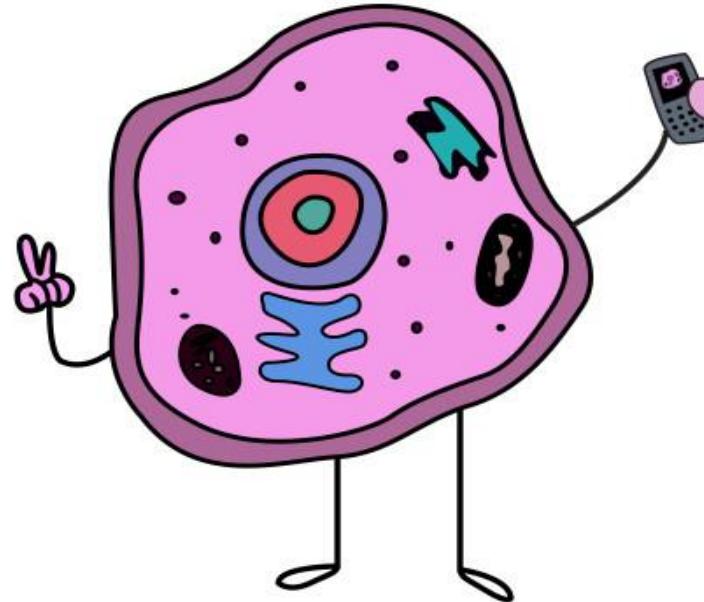


# Dynamic modeling of Protein Kinetics

Uchenna Alex Anyaegbunam, Ph.D.

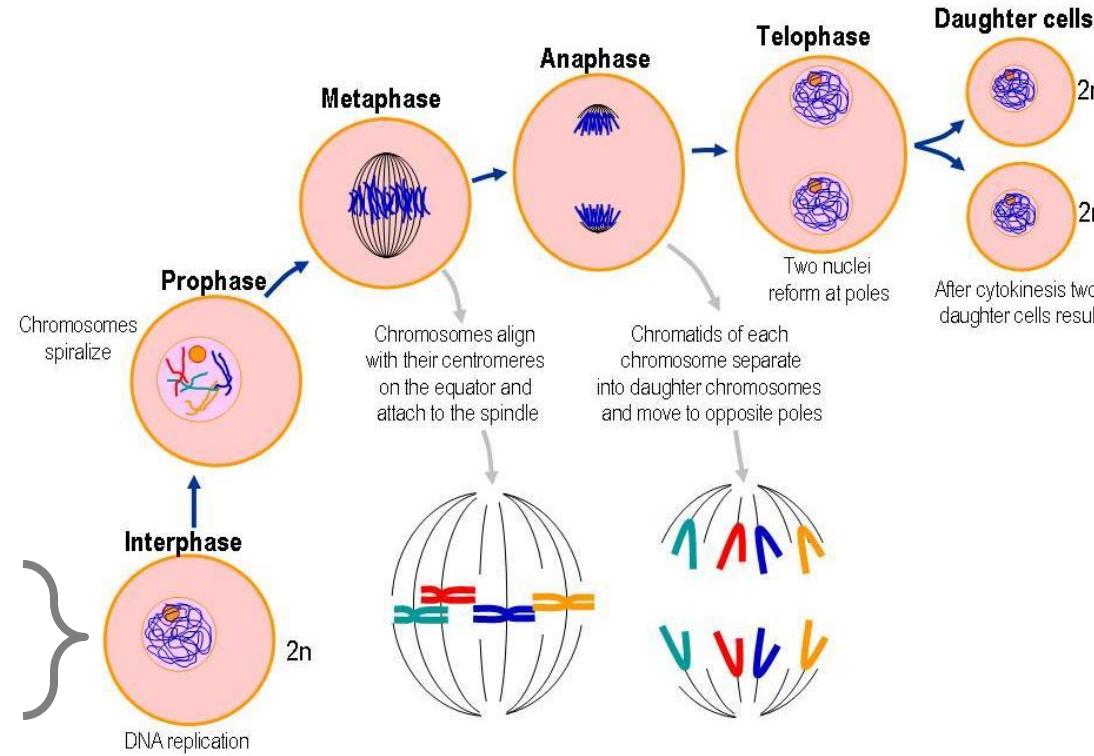
A.G. Prof. Dr. Miguel Andrade  
Computational Biology and Data Mining group  
Faculty of Biology

The cell reproduces by making an exact copy of itself

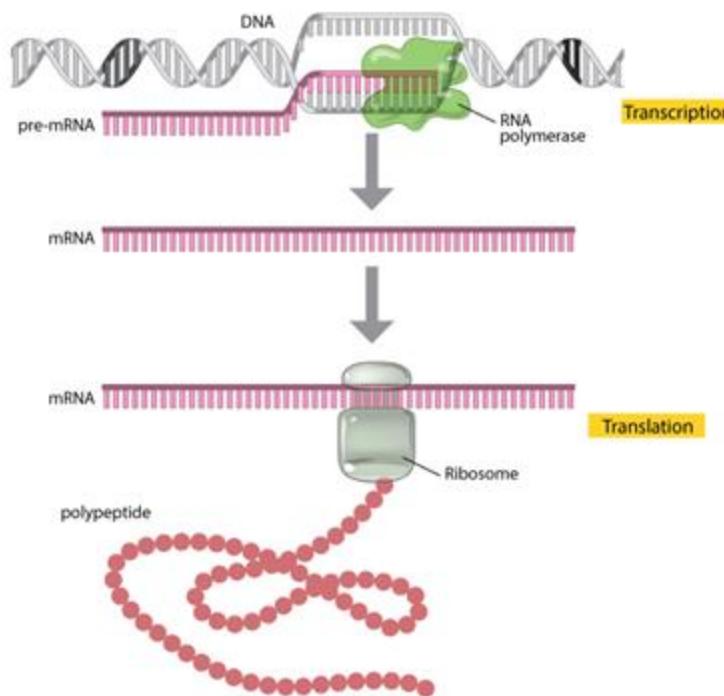


Cell-*file*

# The cell reproduces by undergoing several processes: cell cycle



# DNA replication: Quantitative description of protein expression



**What determines the kinetics of mRNA and protein expression?**

How can we describe heterogeneous gene expression at the single-cell level?

