# Cellular Control Systems with Delays

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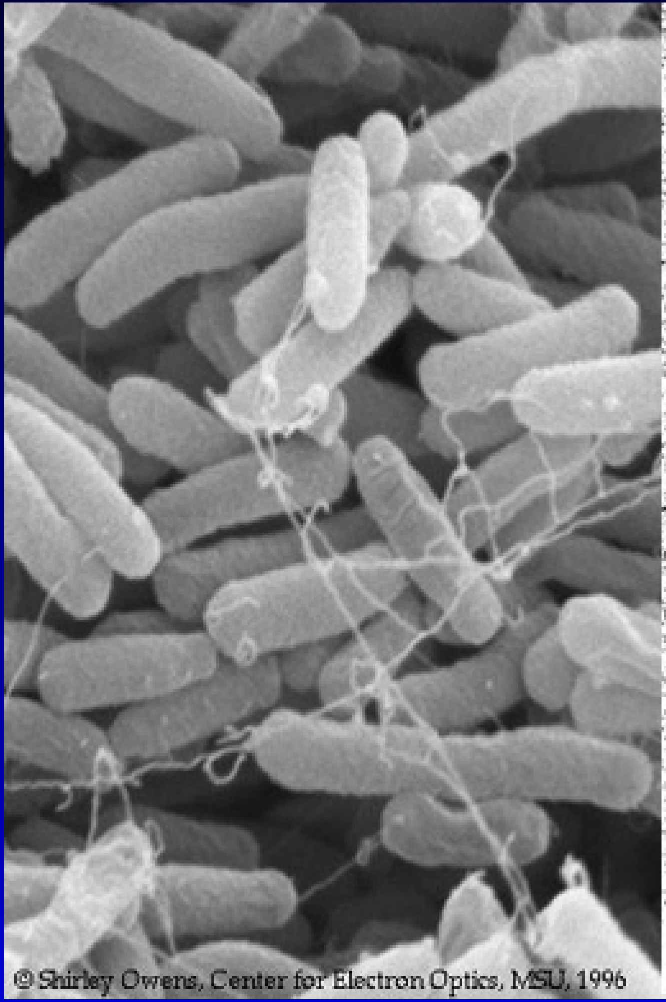
# Abstract

Genetic control models for *Escherichia coli* are presented with delays for transcription and translation. Feedback controls for induction and repression are developed using biochemical kinetics. These techniques are applied to develop models for the *lac* operon, including catabolite repression. Mathematical analyses of the models show Hopf bifurcations and hysteresis effects. The modeling techniques are extended to the regulation of DNA replication and cell growth in *E. coli*.

