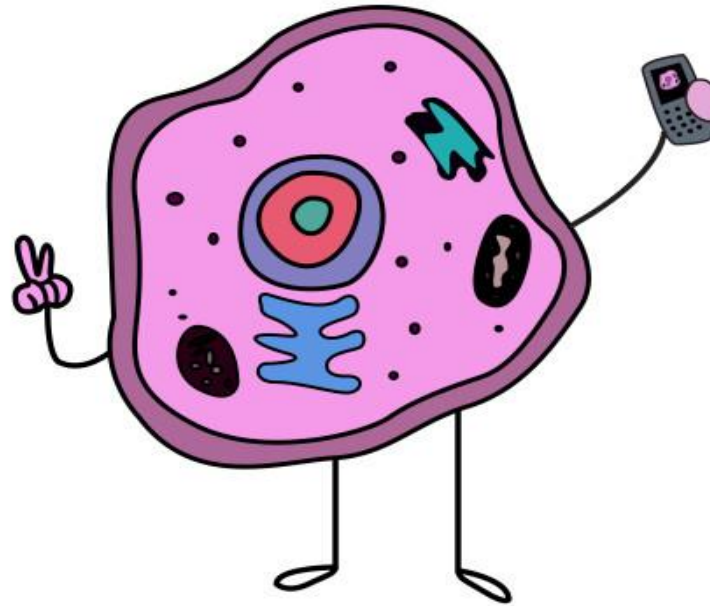


Dynamic modeling of Protein Kinetics

Uchenna Alex Anyaegbunam, Ph.D.

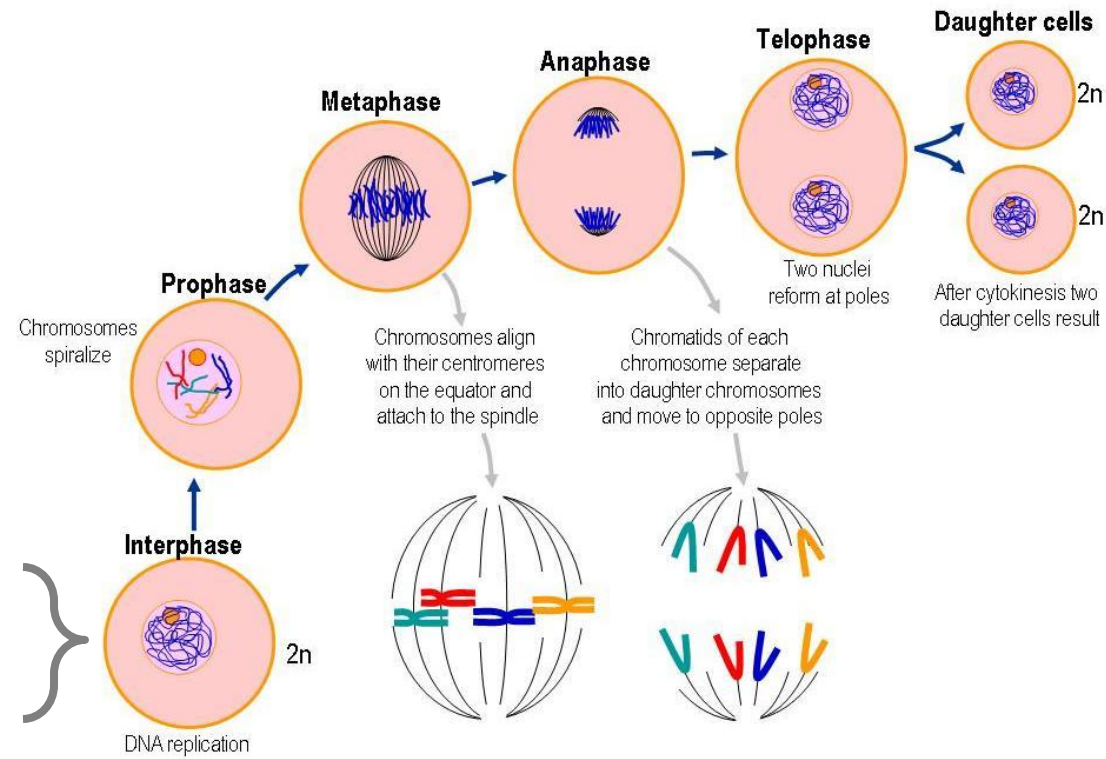
A.G. Prof. Dr. Miguel Andrade
Computational Biology and Data Mining group
Faculty of Biology

The cell reproduces by making an exact copy of itself

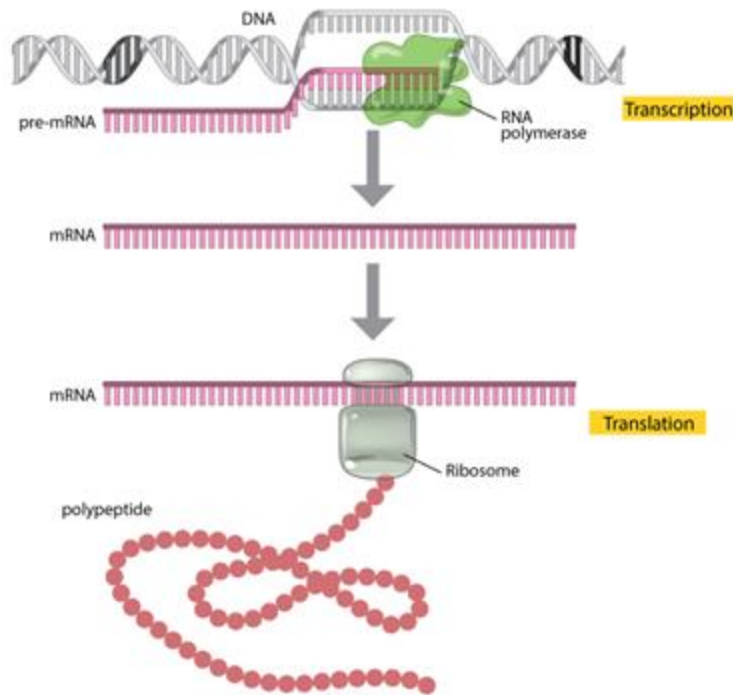


Cell-fie

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?