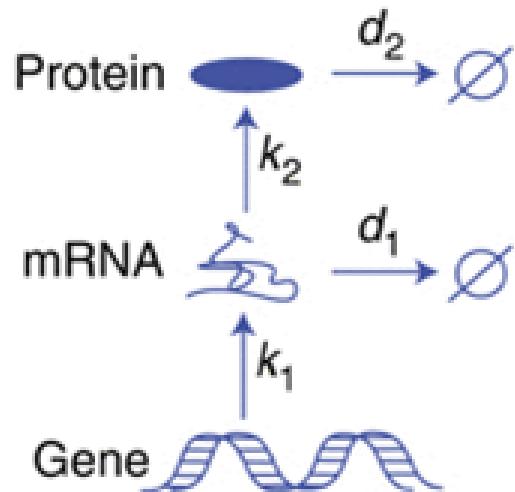
# Outline

## **Deterministic model of gene expression**

Stochastic model of gene expression  
captures cellular heterogeneity

Applications: Deterministic modeling of proteins  
controlling anaphase

# A simple model for transcriptional regulation of protein expression



$$\frac{d(\text{mRNA})}{dt} = k_1 - d_1 \cdot \text{mRNA}$$

$$\frac{d(\text{Protein})}{dt} = k_2 \cdot \text{mRNA} - d_2 \cdot \text{Protein}$$

## Assumptions

- Translation proportional to mRNA concentration
- First-order decay of mRNA and protein

**mRNA, Protein**  
 $k_i, d_i$

Variables/Concentrations  
Kinetic parameters

# Assumptions underlying ordinary differential equation models

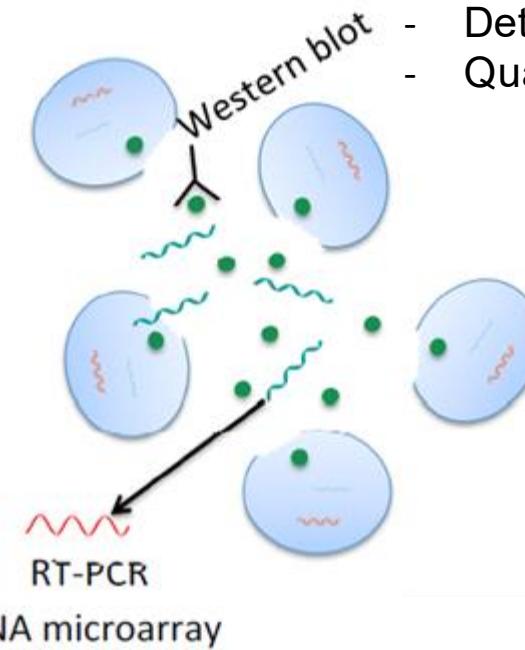
## Continuous

Real concentration of mRNAs/proteins

## Deterministic

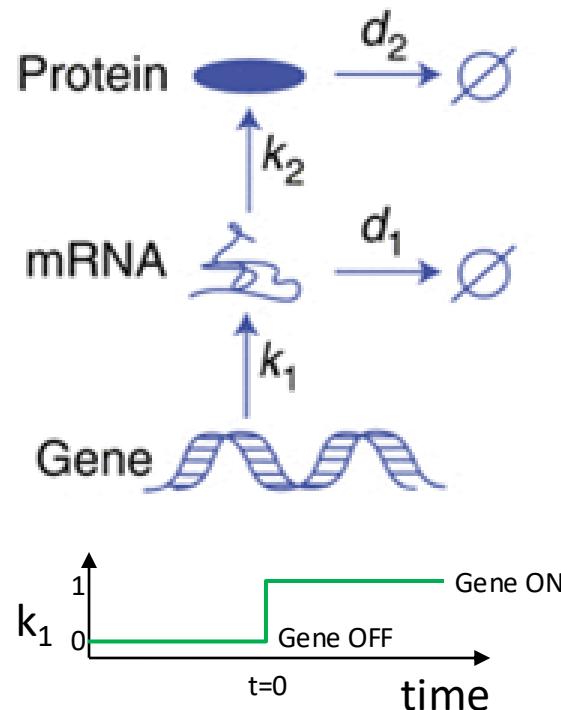
Average behavior of large molecule numbers

### Population techniques



- Detects specific proteins
- Quantifies protein

# What determines the protein dynamics in response to changes in transcription?



$$\frac{d(\text{mRNA})}{dt} = k_1 - d_1 \cdot \text{mRNA}$$

$$\frac{d(\text{Protein})}{dt} = k_2 \cdot \text{mRNA} - d_2 \cdot \text{Protein}$$