# *Escherichia coli*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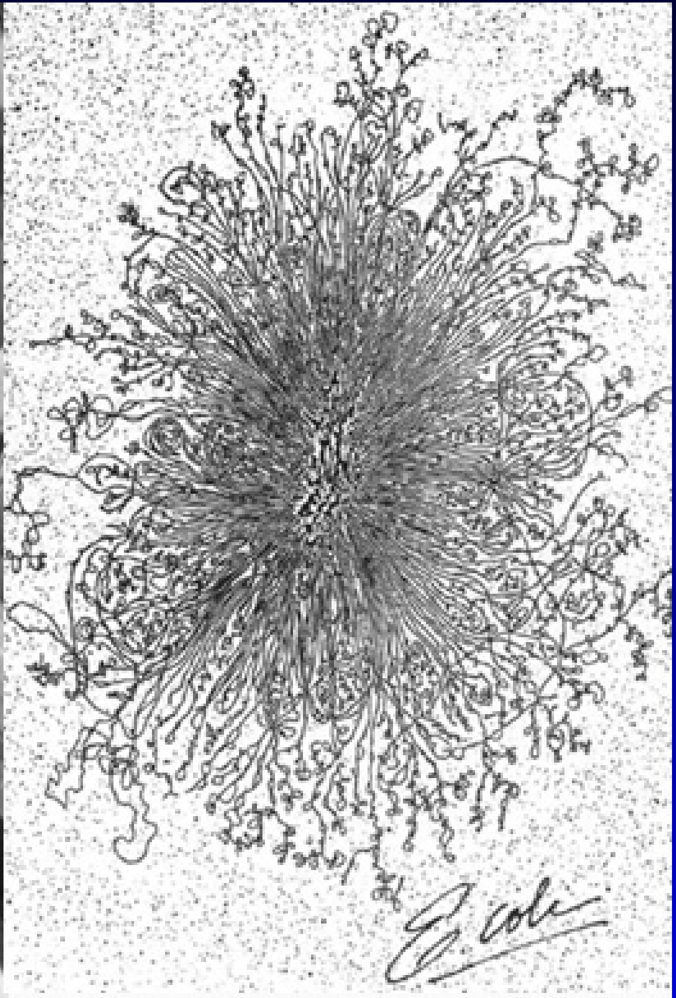

Cells

DNA

# Outline

- Brief History of Induction and Repression Models
- Description of Repression
- Biochemical Kinetics
- Repression Models
- Cellular Control of *lac* Operon
- Models for *lac* Operon
- Results for the Models
- Future Directions

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  - Require negative feedback
  - Enhanced by delays

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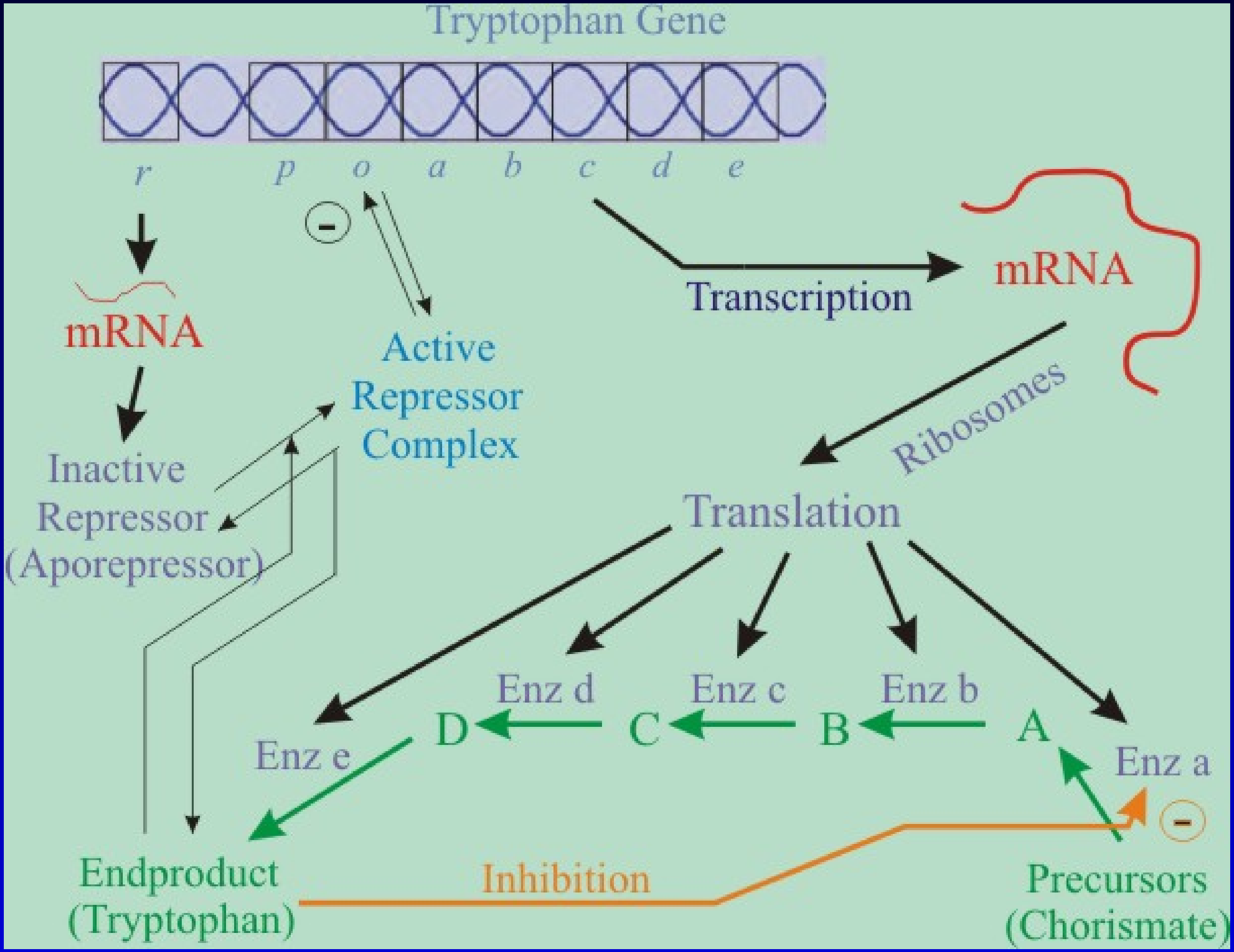
# Repression - *trp* Operon