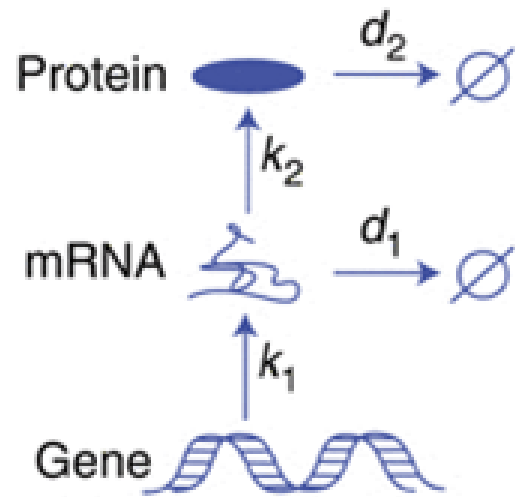
Outline

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

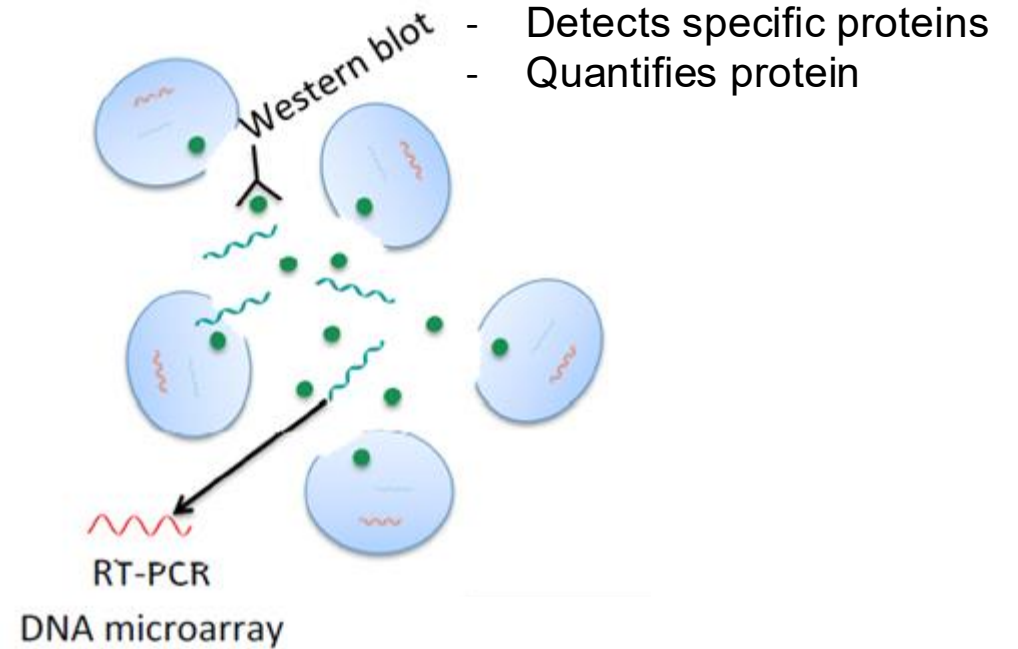
Continuous

Real concentration
of mRNAs/proteins

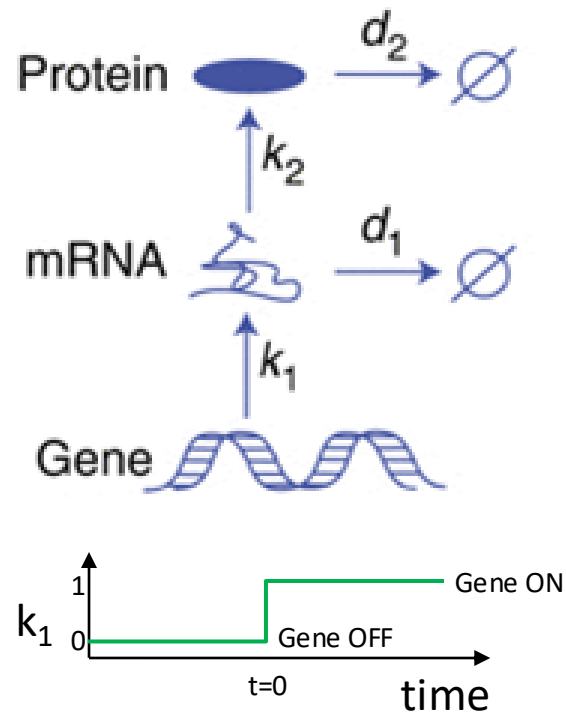
Deterministic

Average behavior of
large molecule numbers

Population techniques



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