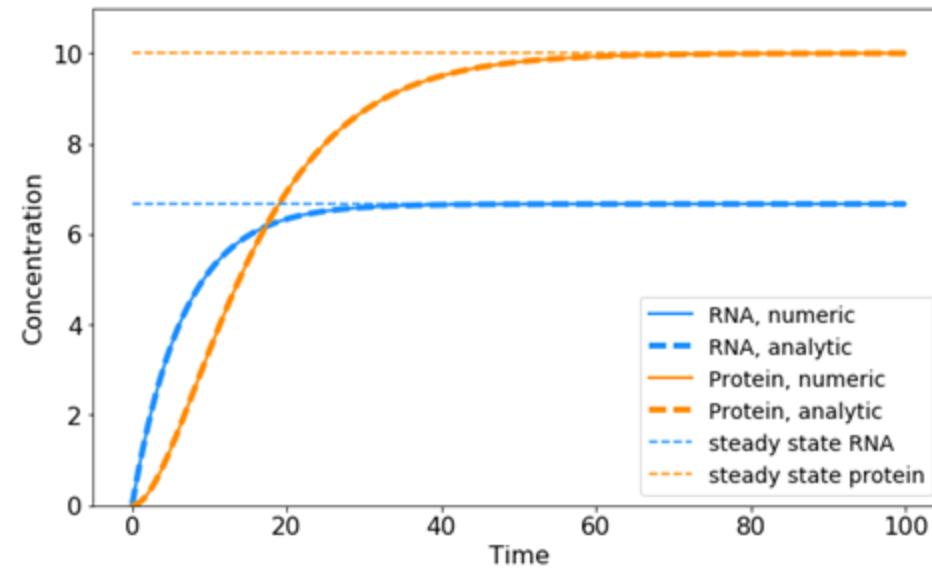
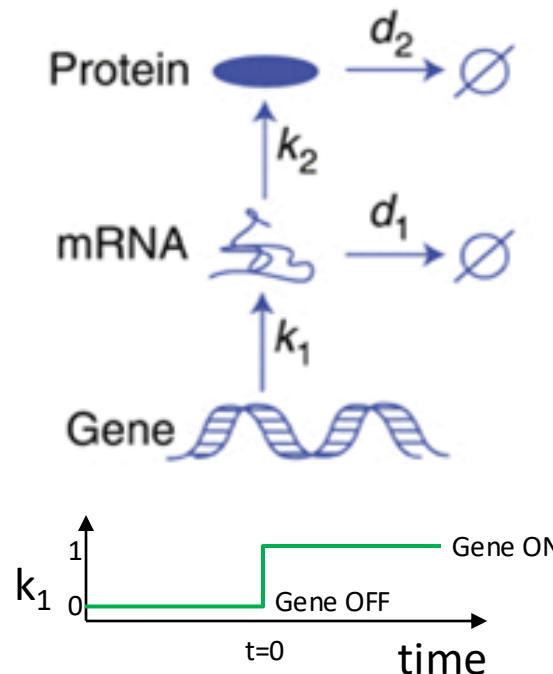
## Analytical Solution (by integration)

$$\text{mRNA}(t) = \overline{\text{mRNA}} \cdot (1 - e^{-d_1 t})$$

$$\text{Protein}(t) = \overline{\text{Protein}} \cdot \left( 1 - \frac{d_1 e^{-d_2 t} - d_2 e^{-d_1 t}}{d_1 - d_2} \right)$$

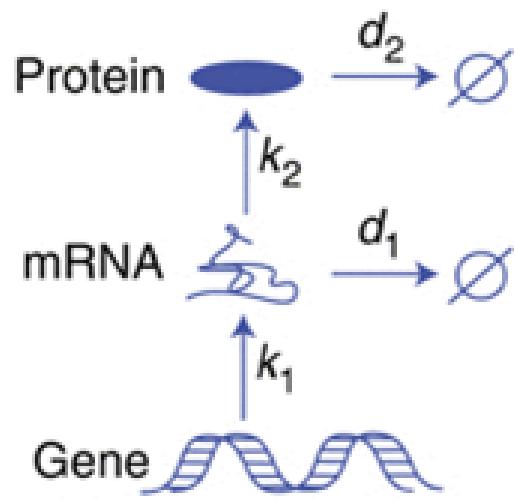
⇒ Approximate solution using numerical integration

# Time course of mRNA and protein in response to gene activation



System asymptotically approaches steady state  
Protein dynamics has a "Response time"

# What determines protein expression level at steady state?



Steady state

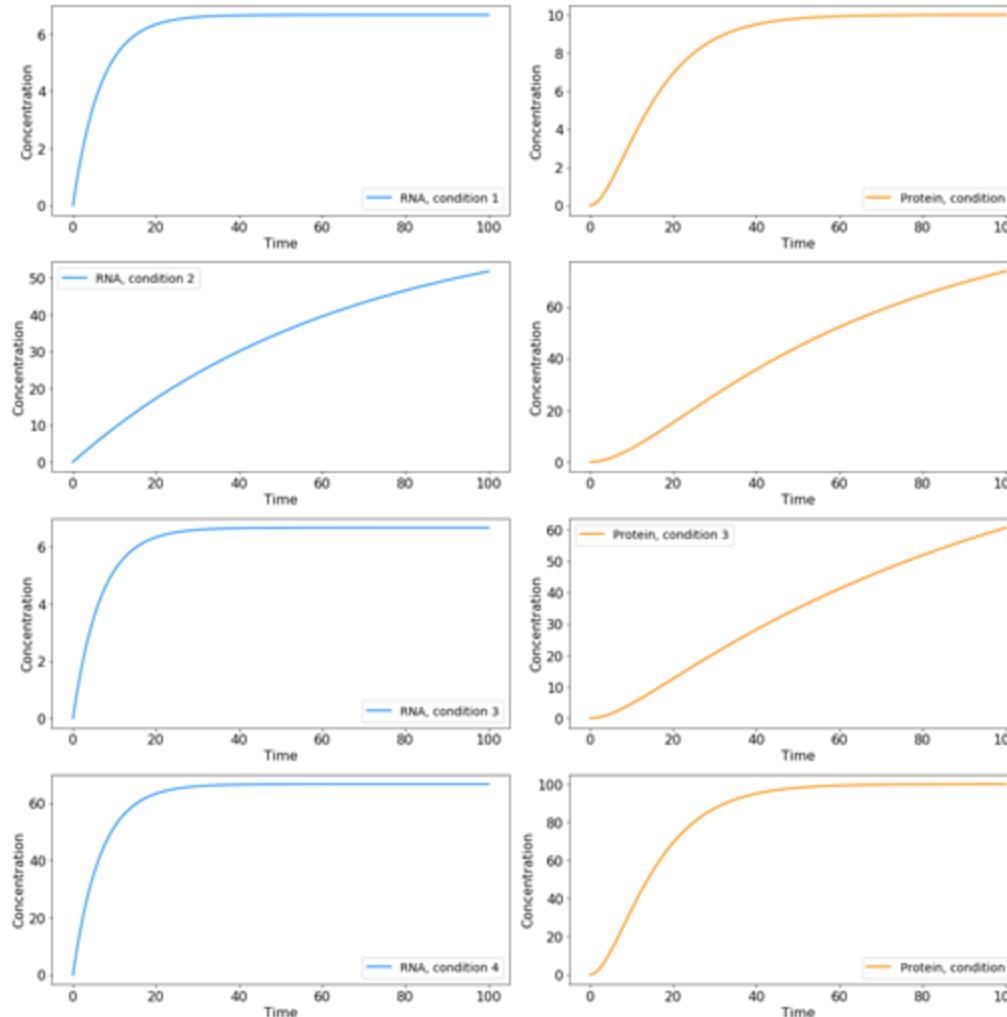
$$k_1 - d_1 \cdot \text{mRNA} = 0$$
$$k_2 \cdot \text{mRNA} - d_2 \cdot \text{Protein} = 0$$