# Biochemical Equations

## Transcription

With the $\sigma_{70}$ factor, RNA polymerase melts the DNA to form an opening complex. The polymerase sequentially reads the DNA, adding nucleotide triphosphates (NTPs), to produce the completed mRNA.

$$\begin{aligned}
\mathrm{DNA} + \mathrm{NTP} \quad & \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \quad \mathrm{DNA} \cdot \mathrm{NTP} \\
& \underset{+n\mathrm{NTP}}{\overset{k_2}{\longrightarrow}} \quad \mathrm{DNA} + \mathrm{mRNA}
\end{aligned}$$

# Biochemical Equations

## Translation

Shortly after transcription begins, ribosomes attach to the elongating mRNA and translate the triplet codons by accepting the appropriate charged tRNAs and adding amino acids (AA) to the new protein (R).

$$\begin{aligned}
\mathrm{mRNA} + \mathrm{tRNA}_{\mathrm{fMet}} \quad & \overset{k_{+3}}{\underset{k_{-3}}{\rightleftharpoons}} \quad \mathrm{mRNA} \cdot \mathrm{tRNA}_{\mathrm{fMet}} \\
& \overset{k_4}{\underset{+i\mathrm{AA}}{\longrightarrow}} \quad \mathrm{mRNA} + \mathrm{R}
\end{aligned}$$

# Biochemical Equations

## Repressor Binding

This simplified model assumes that $\rho$ molecules of the endproduct/repressor protein, R, bind to the operator region of the DNA to prevent transcription.

$$\rho\mathrm{R} + \mathrm{DNA} \underset{k_{-5}}{\overset{k_{+5}}{\rightleftharpoons}} \mathrm{DNA} \cdot \rho\mathrm{R}$$

# Biochemical Kinetics

## Quasi-Steady State

Assume the intermediate complexes are formed rapidly and are essentially in equilibrium.

$$\begin{aligned}\frac{d[\mathrm{DNA}\cdot\mathrm{NTP}]}{dt} &= k_{+1}[\mathrm{DNA}][\mathrm{NTP}] \\ &\quad -(k_{-1}+k_2)[\mathrm{DNA}\cdot\mathrm{NTP}] = 0\end{aligned}$$

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Similar argument for the translation intermediate.

# Biochemical Kinetics

## Fast Equilibrium

Assume the repressor and operator region of tryptophan operon rapidly equilibrate.

$$\begin{aligned}\frac{d[\mathrm{DNA}\cdot\rho\mathrm{R}]}{dt} &= k_{+5}[\mathrm{DNA}][\mathrm{R}]^{\rho} - k_{-5}[\mathrm{DNA}\cdot\rho\mathrm{R}] \\ &= 0\end{aligned}$$

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# Conservation Law

Assume the total DNA is in constant concentration and satisfies the conservation law

$$\begin{aligned}[\mathrm{DNA}]_T &= [\mathrm{DNA}] + [\mathrm{DNA}\cdot\mathrm{NTP}] + [\mathrm{DNA}\cdot\rho\mathrm{R}] \\ &= [\mathrm{DNA}](1 + K_1[\mathrm{NTP}] + K_5[\mathrm{R}]^{\rho})\end{aligned}$$

