Mathematical Modelling and Scientific Computing in the Biosciences

5 June 2007

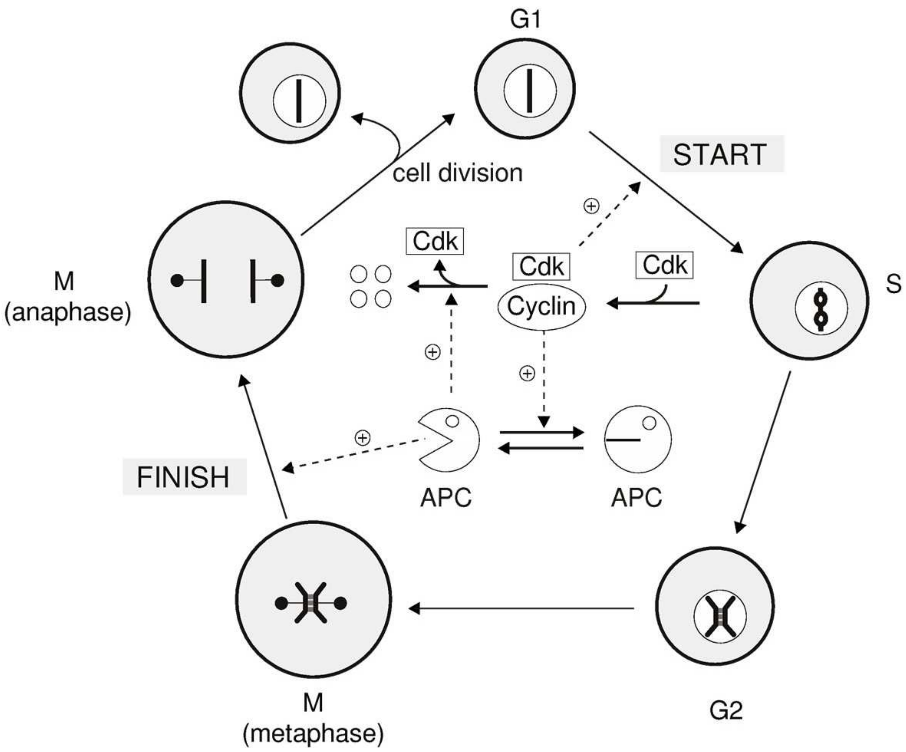
Lecture 8: Overview

- **Cell Cycle Controls**
  - **Biological description**
  - **Simple mathematical model and analysis**

Cell Cycle

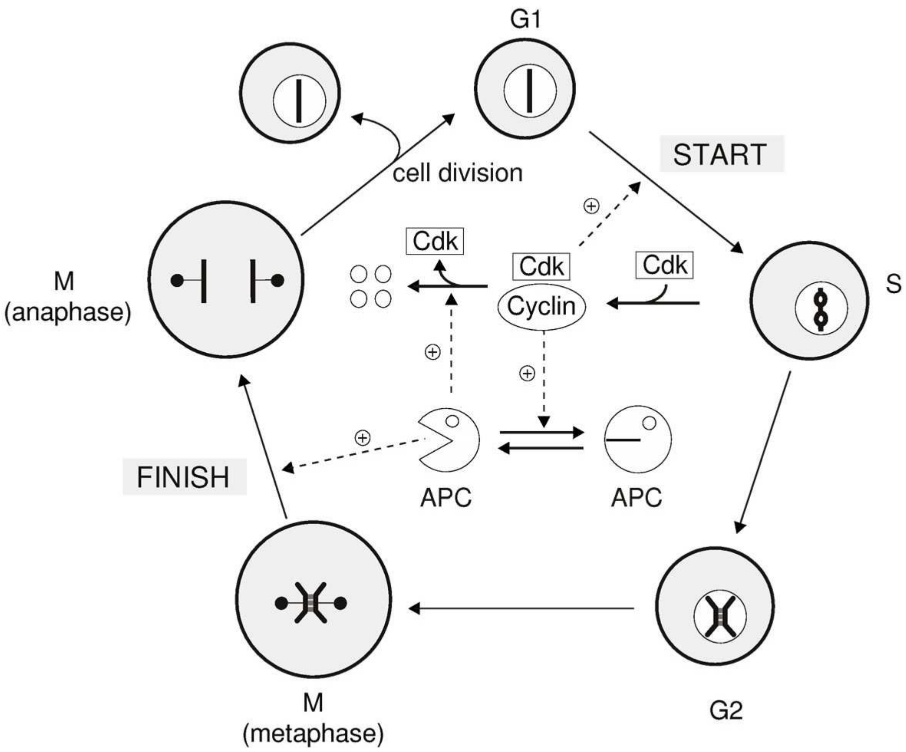
• Cell cycle: a sequence of events whereby a cell duplicates its components (including chromosomes) and divides into 2 daughter cells

• Complex set of regulation mechanisms underlie cell cycle; cannot be under−stood just by verbal arguments. Need mathematical modelling and analysis



Cell Cycle: Chromosome Cycle

- Phases of cell cycle: Start (S), Gap (G1, G2), Mitosis (M)



