbit follows the attractors of the control system.

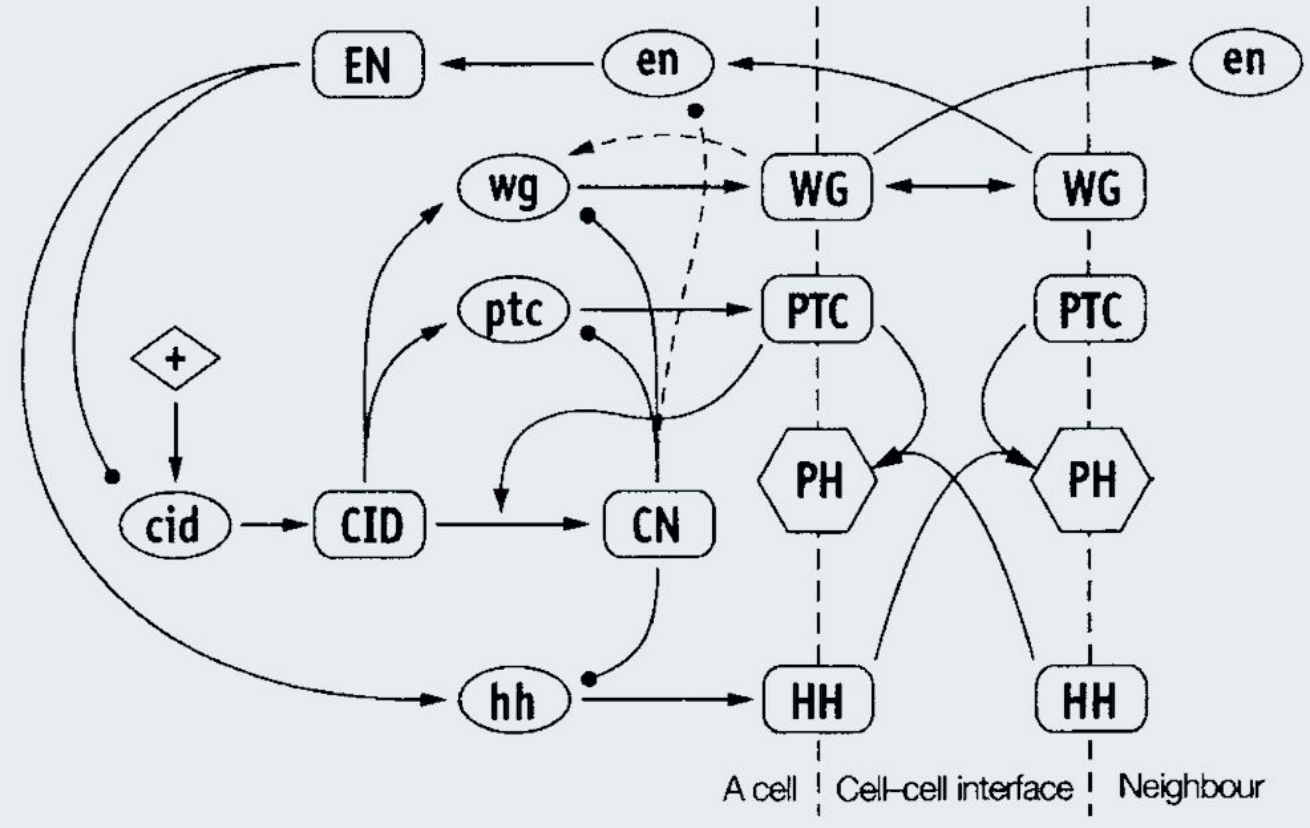
Tyson (2001) Nat. Rev. Mol. Cel. Biol.

Modeling segment polarity



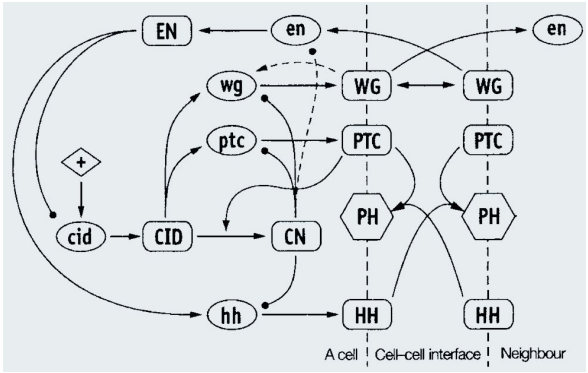
Dearden, Akam (2000) Nat.

Modeling segment polarity



Von Dassow (2000) Nat.

Modeling segment polarity



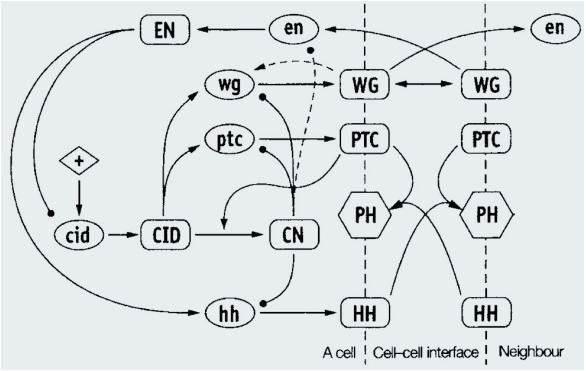
$$\frac{d[hh]_i}{dt} = T_{\max}\rho_{hh}\left[\frac{[EN]_i^{\nu_{ENhh}}}{K_{ENhh}^{\nu_{ENhh}} + [EN]_i^{\nu_{ENhh}}}\right] - \frac{[hh]_i}{H_{hh}}$$

$$\frac{d[HH]_{i,j}}{dt} = \frac{P_{\max}\sigma_{HH}[hh]_i}{6} - \frac{[HH]_{i,j}}{H_{HH}} - k_{PTCHH}[HH]_{i,j}[PTC]_{n,j+3}$$

$$\frac{d[PH]_{i,j}}{dt} = k_{PTCHH}[HH]_{n,j+3}[PTC]_{i,j} - \frac{[PH]_{i,j}}{H_{PH}}$$

Von Dassow (2000) Nat.