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Negative feedback by the repressor, R

# DE for Transcription

Let $\mu$ be the decay and dilution rate for [mRNA], then from the kinetic equations above the differential equation describing the production of mRNA is

$$\begin{aligned}\frac{d[\mathrm{mRNA}]}{dt} &= k_2[\mathrm{DNA}\cdot\mathrm{NTP}] - \mu[\mathrm{mRNA}] \\ &= \frac{k_2[\mathrm{DNA}]_T[\mathrm{NTP}]}{1 + K_1[\mathrm{NTP}] + K_5[\mathrm{R}]^\rho} - \mu[\mathrm{mRNA}]\end{aligned}$$

# Repression Models

Let $x_1(t)$ be the concentration of mRNA and $x_n(t)$ be the endproduct.

$$\begin{aligned} \dot{x}_1 &= \frac{a_1}{1 + K x_n^\rho} - b_1 x_1 \\ \dot{x}_i &= a_i x_{i-1} - b_i x_i, \quad i = 2 \ldots n \end{aligned}$$

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Adding delays for transcription and translation

$$\begin{aligned}\dot{x}_1(t) &= \frac{a_1}{1 + K x_n^\rho(t-\tau)} - b_1 x_1(t) \\ \dot{x}_i(t) &= a_i x_{i-1}(t) - b_i x_i(t), \quad i = 2 \ldots n\end{aligned}$$

# Mathematical Results

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  - Periodic solutions after Hopf bifurcation
  - Period of oscillation is 2-4 times delay

# Linear Analysis - DDE

$$\begin{aligned}\begin{pmatrix}\dot{x}_1(t)\\ \dot{x}_2(t)\end{pmatrix} &= \begin{pmatrix}-b_1 & 0\\ a_2 & -b_2\end{pmatrix}\begin{pmatrix}x_1(t)\\ x_2(t)\end{pmatrix}\\ &\quad + \begin{pmatrix}0 & f'(\bar{x}_2)\\ 0 & 0\end{pmatrix}\begin{pmatrix}x_1(t-\tau)\\ x_2(t-\tau)\end{pmatrix}\end{aligned}$$

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Characteristic equation

$$\begin{vmatrix} -b_1 - \lambda & f'(\bar{x}_2)e^{-\lambda\tau} \\ a_1 & -b_2 - \lambda \end{vmatrix} = 0$$

or

$$(\lambda + b_1)(\lambda + b_2) - a_2 f'(\bar{x}_2)e^{-\lambda\tau} = 0$$

# Hopf Bifurcation

Since $f'(\bar{x}_2) < 0$, the characteristic equation with $A \equiv -a_2 f'(\bar{x}_2)$ is