$$\overline{\text{mRNA}} = \frac{k_1}{d_1} \quad \overline{\text{Protein}} = \frac{k_1 k_2}{d_1 d_2}$$

Steady state level set by ratio of synthesis and degradation rates

Transcription induces proportional changes in mRNA and protein levels

# Protein dynamics solely determined by mRNA and protein degradation rates



$$\text{Protein}(t) = \overline{\text{Protein}} \cdot \left( 1 - \frac{d_1 e^{-d_2 t} - d_2 e^{-d_1 t}}{d_1 - d_2} \right)$$

mRNA degradation rate  
changes final steady state  
and response time

protein degradation rate  
changes final steady state  
and response time

mRNA and protein synthesis rates  
change only final steady state

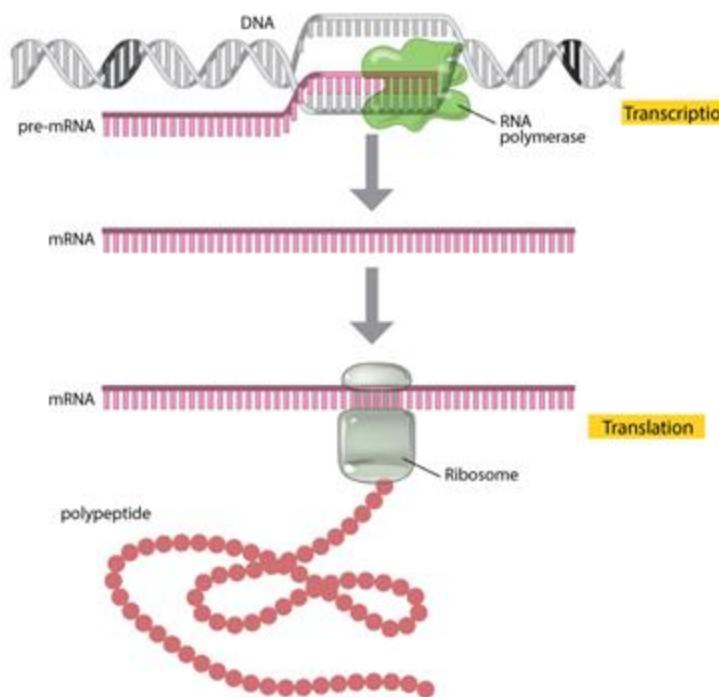
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**Stochastic model of gene expression  
captures cellular heterogeneity**

Applications: Deterministic modeling of proteins  
controlling anaphase

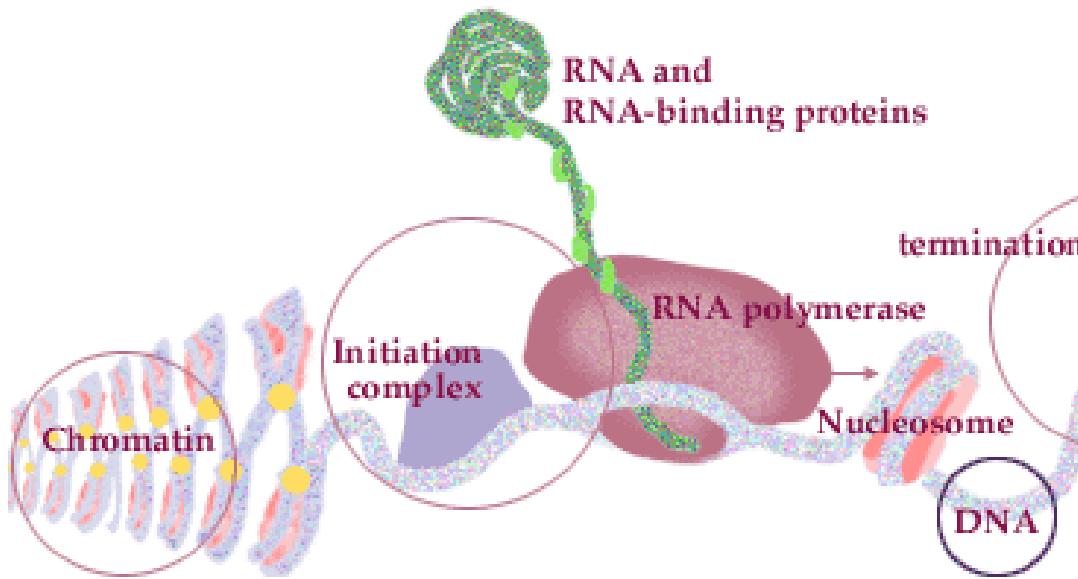
# DNA replication: Quantitative description of protein expression



What determines the kinetics of mRNA and protein expression?

How can we describe heterogeneous gene expression at the single-cell level?