Modeling segment polarity



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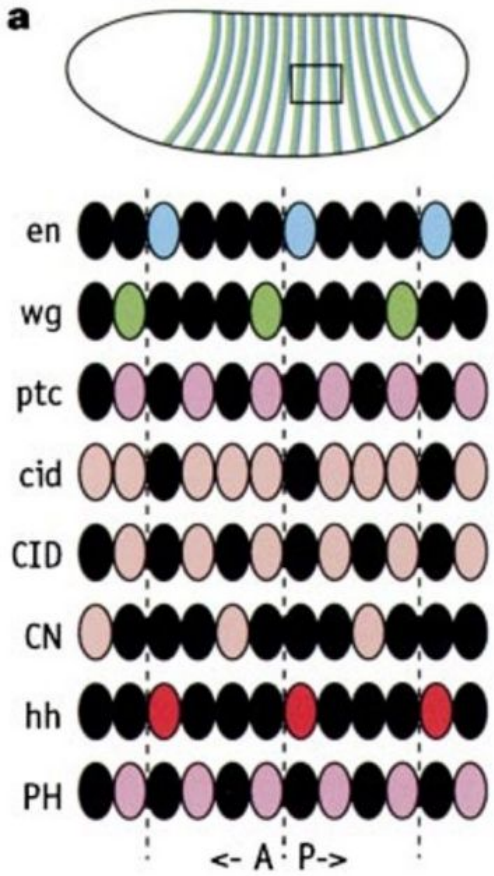

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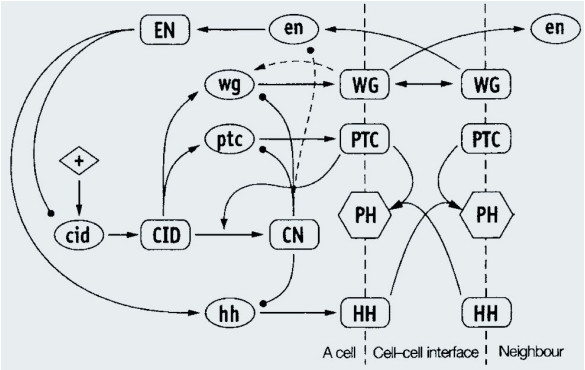

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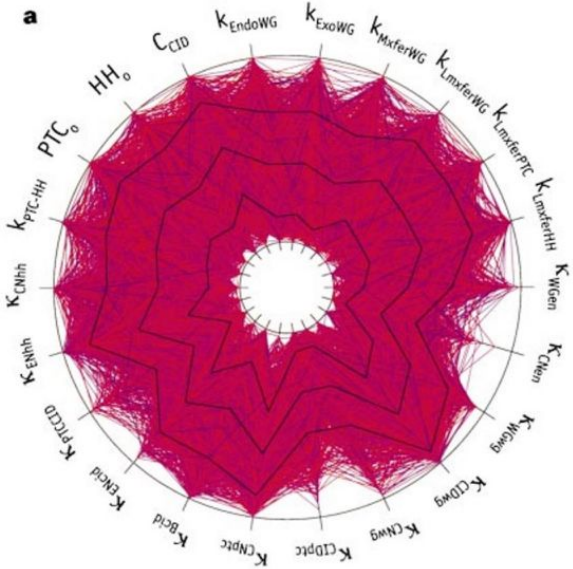

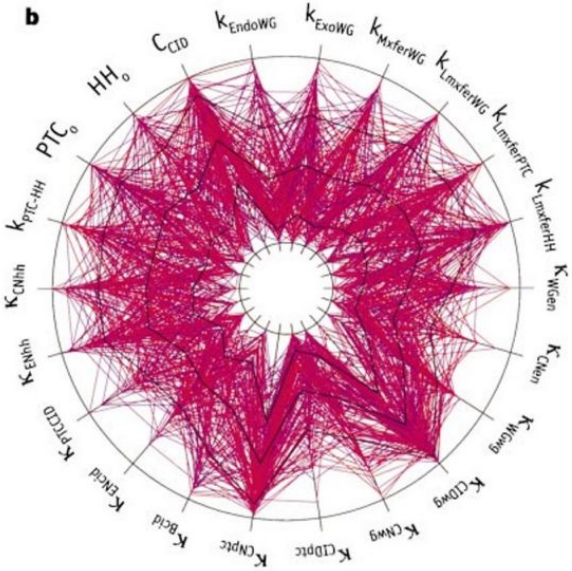

Von Dassow (2000) Nat.

Broad ideas

Kinetic modelling and bifurcation theory provide a precise, mathematical connection between the molecular networks and cellular physiology.

Can be used to make powerful predictions.

Several modeling strategies:

- Rate equations
- Boolean (& hybrid) modeling
- Stochastic simulations