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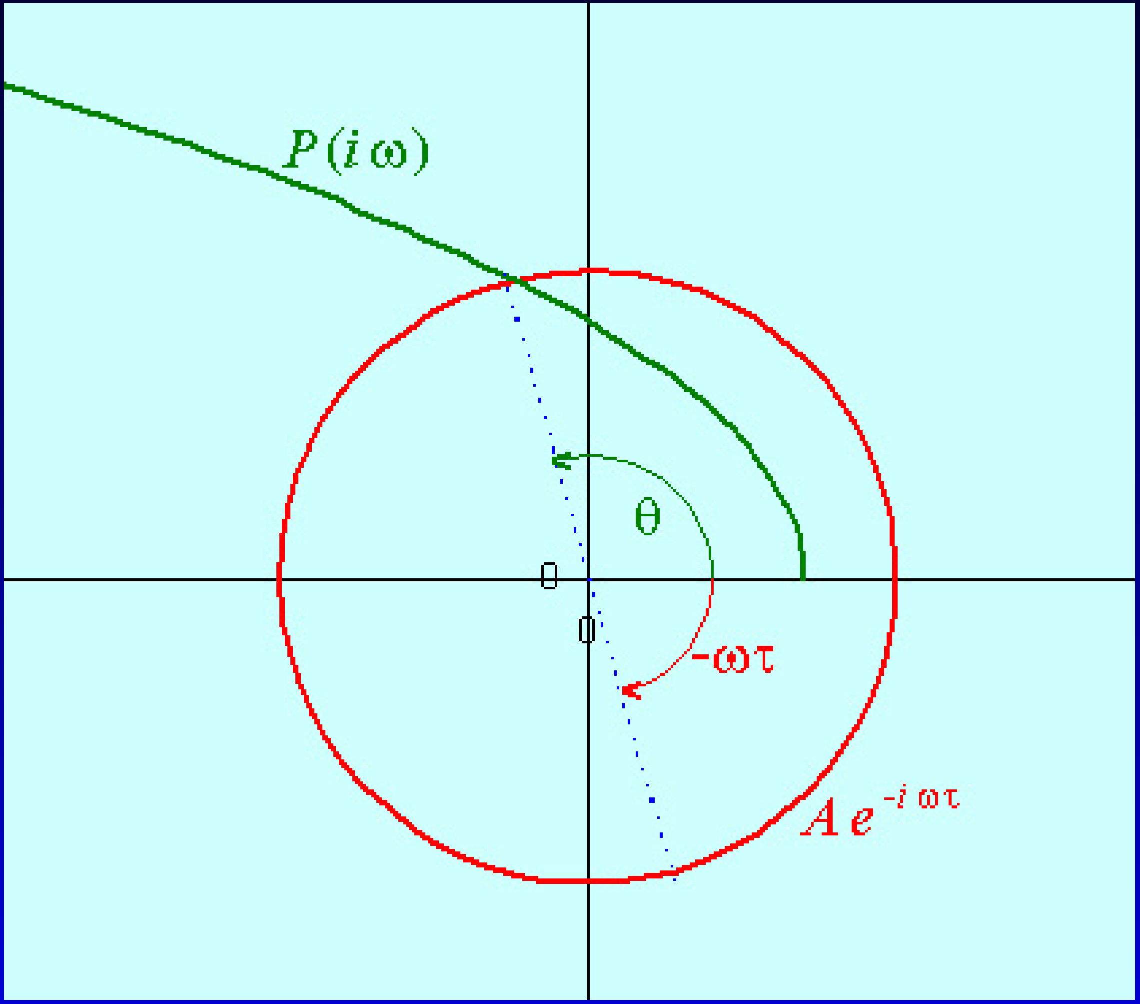
and

$$\begin{aligned} \arg(P(i\omega)) &= \arctan\left(\frac{i\omega}{b_1}\right) + \arctan\left(\frac{i\omega}{b_2}\right) \\ \text{or} \quad \theta &= \pi - \omega\tau \end{aligned}$$