# Gene expression – a stochastic process

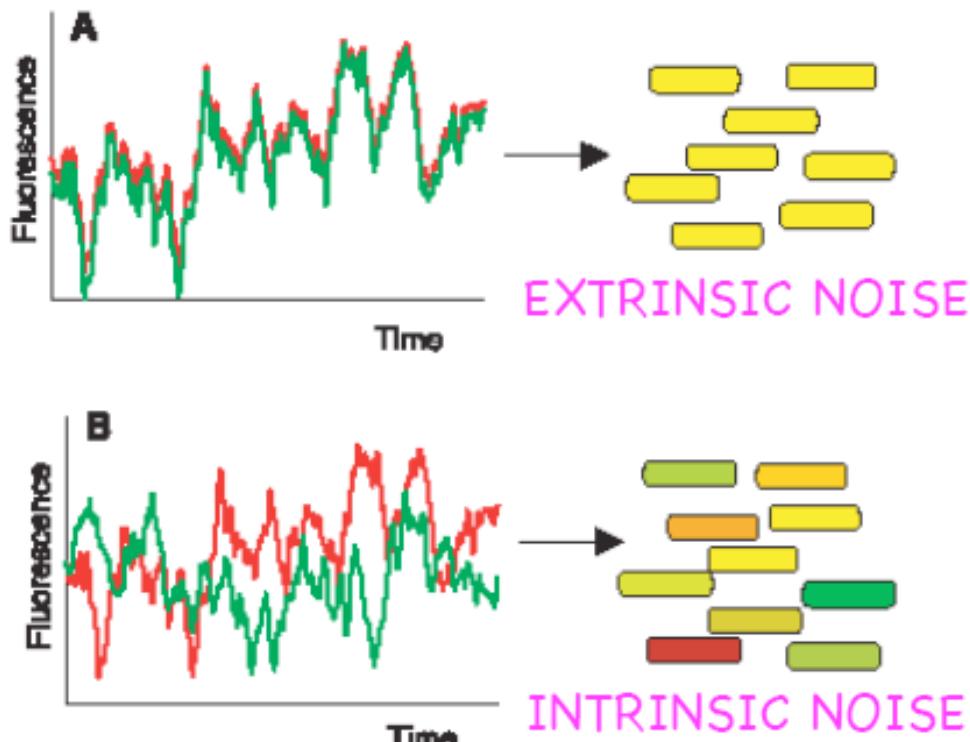


Stochastic dynamics shown for transcription initiation and elongation

**Randomness arises from low molecule numbers!**

- each cell contains few copies of each gene
- transcription factors often present in low amounts

# Intrinsic and extrinsic sources of gene expression variability



Fluctuations in biosynthetic machinery (polymerases, ribosomes)  
Eukaryotes

Random binding of transcription machinery to each promoter (low copy numbers!)  
Bacteria  
Eukaryotes

# Stochastic models account for event probabilities at low molecule numbers

**Deterministic ODE model**      vs.      **Stochastic model**

Average behavior of  
large molecule numbers

Continuous: Concentration  
of mRNAs/proteins

Probabilistic behavior (randomness)  
at the single-molecule level

Discrete: Absolute  
molecule counts

# Stochastic version of simple protein expression model

1. **RNA production:**  $RNA \xrightarrow{\beta} RNA + 1$
2. **RNA decay:**  $RNA \xrightarrow{\gamma_m \cdot RNA} RNA - 1$
3. **Protein production:**  $protein \xrightarrow{k \cdot RNA} protein + 1$
4. **Protein decay:**  $protein \xrightarrow{\gamma_p \cdot protein} protein - 1$

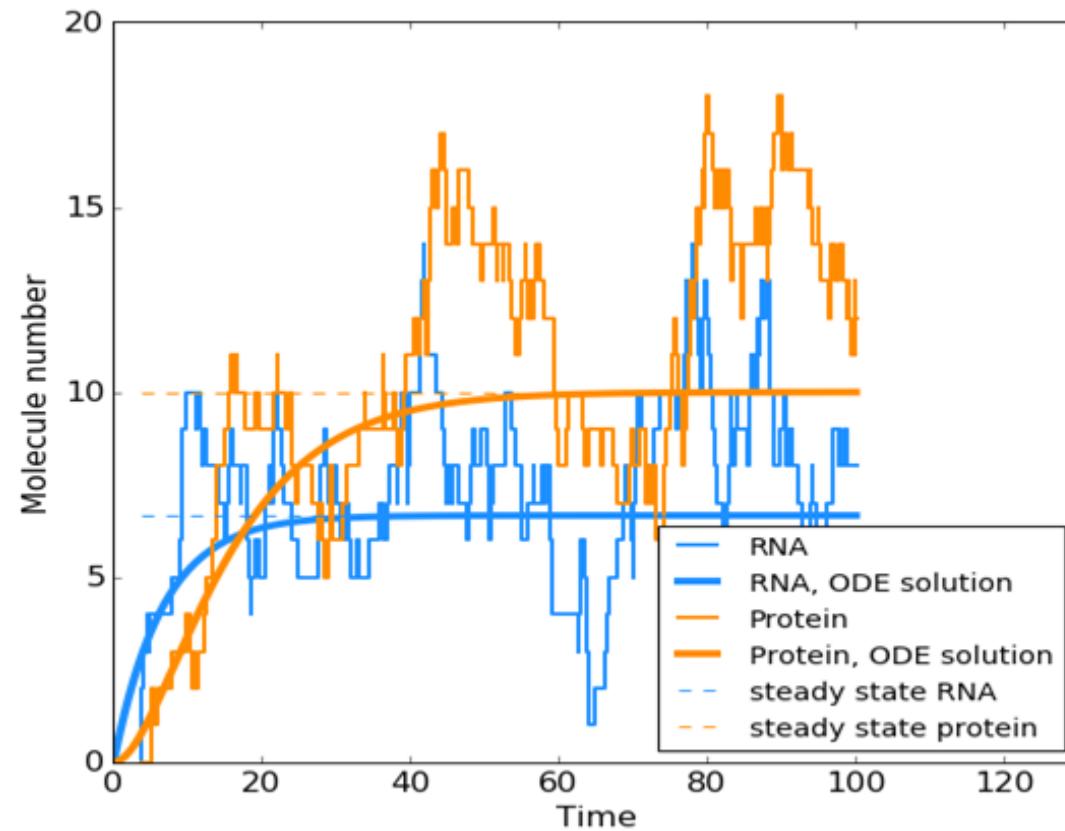
Reactions occur with certain probabilities

mRNA and protein given as *absolute* molecule count (discrete)