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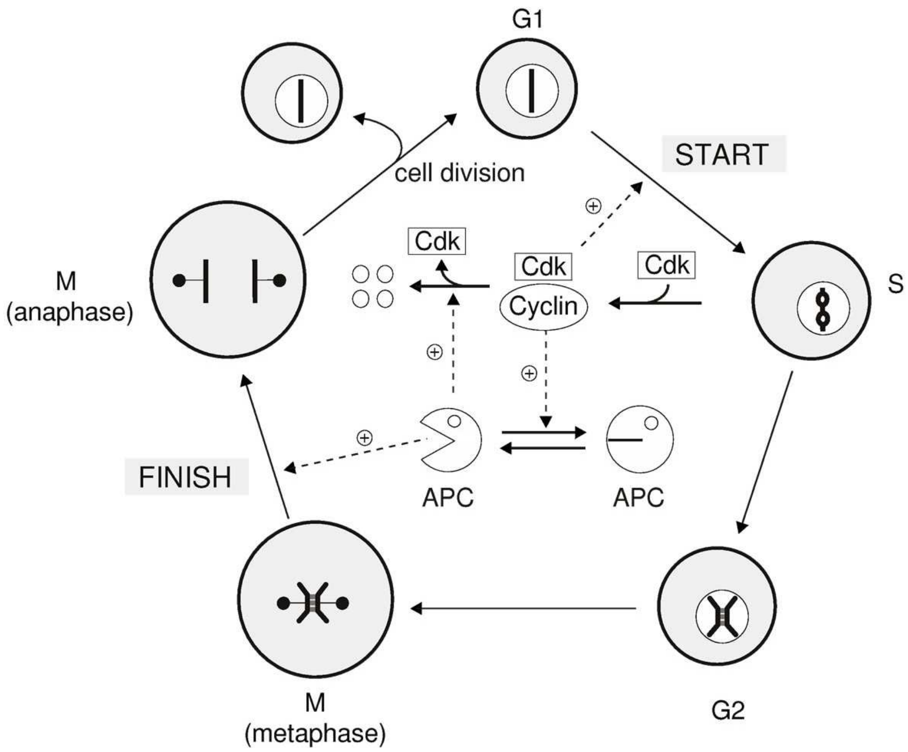
Cell Cycle: Chromosome Cycle

• G1−S transition: DNA is replicated. At end of phase, sister chromatids are held together by tethering proteins



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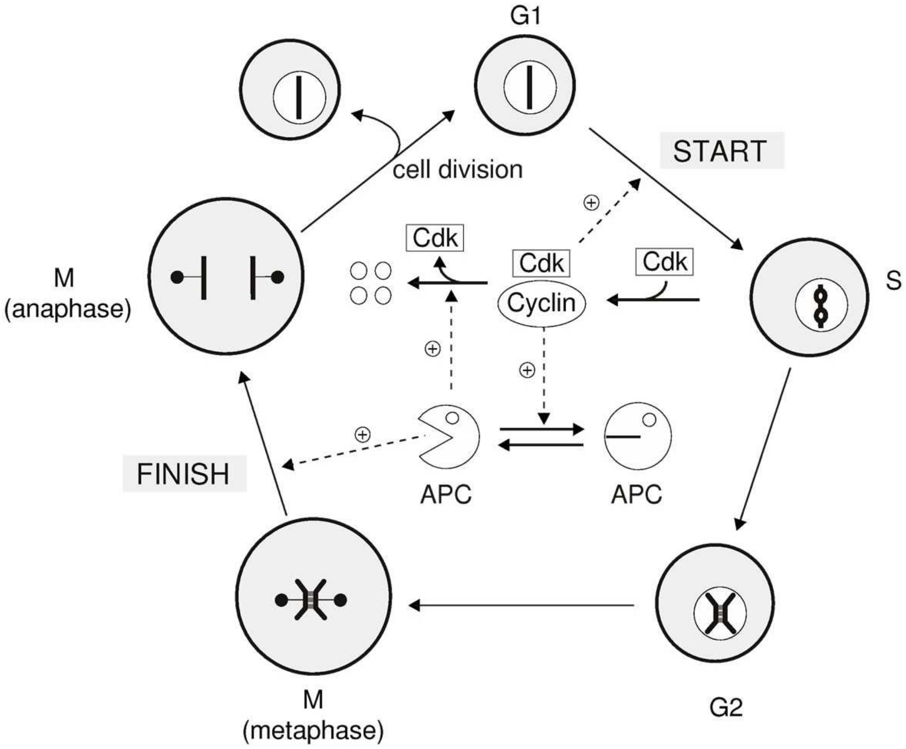
Cell Cycle: Chromosome Cycle

- Mitosis: after the G2 (gap) phase, replicated chromosomes are aligned on the metaphase spindle, sister chromatids are attached to opposite poles of the spindle by microtubules