# Hopf - Argument Principle



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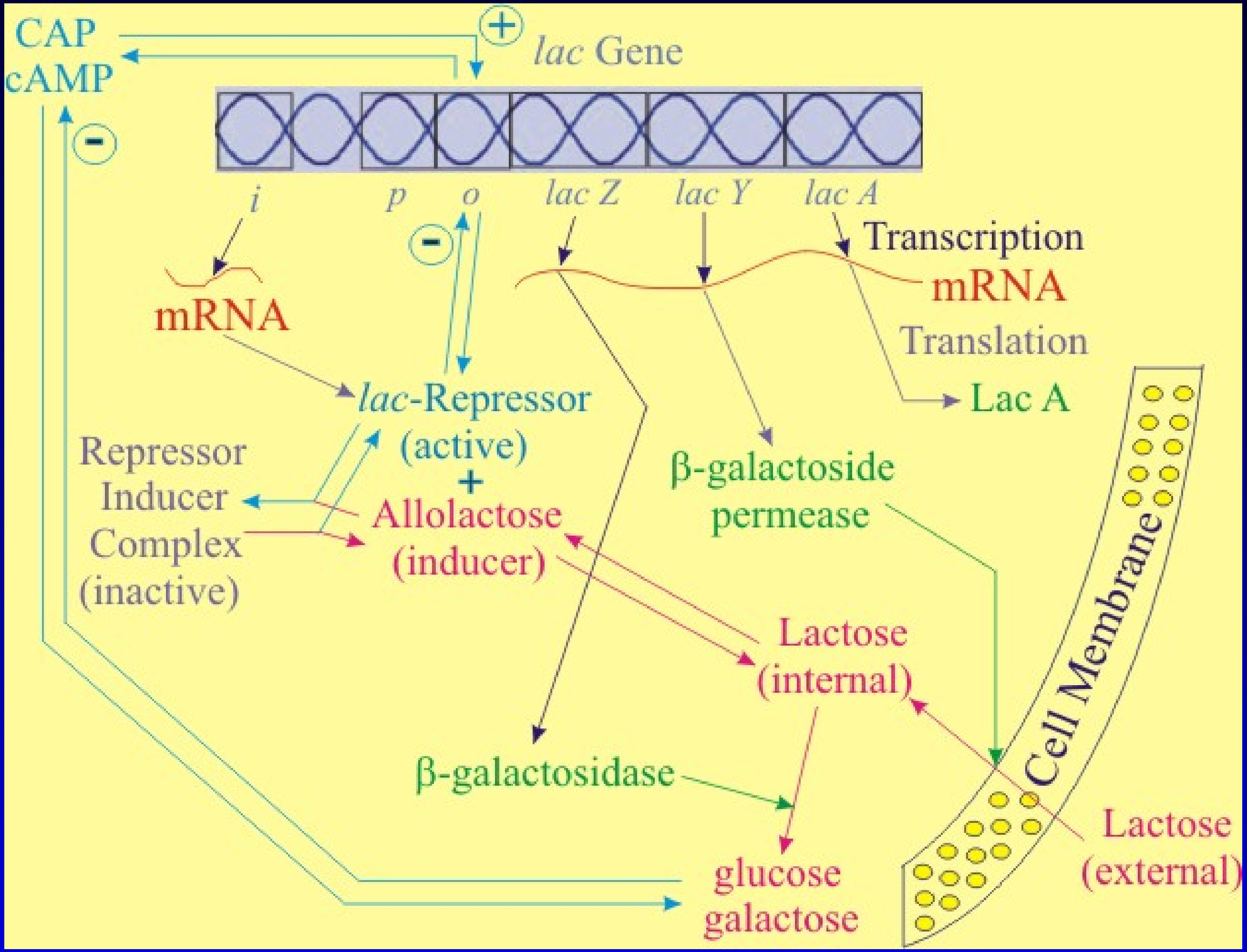
    - Stable Model that matches Experiments

# The *lac* Operon



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Saturation enzyme kinetic or S-curve function

# Mathematical Results

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- Delays destabilize the Model
- No oscillations in the Physiological range

# *lac* Model A - Mahaffy(1984)

Let $x_1$ be [cAMP], $x_2$ be [mRNA], $x_4$ be [Lactose$_i$], $x_3$ be [$\beta$-galactosidase], and $x_5$ be [Glucose]

$$\begin{aligned}
\dot{x}_1(t) &= \frac{1}{1 + x_5^\gamma(t-\tau_1)} - b_1 x_1(t) \\
\dot{x}_2(t) &= \frac{x_1(t)(1 + K_2 x_4^\rho(t-\tau_2))}{(1 + K_3 x_1(t))(1 + K_4 x_4^\rho(t-\tau_2)) + K_5} \\
&\quad -b_2 x_2(t) \\
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Assumes $\beta$-galactosidase is rate limiting.

# *lac* Model B - Mahaffy(1984)

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# Results - $lac$ Models (1984)

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Simplified with no catabolite repression
Let $x_1$ be [mRNA], $x_2$ be [$\beta$-galactoside permease],
$x_3$ be [$\beta$-galactosidase], and $x_4$ be [Lactose]

$$\begin{aligned}
\dot{x}_1(t) &= \frac{1 + k_1 x_4^\rho(t-\tau)}{1 + x_4^\rho(t-\tau)} - b_1 x_1(t) \\
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Examines the induction of both enzymes by lactose.