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

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

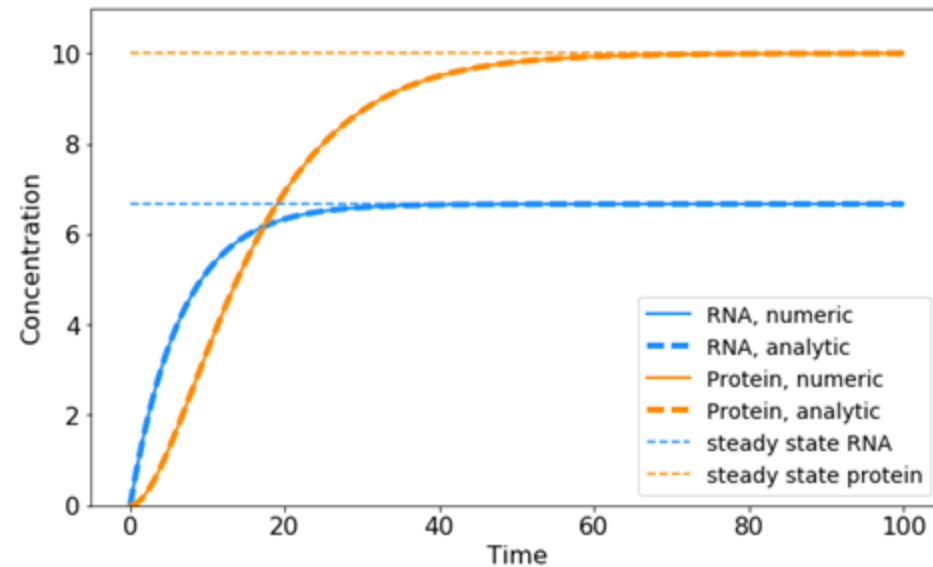
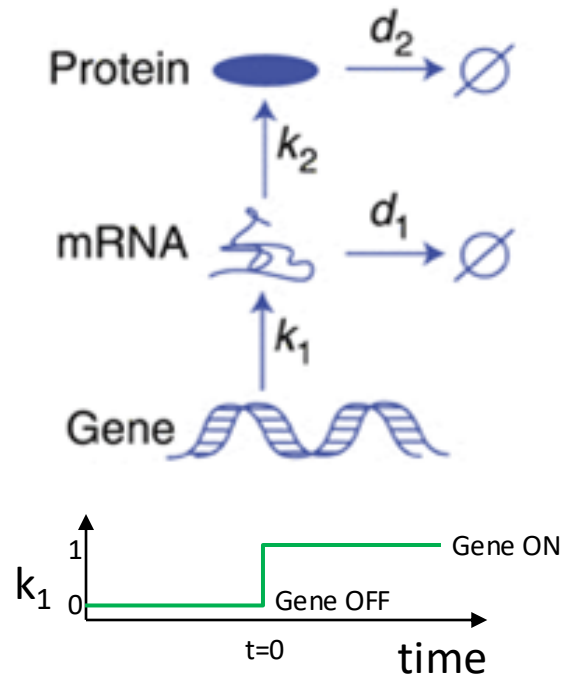
Analytical Solution (by integration)

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

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

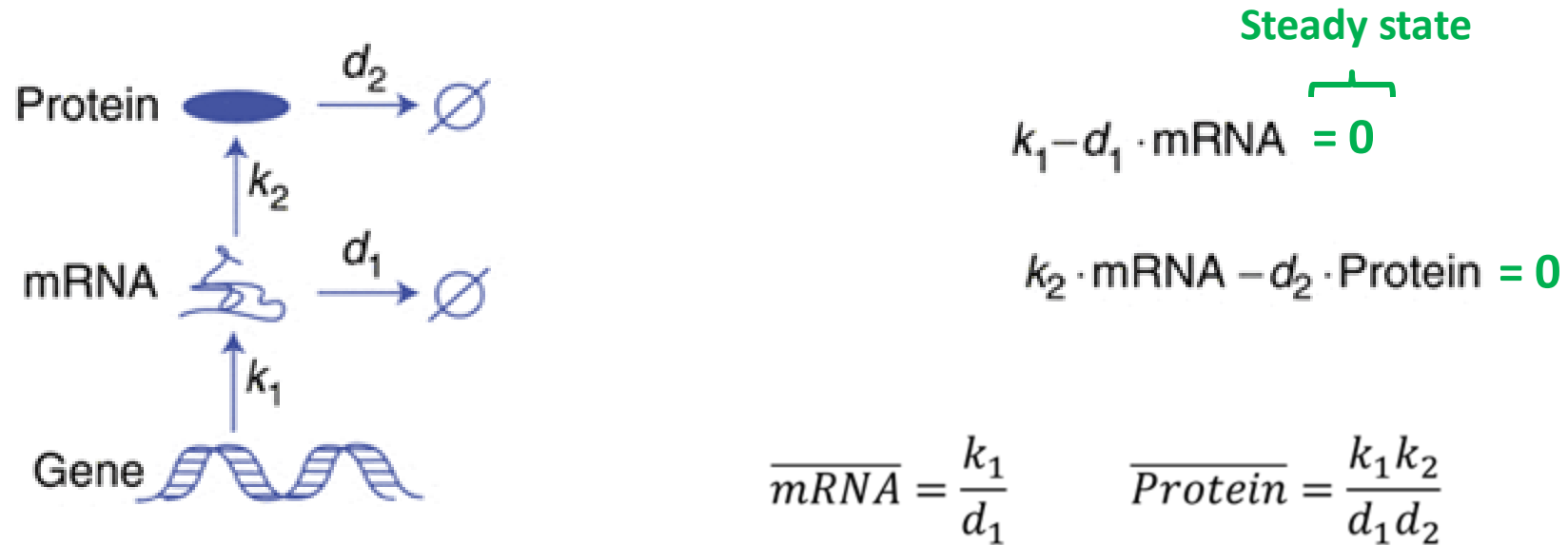
⇒ Approximate solution using numerical integration