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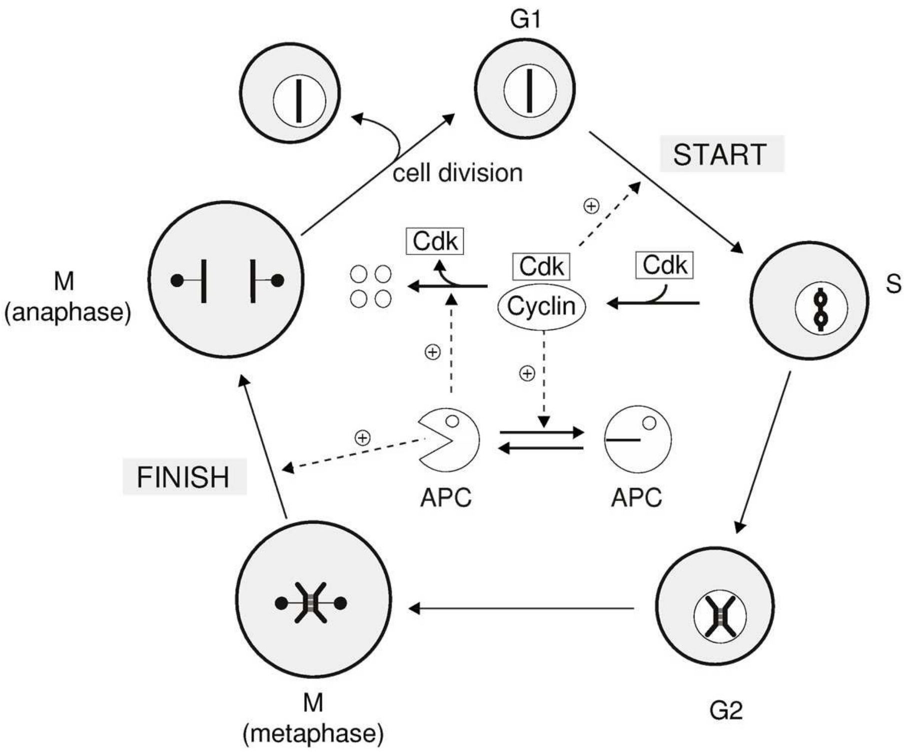
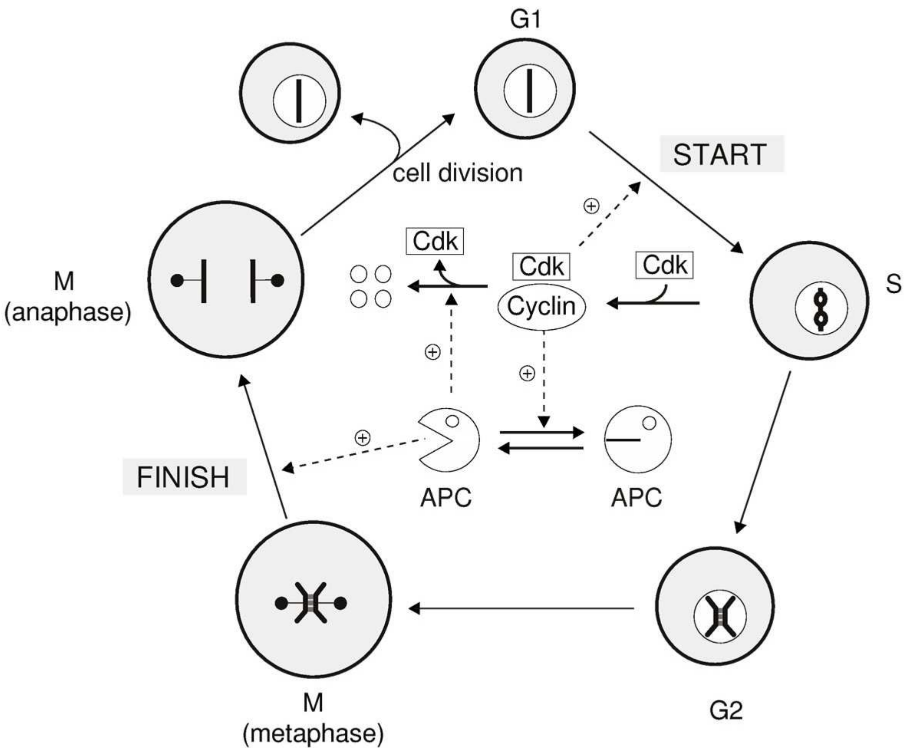
Cell Cycle: Chromosome Cycle

- Anaphase: tether proteins are removed so that sister chromatids can be segregated to opposite sides of the cell
- Cell then divides and the process repeats



Cell Cycle: Molecular Machinery

- Start phase triggered by the protein, cyclin−dependent kinase (Cdk)
- Cdk drives the cell through S, G2 phases, up to metaphase



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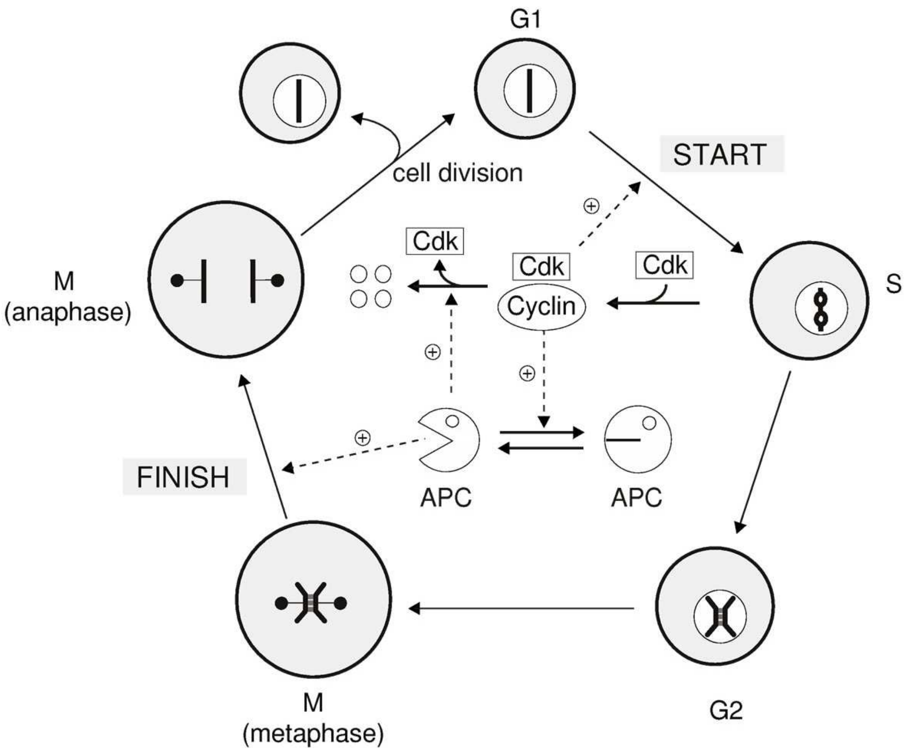
Cell Cycle: Molecular Machinery

• Finish is accomplished by the proteolytic machinery, anaphase−promoting complex, (APC)