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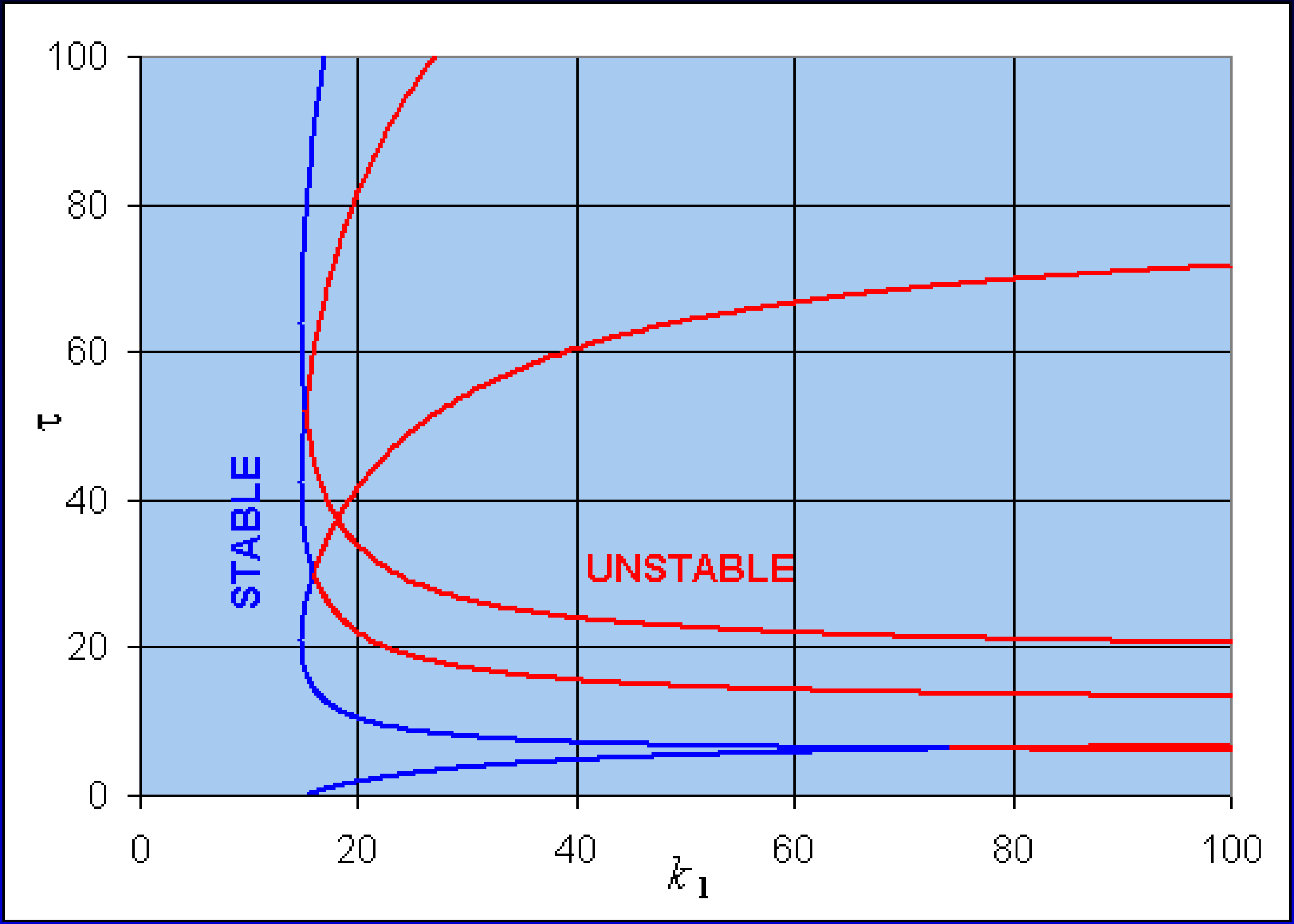
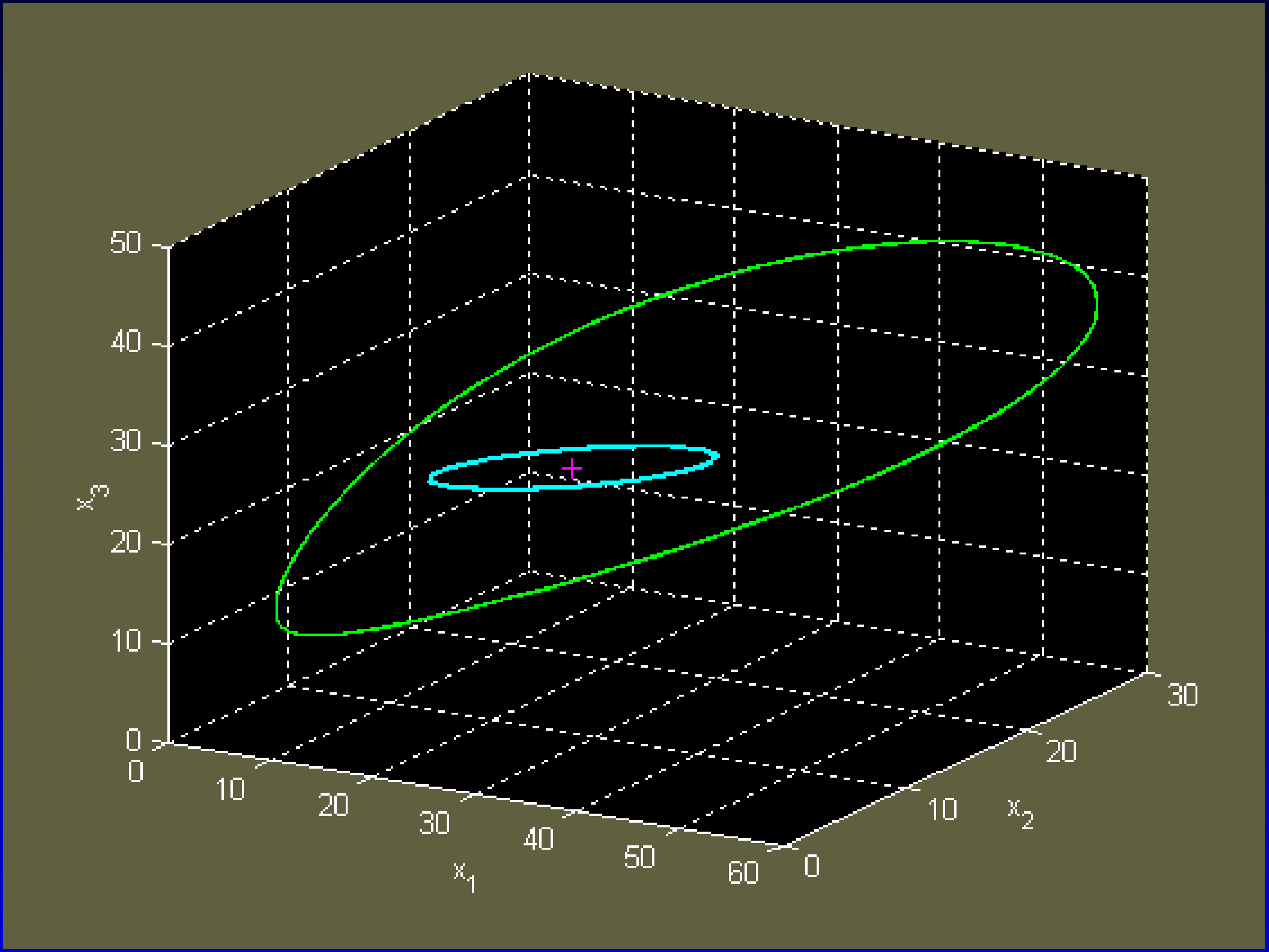
- Only stable solutions in Physiological range

# Bifurcation Diagram



# Model Simulation



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