Time course of mRNA and protein in response to gene activation



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

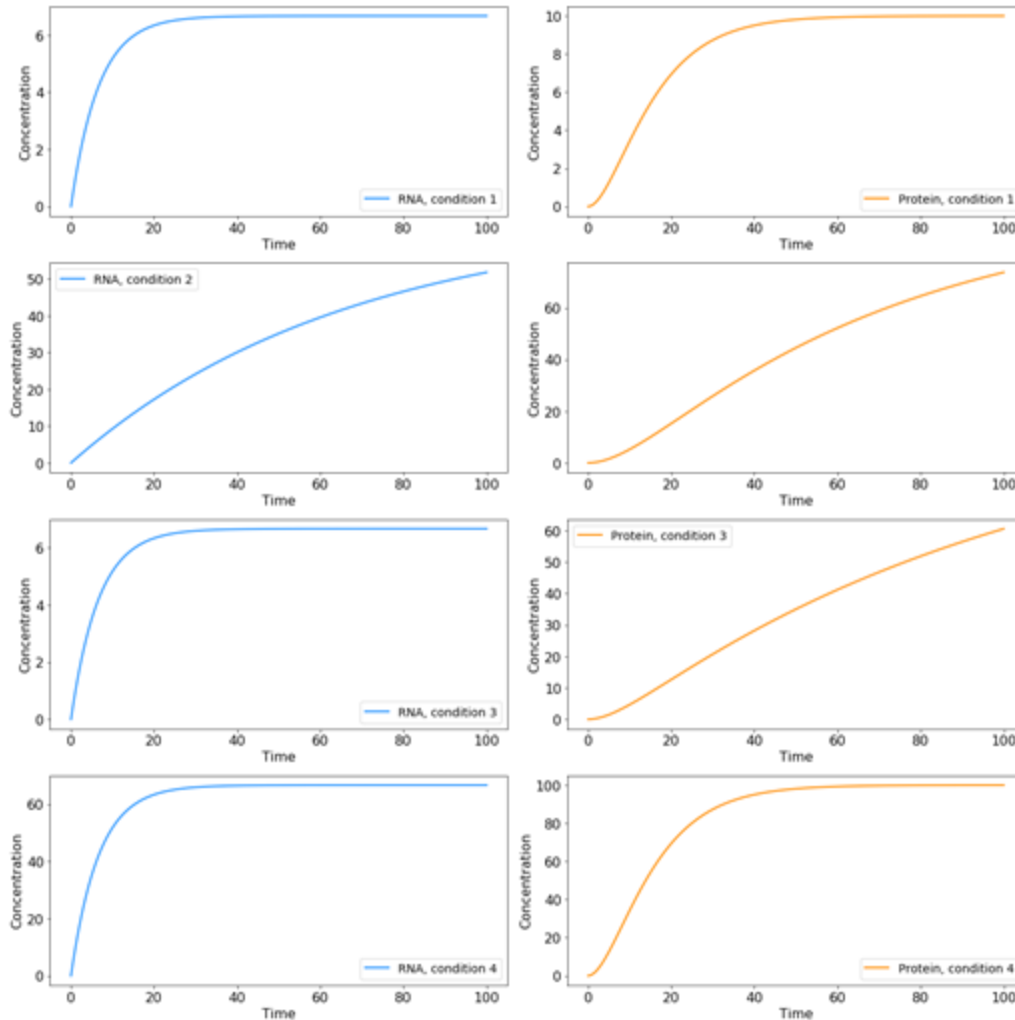
What determines protein expression level at steady state?



Steady state 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



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

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

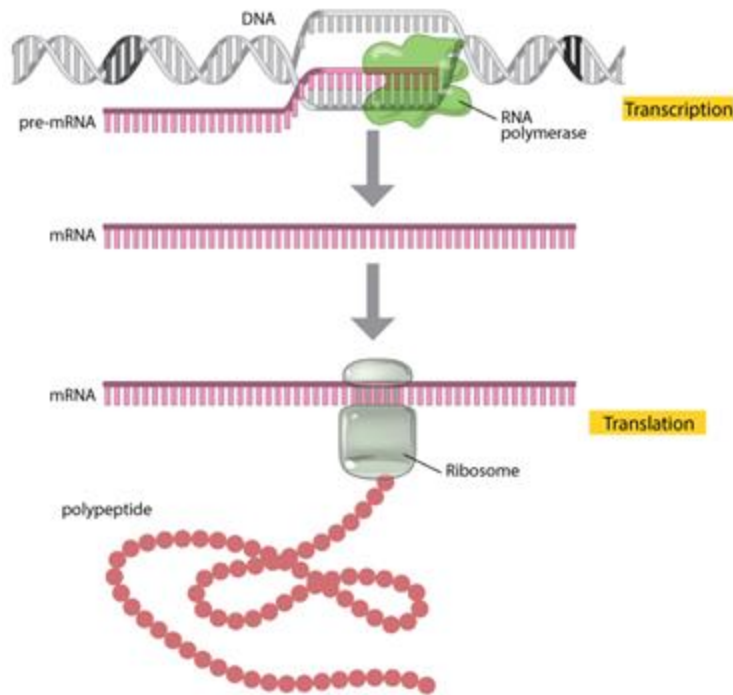
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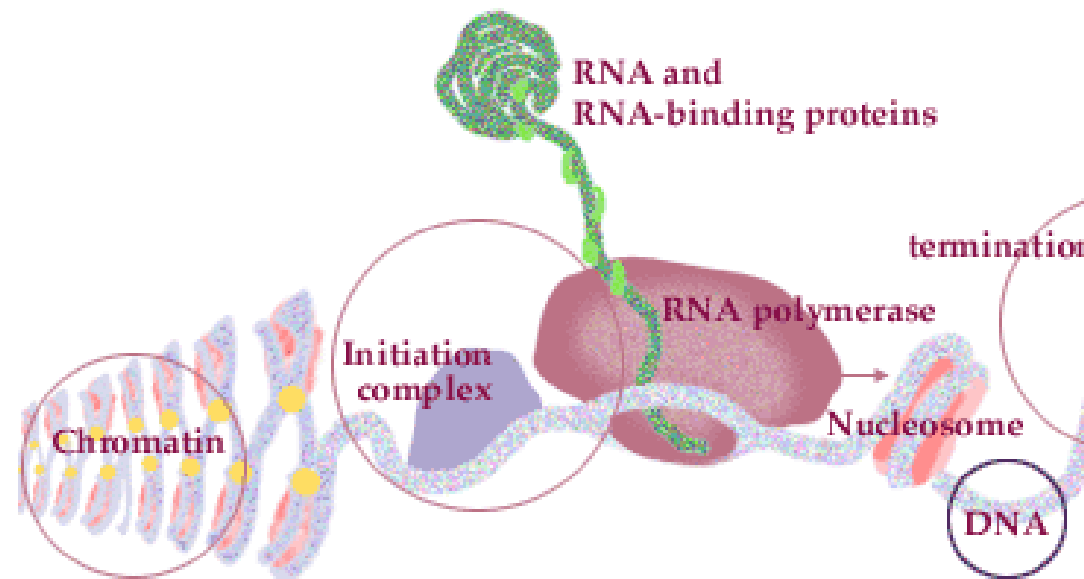
DNA replication: Quantitative description of protein expression