• APC destroys tethers and cyclin molecules



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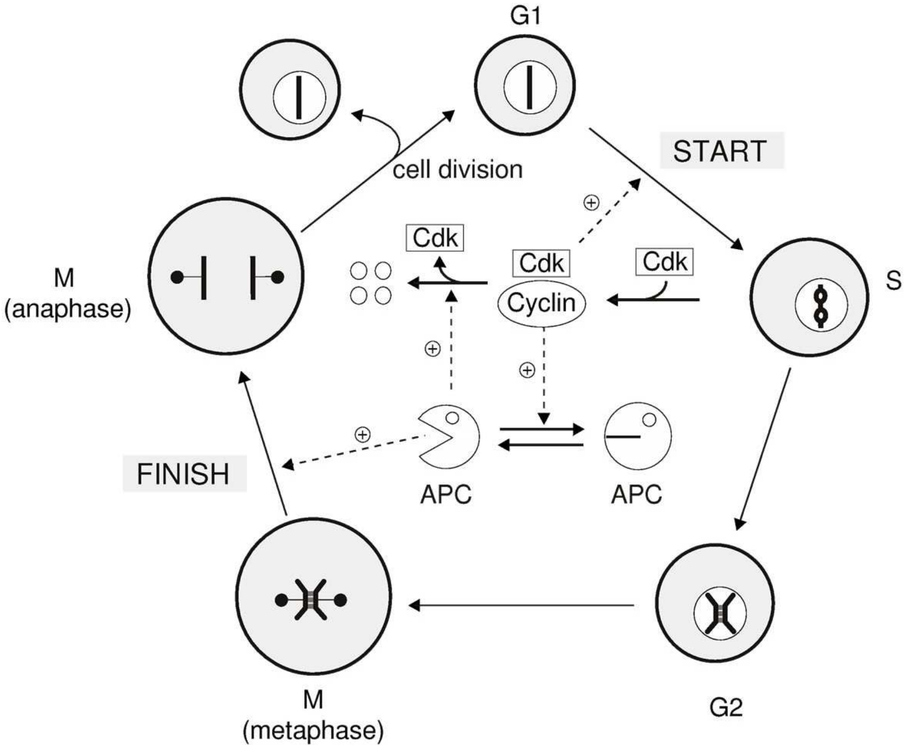
Cell Cycle: Molecular Machinery

• In the G1 phase that follows anaphase, Cdk is inactive due to the presense of APC which reduces the abundance of cyclin molecules



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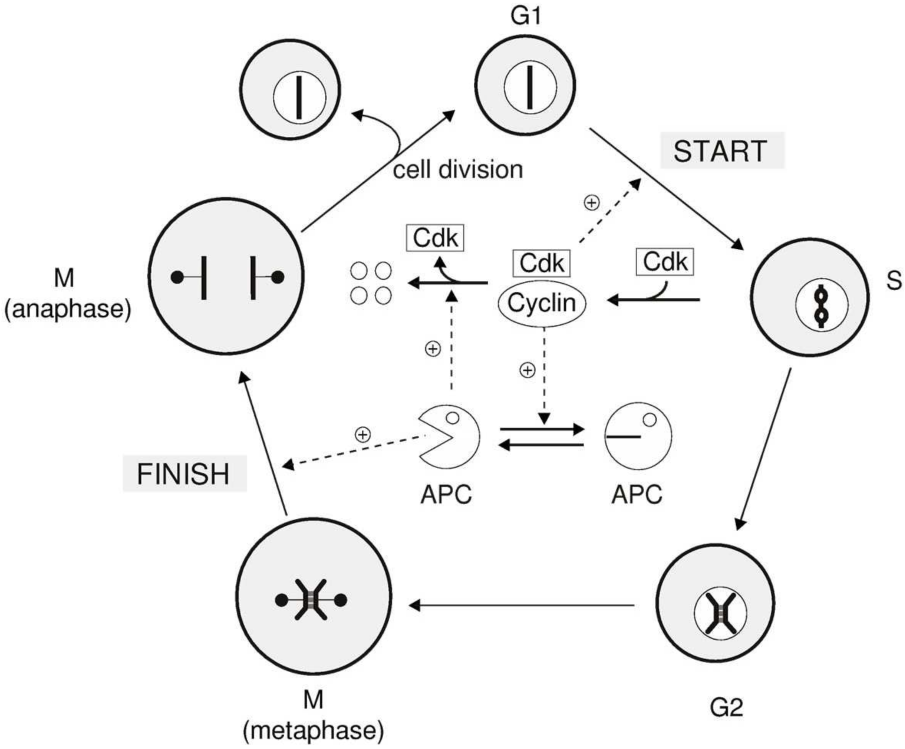
Cell Cycle: Molecular Machinery

• At the subsequent Start phase, APC must be turned off so that Cdk can accumulated

• Antagonistic effects: APC destroys cyclins needed for Cdk, Cdk inactivate APC by phosphorylating its subunits

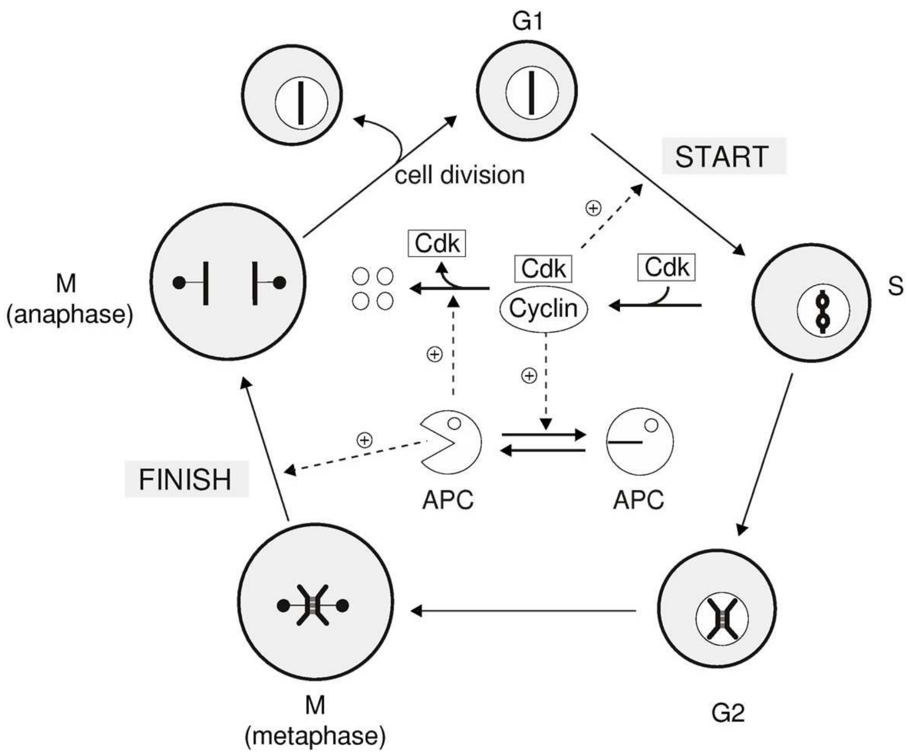


Cell Cycle: Regulation Constraints

• Major transitions of cell cycle must be tightly regulated; e.g.:

− cell must grow to a critical size before chromosome replication and division

− if there are problems with DNA replication, the Finish transition must be delayed, else it would be a fatal error



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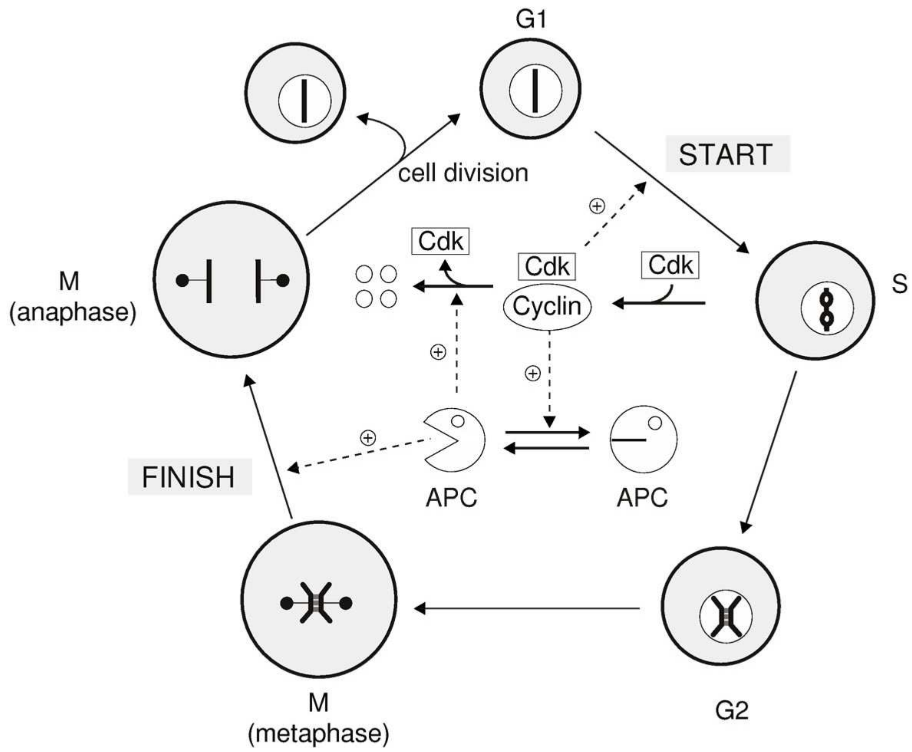
Cell Cycle: Regulation Constraints

- Roughly, 2 alternative states: G1 and S−G2−M
- Transition from G1 to S−G2−M is irreversible: once DNA synthesis starts, it cannot stop but go to completion
- With respect to moleculer machinery, G1: high APC, low Cdk

  S−G2−M: high Cdk, low APC



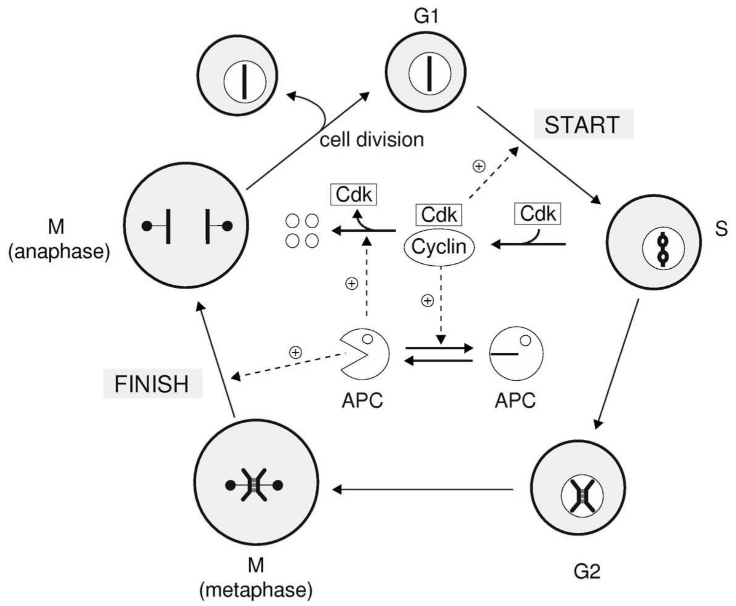
Cell Cycle: Simple Model

• The core biochemical reactions can be described by a pair of nonlinear ODEs:

$$X'(t) = \mathrm{k1} - X(t)\,(\mathrm{k2} + \mathrm{k2p}\,Y(t))$$

$$Y'(t) = \frac{(\mathrm{k3}+A\,\mathrm{k3p})\,(1-Y(t))}{\mathrm{J3}-Y(t)+1} - \frac{\mathrm{k4}\,m\,X(t)\,Y(t)}{\mathrm{J4}+Y(t)}$$

where X and Y are concentrations of Cdk, APC; m is cell mass, A the concentration of a protein activating APC complex at Finish



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where X and Y are concentrations of Cdk, APC; m is cell mass, A the concentration of a protein activating APC complex at Finish

• Assumptions:

– cyclins are synthesized at a constant rate k1 in the cytoplasm

– cyclins are degraded at a constant rate, as well as additionally destroyed by APC at a rate proportional to APC concentration

– inactive (phosphorylated) APC $(1-Y(t))$ is turned on to active APC, described by Michaelis–Menten kinetics, with Michaelis constant J3

– active APC is phosphorylated (deactivated) at a rate proportional to the mass of cell, *m*, and depends on the concentration of Cdk in the Michaelis−Menten manner