Simulation by Gillespie algorithm

- selects most probable next reaction
- updates molecule counts

# Simulated temporal evolution of mRNA and protein in a stochastic model



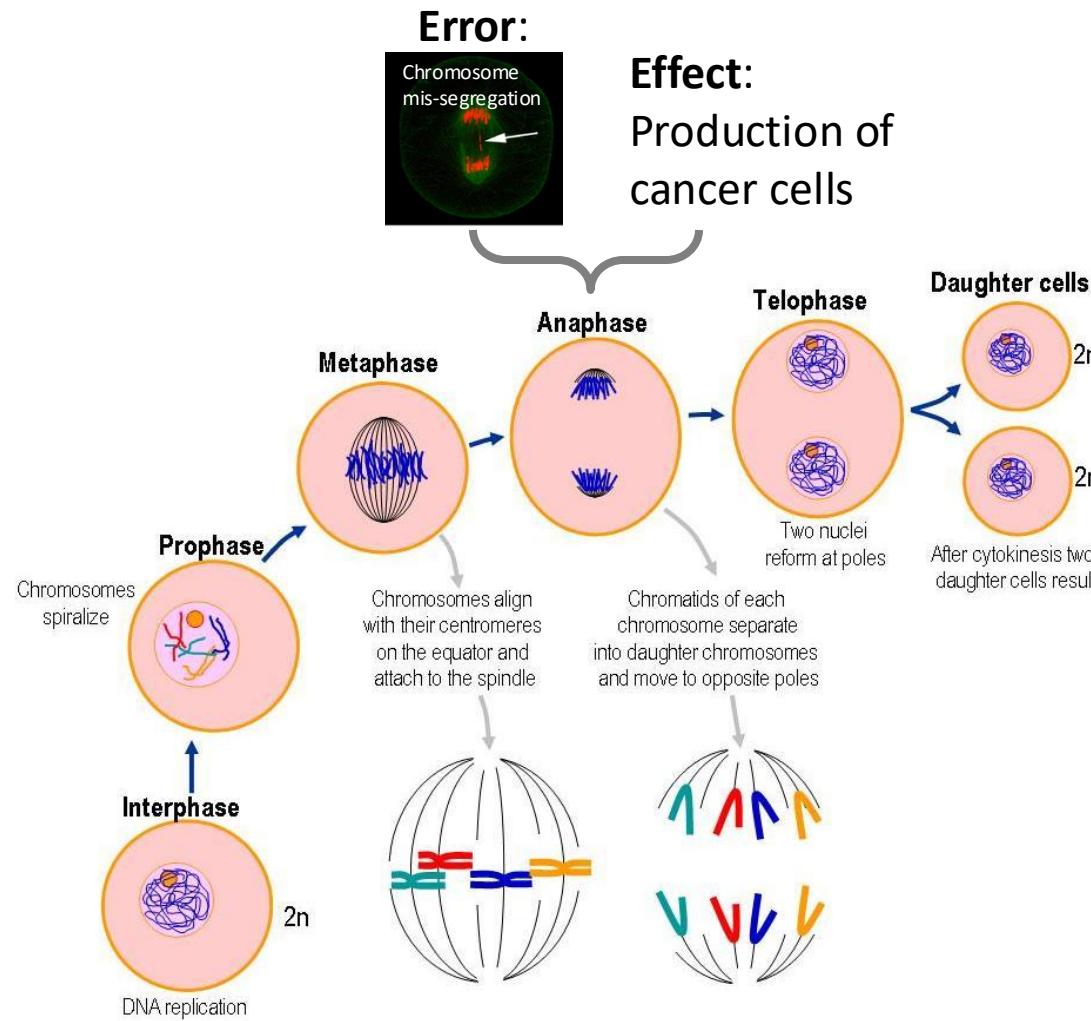
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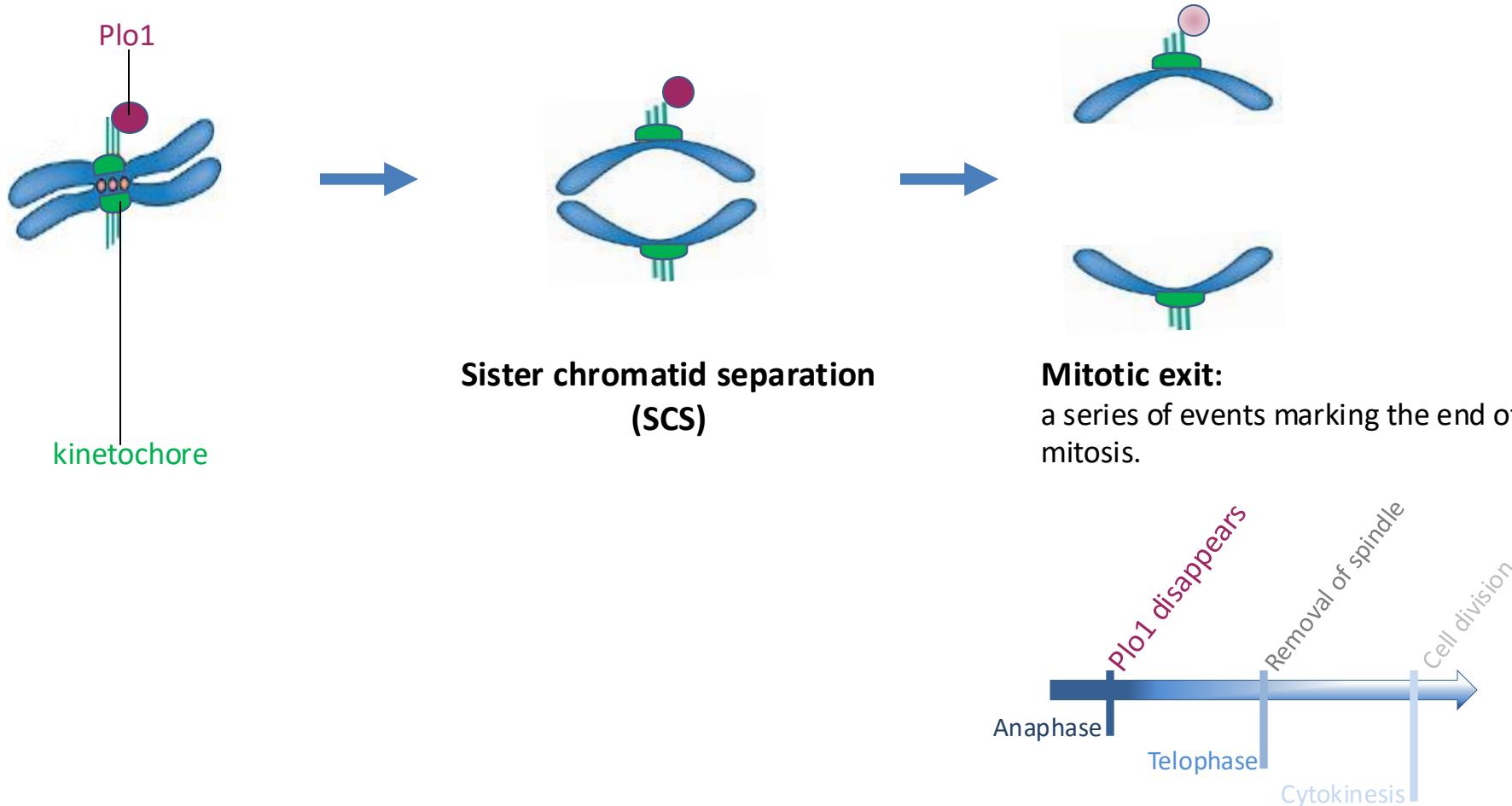
# Anaphase is characterized by chromosome segregation