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

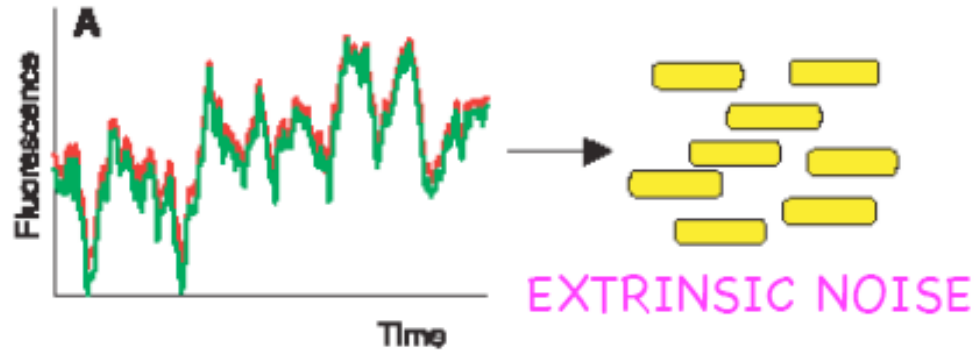


Stochastic dynamics shown for transcription initiation and elongation

Randomness arises from low molecule numbers!

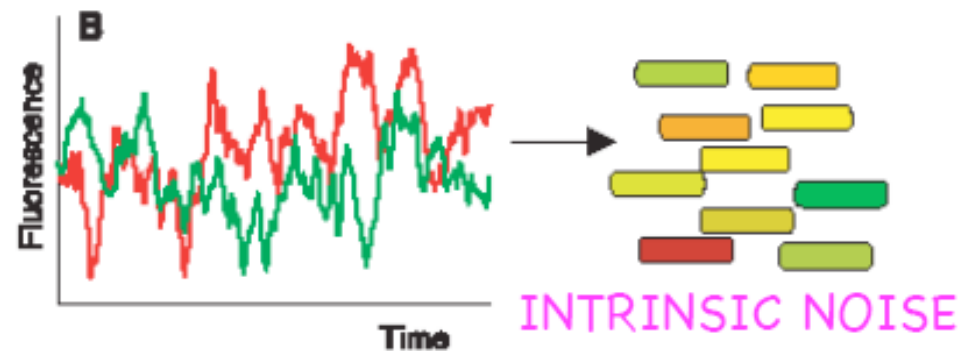
- each cell contains few copies of each gene
- transcription factors often present in low amounts

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

Probabilistic behavior (randomness)
at the single-molecule level

Continuous: Concentration
of mRNAs/proteins

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: $protein \xrightarrow{\gamma_p \cdot protein} protein - 1$

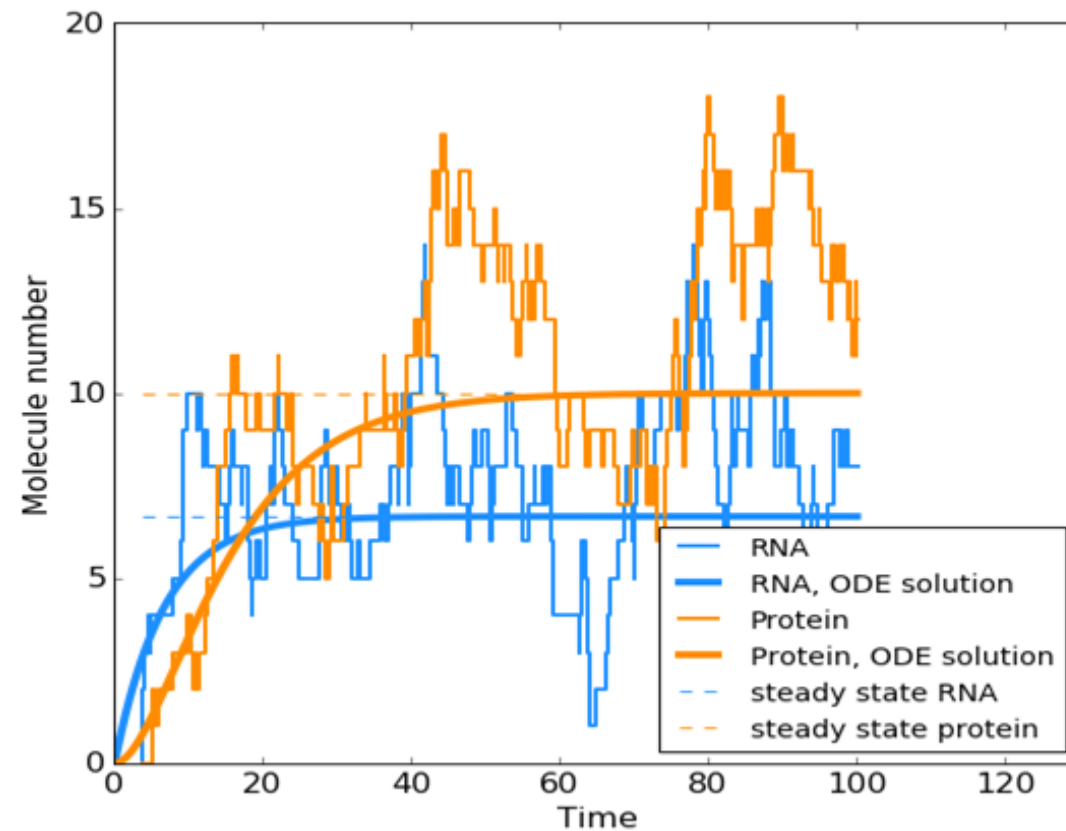
Reactions occur with certain probabilities