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Cell Cycle: Simple Model

- Dimensional, nonlinear ODEs:

$$X'(t) = \text{k1} - X(t)\,(\text{k2} + \text{k2p}\,Y(t))$$

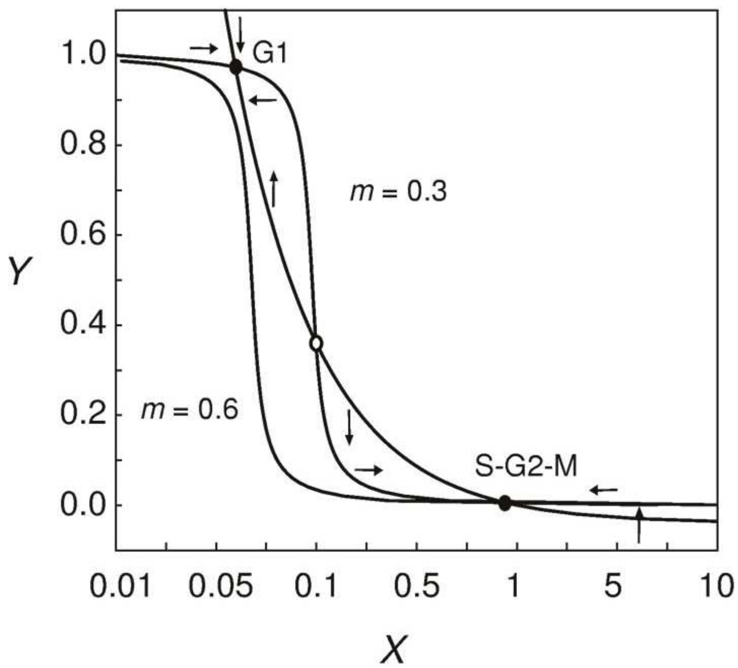
$$Y'(t) = \frac{(\text{k3}+A\,\text{k3p})\,(1-Y(t))}{\text{J3}-Y(t)+1} - \frac{\text{k4}\,m\,X(t)\,Y(t)}{\text{J4}+Y(t)}$$

- After non−dimensionalization, obtain null−cline equations:

X null−cline : $X = \frac{\beta}{\text{J2}+Y}$

Y null−cline : $X = \frac{p\,(1-Y)\,(\text{J4}+Y)}{(\text{J3}-Y+1)\,Y}$

where β = k1/k2p, J2=k2/k2p, p=(k3+k3p A)/(k4 m)



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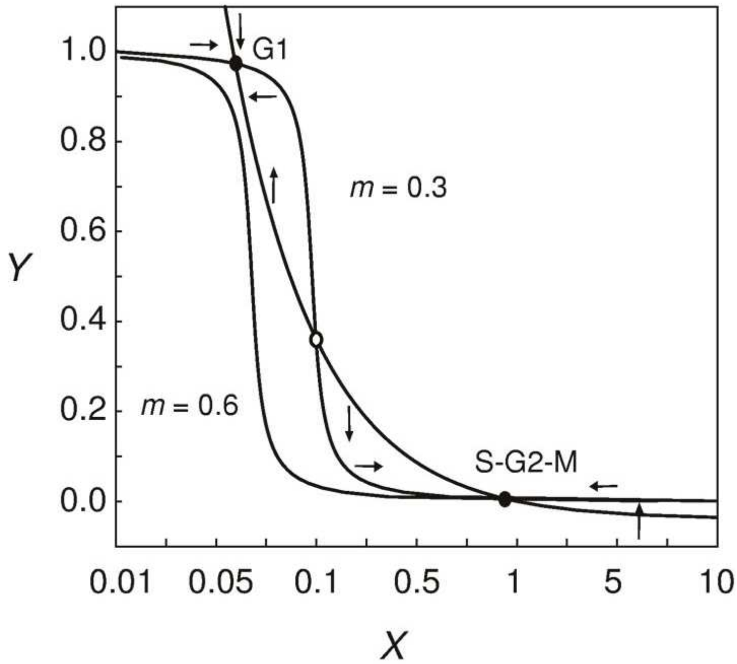
Cell Cycle: Simple Model



• Interpretations:

− for m=0.3, the system has 3 steady states: 2 stable nodes (dots), 1 unstable saddle−node (circle)

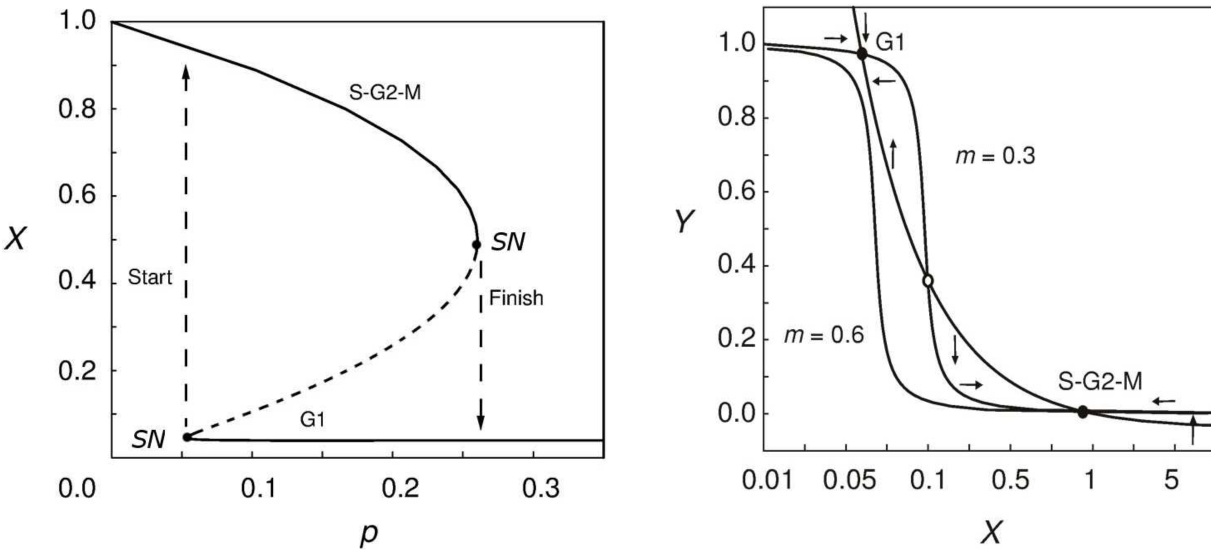
− for m=0.6, the system has only 1 steady state: S−G2−M point

− hence, as the cell grows, the G1 point is lost through a saddle−node bifurcation, and the system is forced to go to the S−G2−M point

Cell Cycle: Simple Model

• How does the solution change as the parameter *p* changes?