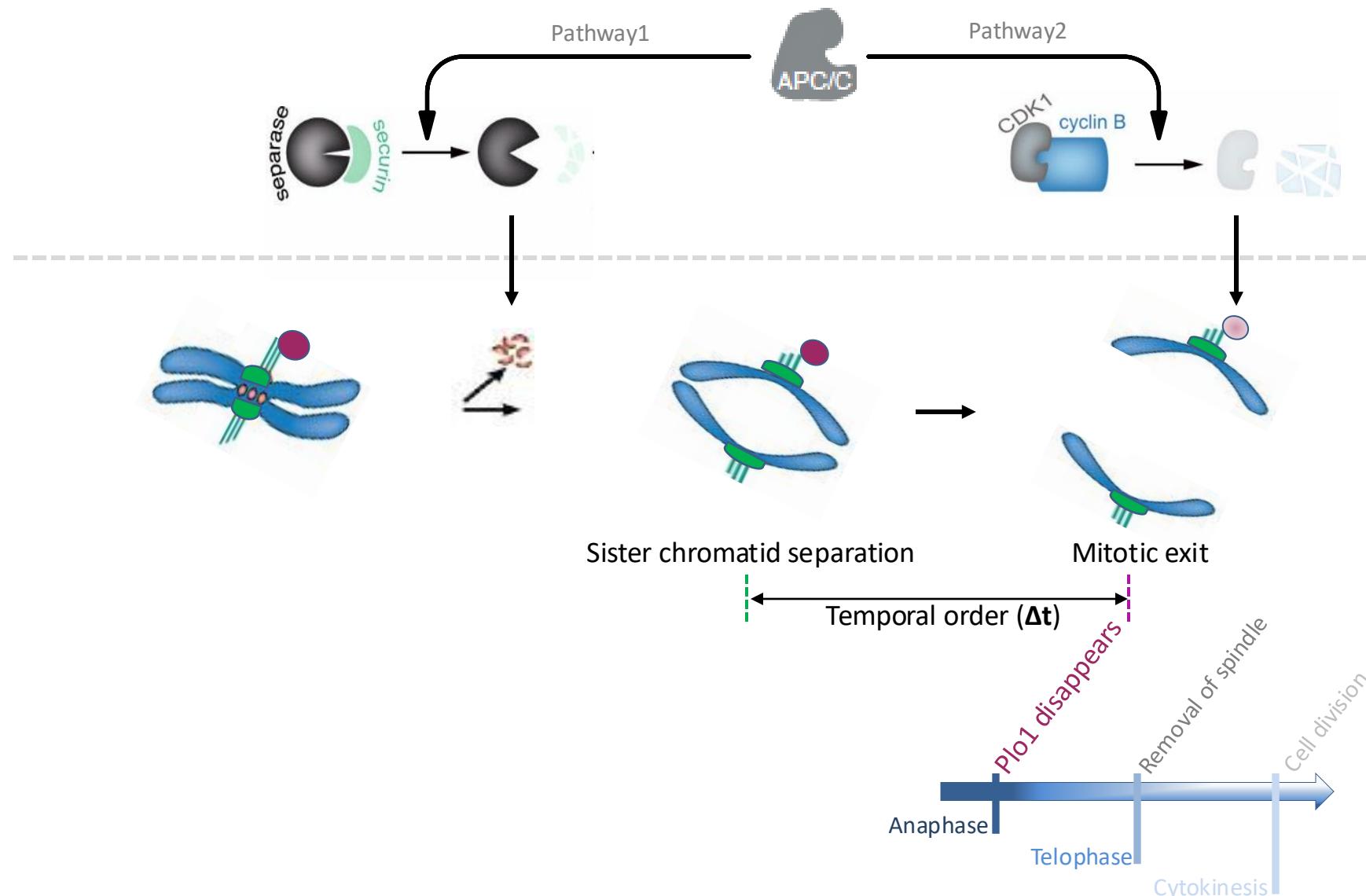
# Anaphase events are temporally ordered