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



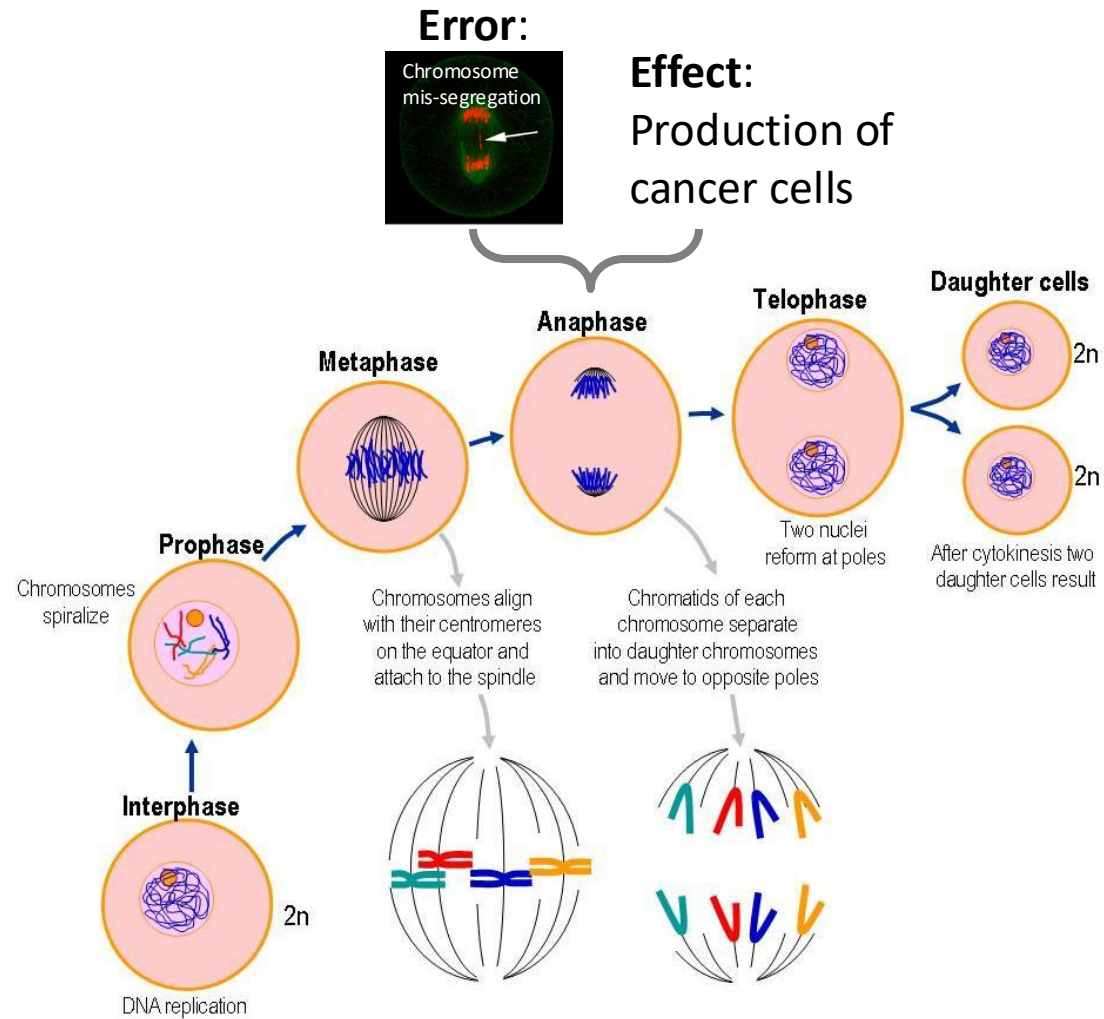
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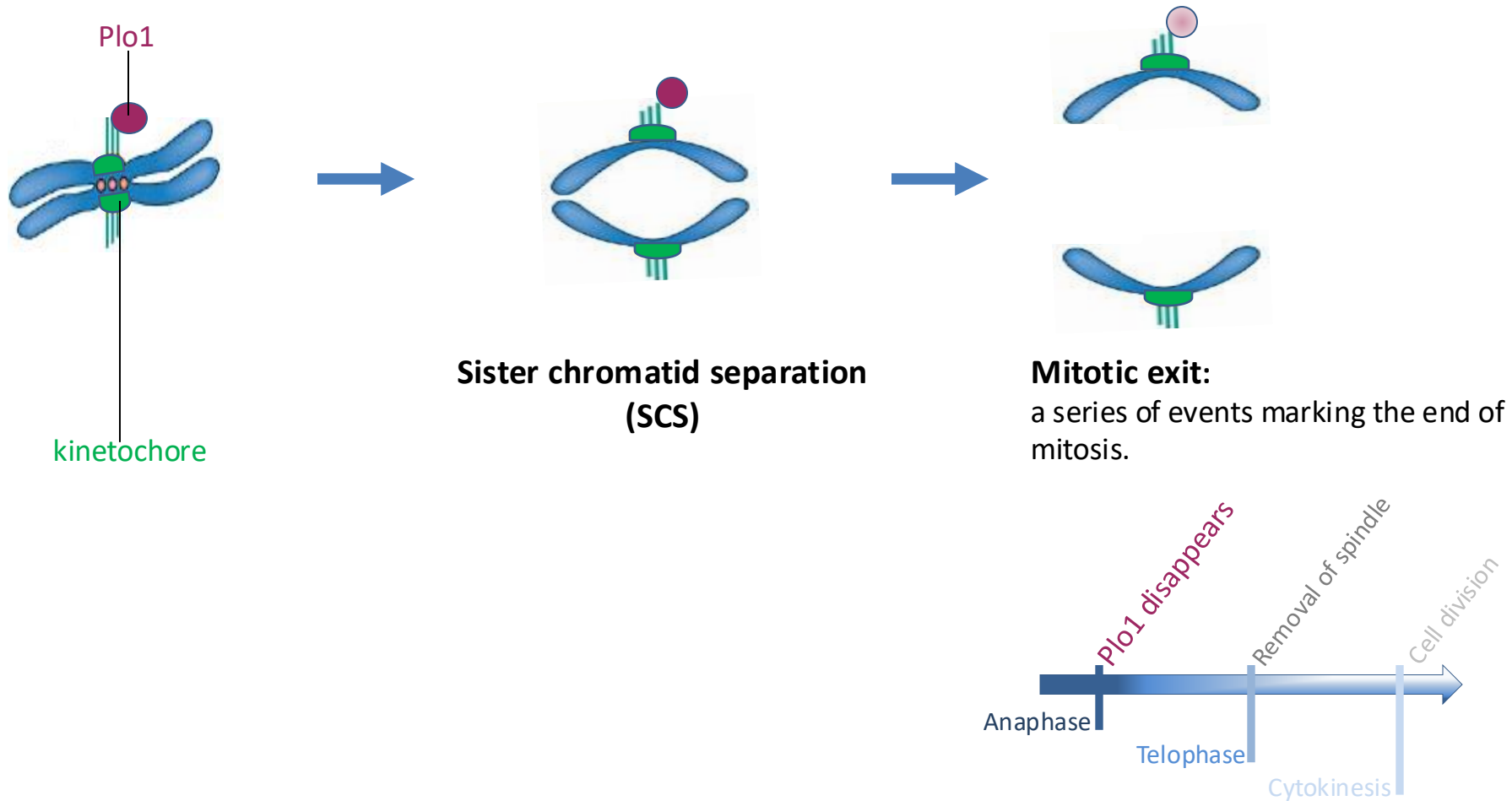
Anaphase is characterized by chromosome segregation