Perform bifurcation analysis



• Stable, steady−state solutions coalesce/collide with unstable solutions at saddle−node bifurcation (SN) points

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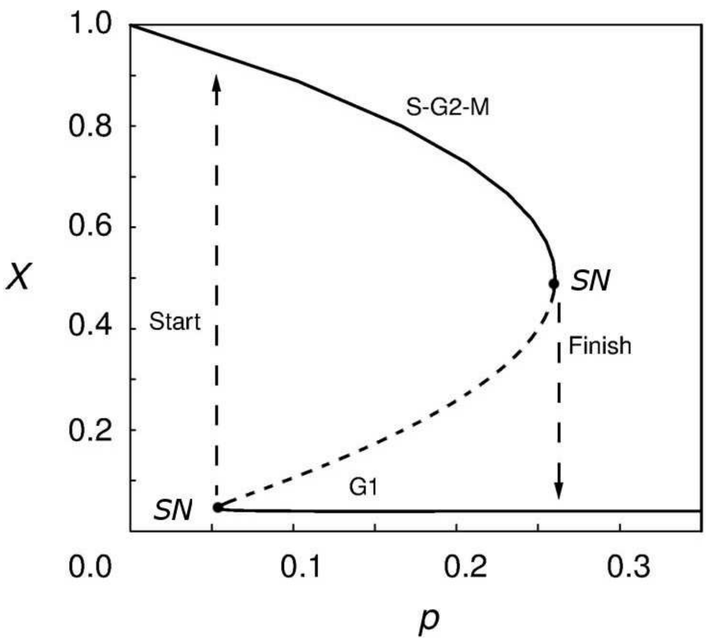
Cell Cycle: Simple Model

• The bifurcation diagram shows that the system exhibits hysteresis: i.e., the state depends on the history of the trajectory

• E.g., after the systems goes from S−G2−M to G1 by increasing bifurcation parameter *p*, a subsequent decrease in *p* does not switch the system back to S−G2−M

• Hysteresis effect makes the system less sensitive to fluctuations in signal strengths



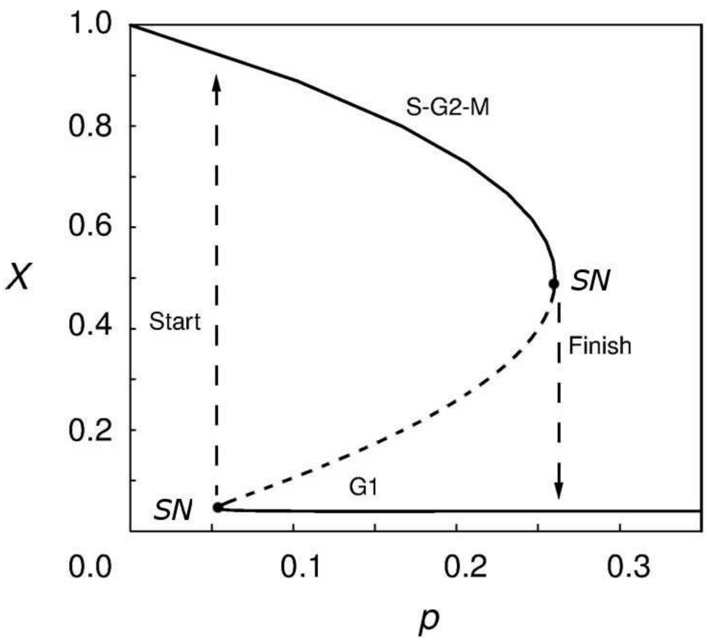
Cell Cycle: Simple Model

• Interpretation of bifurcation diagram in biological setting:

− progress through cell cycle can be seen as a tour through the hysteresis loop

• Small new born cell: $A \approx 0$, hence $p=(k3+k3p\ A)/(k4\ \ m) \approx k3/(k4\ \ m)$; so p large, and cell is in the G1 state

• Growth: m increases, so p decreases, until the left saddle−node is reached and X jumps up to the high, S−G2−M state



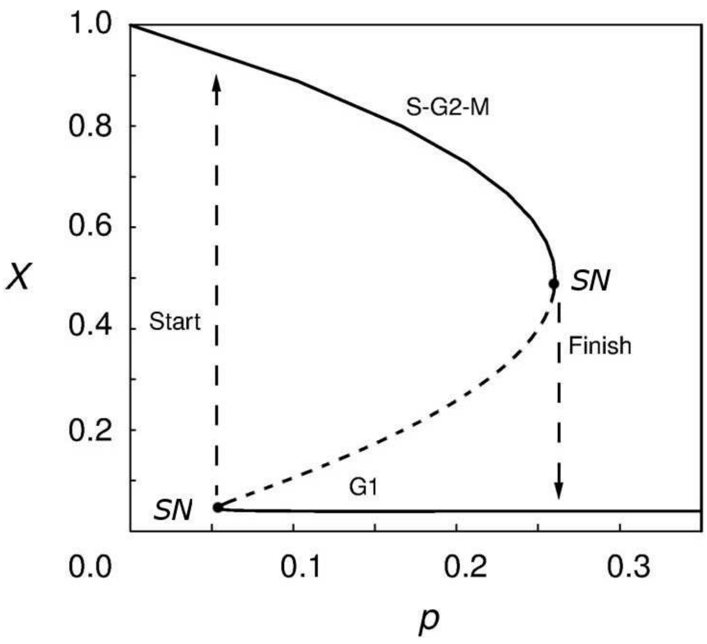
Cell Cycle: Simple Model

• High X (cyclin) activates process of DNA synthesis and mitosis.