## Anaphase:

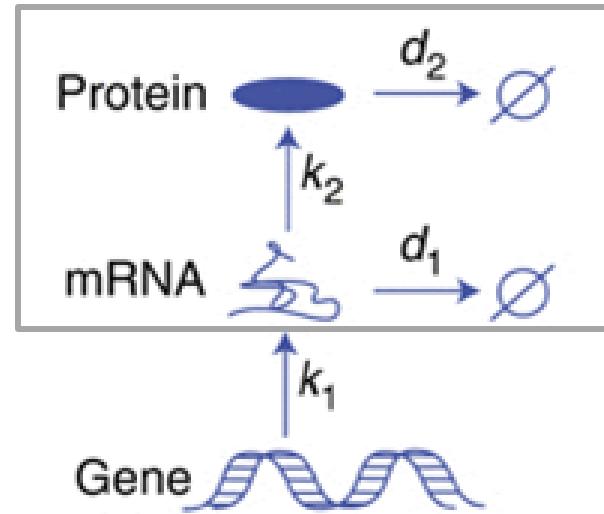
the stage of the cell cycle characterized by chromosome segregation.



# Two independent pathways control anaphase events

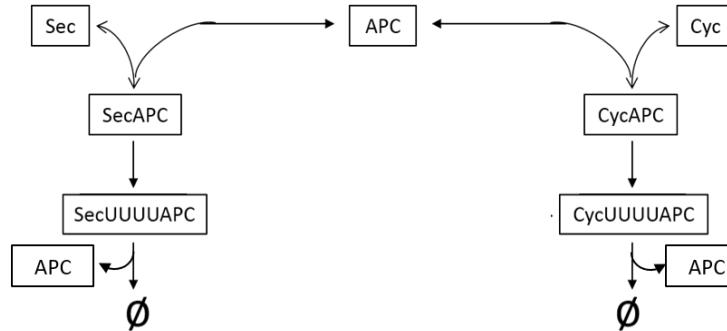


# Deterministic modeling of protein-protein interaction (competition for substrate)



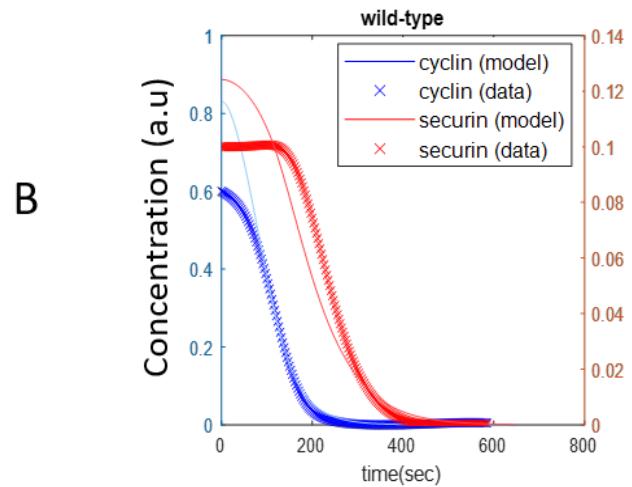
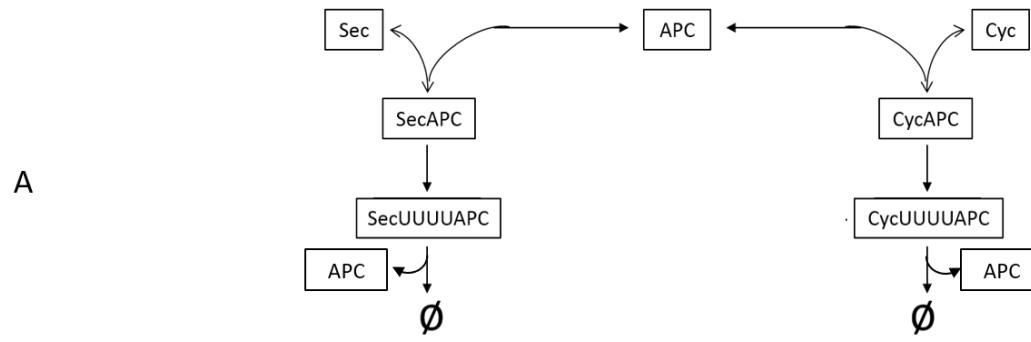
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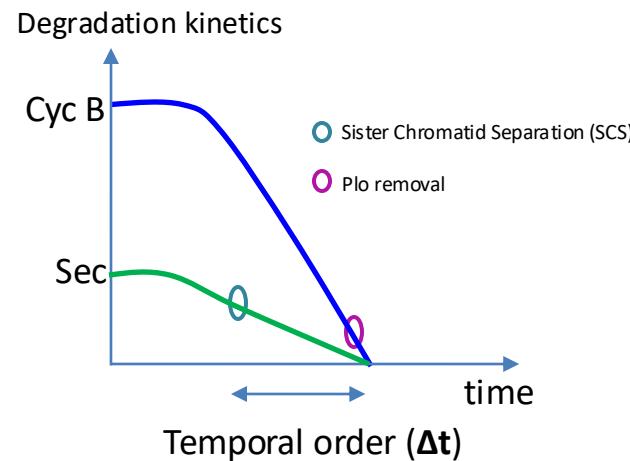


species	rate equations
'Sec'	'SecApc*koff_sec - Apc*Sec*kon_sec'
'Cyc'	'CycApc*koff_cyc - Apc*Cyc*kon_cyc'

# Simulation of protein degradation kinetics (rate equations)



# Kinetic model can be used to predict temporal order



# What do we learn from the calibrated model?

- Mechanism of temporal order maintenance
- Experimental Conditions for reversal of temporal order
- Which proteins drive temporal order variability?

# Double perturbation: a method for terminating cancerous cells in humans