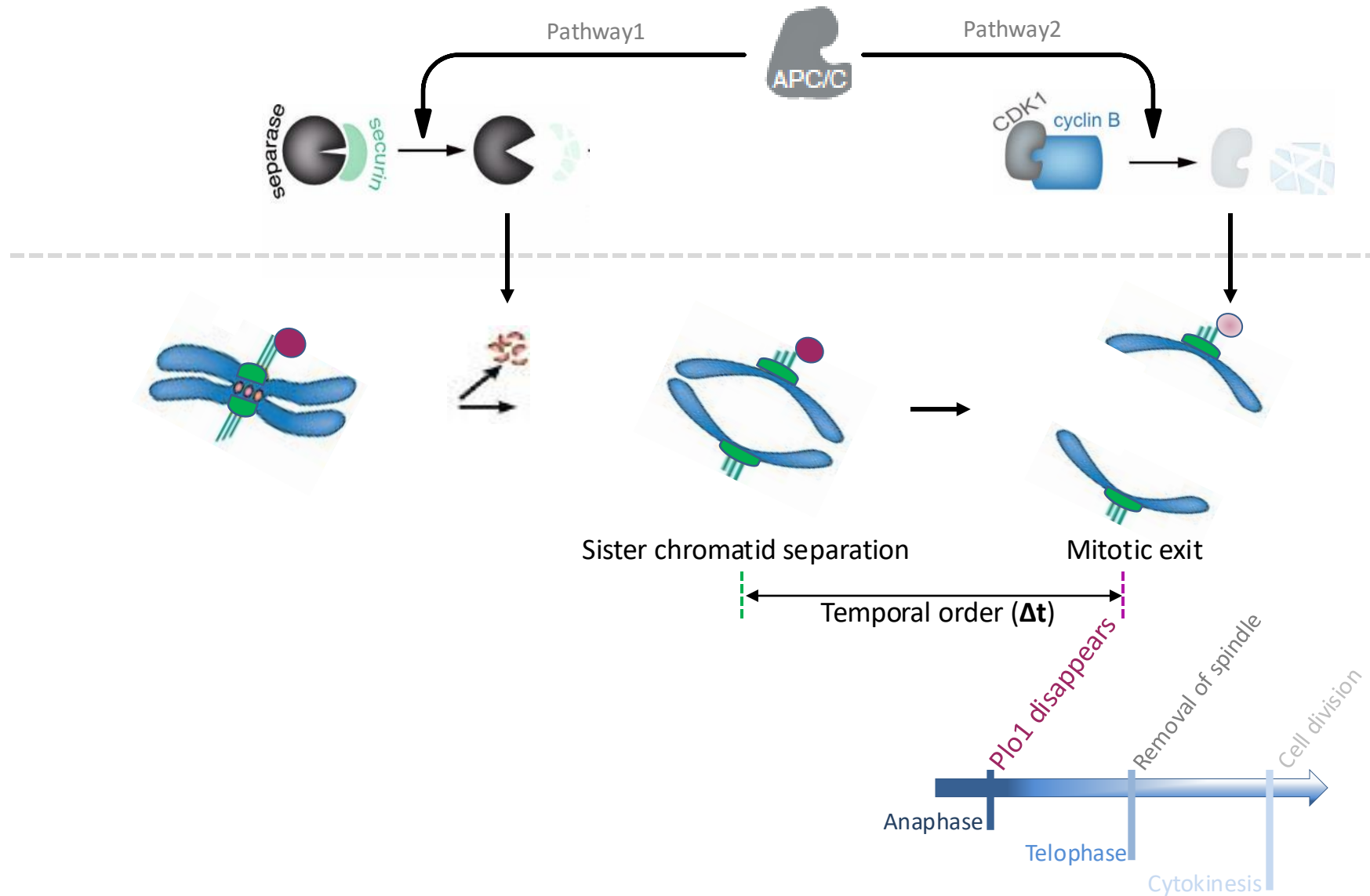
Anaphase events are temporally ordered

Anaphase:

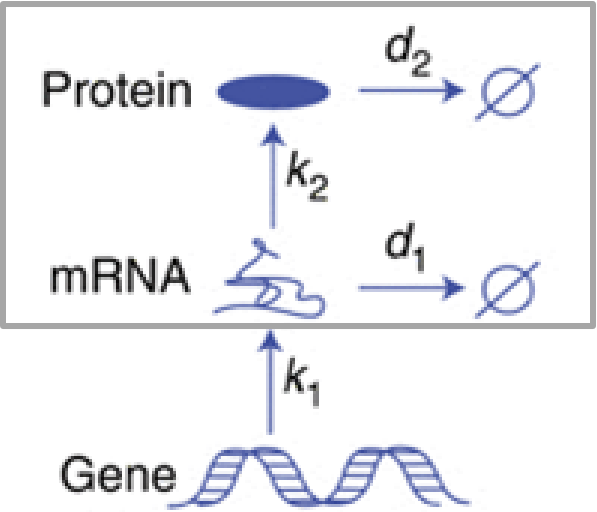
the stage of the cell cycle characterized by chromosome segregation.



Two independent pathways control anaphase events

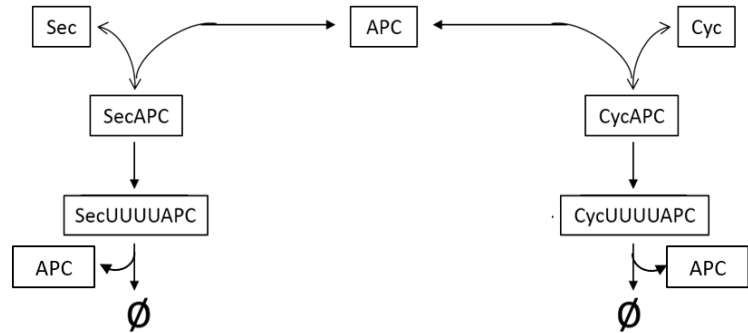


Deterministic modeling of protein-protein interaction (competition for substrate)



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

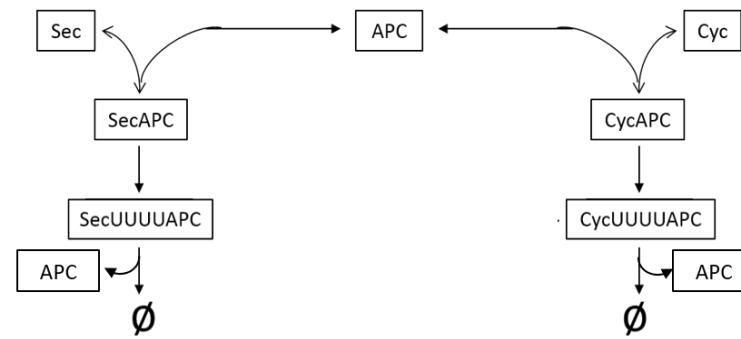
$$\frac{d(\text{Protein})}{dt} = k_2 \cdot \text{mRNA} - d_2 \cdot \text{Protein}$$



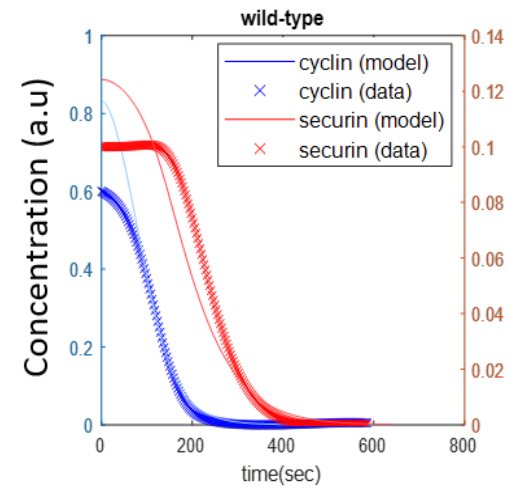
species	rate equations
'Sec'	'SecApc*koff_sec - Apc*Sec*kon_sec'
'Cyc'	'CycApc*koff_cyc - Apc*Cyc*kon_cyc'

Simulation of protein degradation kinetics (rate equations)

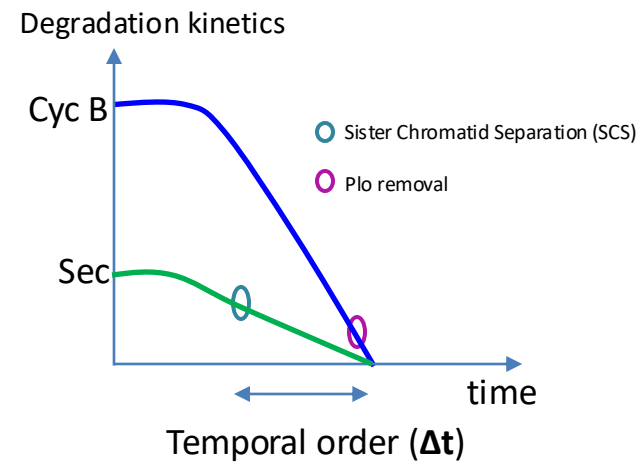
A



B



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