• When DNA replication is complete, the parameter *A* increases;

hence *p*=(k3+k3p *A*)/(k4 *m*) increases, until S−G2−M state is lost via a sad−dle−node bifurcation

• After the cell jumps irreversibly to G1, the cell divides; *m*→*m*/2, *A*→0 and the whole process starts again



Cell Cycle: First Extensions of Simple Model

• In the previous model, no mechanism has been given for:

− increase in parameter A at metaphase to anaphase transition

− decrease in parameter A in G1 phase

• Simple model for activator A: production is promoted by cyclin X

$$A'(t) = \frac{\text{k5p}\,(m\,X(t))^n}{\text{J5}^n + (m\,X(t))^n} + \text{k5} - \text{k6}\,A(t)$$

• Hence, cyclin X, activator A and Y are involved in a long, negative feed−back loop:

− X turns on A, which indirectly activates Y, which destroys X

• Negative feedback: possible to obtain oscillations?

Cell Cycle: First Extensions of Simple Model

$$X'(t) = \text{k1} - X(t)\,(\text{k2} + \text{k2p}\,Y(t))$$

$$Y'(t) = \frac{(\text{k3}+\text{k3p}\,A(t))\,(1-Y(t))}{\text{J3}-Y(t)+1} - \frac{\text{k4}\,m\,X(t)\,Y(t)}{\text{J4}+Y(t)}$$

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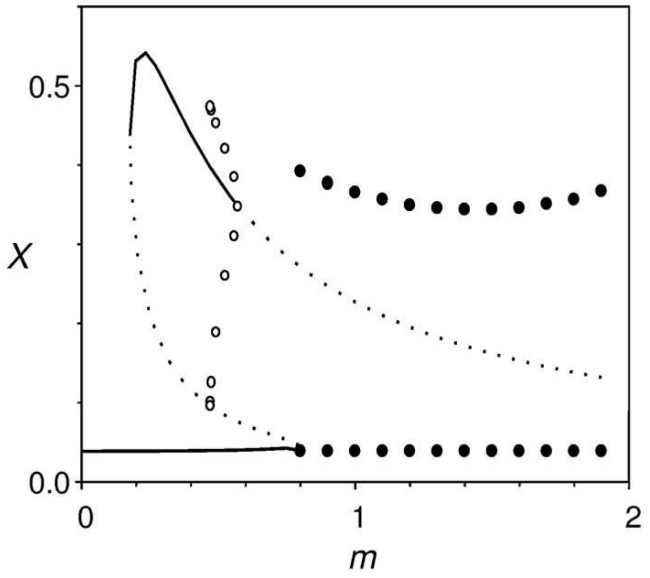

• Analysis shows bifurcation points:

− saddle−node

− Hopf point: loss of stable steady−state, appearance of (limit cycle) oscilla−tions

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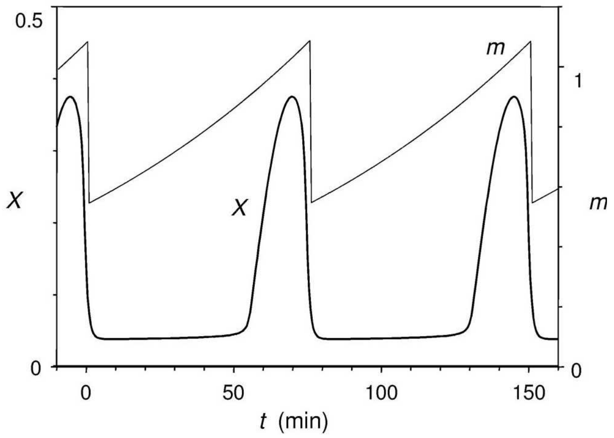
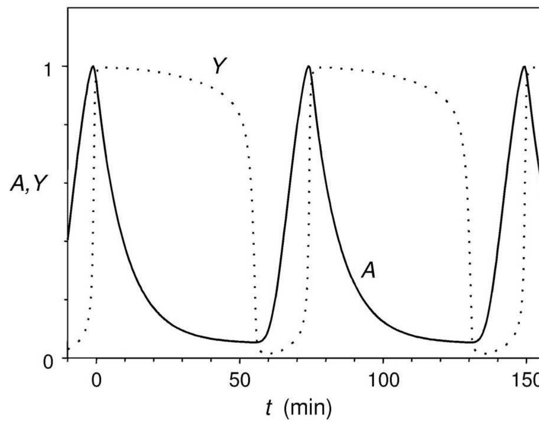
Cell Cycle: First Extensions of Simple Model

• The cell mass was assumed to be an independent parameter; of course, it is time dependent

• Denoting μ to be the growth rate, *ms* the maximum size of the cell, then the ODE for cell growth is taken to be:

$$m'(t) = \mu\, m(t)\left(1 - \frac{m(t)}{\text{ms}}\right)$$





- The cell mass grows almost linearly, with halves periodically when cell divides
- X initially at low value, until mass m becomes sufficiently large to cross the lower saddle−node bifurcation point
- Subsequently, X increases rapidly, causing:
  −Y to be degraded rapidly
  −A to be produced rapidly, thereby raising p
- When p passes the upper saddle−node, level of X drops back to low value

Conclusions

• We have looked at some of the important species participating in controlling cell cycle

• Simple ODE model was constructed, computed bifurcation diagrams, interpreted in biological setting

• Bifurcation diagram captures the qualitative behavior of solutions obtained by doing the full ODE simulation

• <u>Next lectures</u>: bifurcation analysis

- What are the generic bifurcations that can occur?
- Matlab software, MATCONT
- Algorithms for solution continuation and bifurcation detection