Physiological Adaptation

Microbial Physiology
Module 4
Topics

- Coordination of Metabolic Reactions
- Regulation of Enzyme Activity
- Regulation of Gene Expression
- Global Control, Signal Transduction and Two-component System
- Specific Examples
Topic 1: Coordination of Metabolic Reactions

- Adaptation to constantly changing environment could involve the coordination of thousands of chemical reactions
  - respond to changes in...
    - nutrient availability
    - temperature
    - pH
    - harmful agents
      - bacteriocins
- Chemical reactions are driven by enzymes
- Enzymes are encoded by genes
Relationship between genotype and phenotype

Gene

- Regulatory genes
- Gene product interactions
- Environmental effects

Gene (DNA) → RNA → Protein

Phenotypic effect

- Cell-cell interactions
- Effect on cell
  - Effect on cell
  - Effect on population
  - Effect on biosphere
Coordination of Independent Pathways

- Carbohydrates
  - Glucose
  - Phosphoglycerate
  - Phosphoenolpyruvate
  - Pyruvate
  - Acetyl-CoA
  - Oxaloacetate
  - α-Ketoglutarate
- Lipids
  - Fatty Acids
- Proteins
- Nucleic Acids
  - Ribose
  - Pyrimidines
  - Purines
- Amino acids
Experiment 1

- *E. coli* cells cultured in minimal medium
- $^{14}$C-glycerol added as carbon source
  - monitor carbon movement into and out of cell
- Small number of cells added to the medium
  - bacterial growth monitored
  - cells were removed and media examined
Experiment 1: Observations and Conclusions

- **Observations**
  - $^{14}$C was present only as glycerol and $^{14}$CO$_2$
  - when growth stopped
    - no $^{14}$C-glycerol
    - mostly $^{14}$CO$_2$, small traces with macromolecules

- The rate of formation of the basic building blocks closely matches their utilisation rate
  - amino acids
  - nucleotides
Experiment 2

- *E. coli* cells cultured in minimal medium
- Supplemented with $^{14}$C-glycerol and histidine
- Bacterial growth monitored
- Once stopped, amino acid content of cells was examined
Observations
- little or no $^{14}C$-histidine in the cells
- all other amino acids were composed of $^{14}C$
- $^{14}C$ in the medium was as CO$_2$

Conclusion
- histidine present in cells has come from the medium
- all other amino acids were synthesised using the $^{14}C$ provided by glycerol from the medium
- Cell must be able to recognise histidine in the medium, use it and shut down the synthesis mechanism
Experiment 3

- *E. coli* growing in minimal medium supplemented with glucose and lactose
- Glucose is the preferred C-source for *E. coli*
  - can use lactose
- Bacterial growth was monitored
  - also monitored levels of glucose and lactose
Experiment 3: Observations and Conclusions

**Observations**
- Cells grew fastest while glucose was present in the medium
- Lactose levels remained unchanged
- Growth paused when glucose was exhausted
- Growth resumed (at a lesser rate) using lactose

**Conclusions**
- Cells must be able to detect the presence of glucose and react by shutting down other C-source pathways
- Once glucose is exhausted, other pathways are then activated
“All major fuelling, biosynthetic and polymerization pathways of the cell are subject to powerful, independently adjustable controls that bring order out of the potential chaos of a system composed of thousands of working parts”
Topic 2

Regulation of Enzyme Activity
Overview of Regulation

- **Gene A**: Enzyme A is unregulated, catalyzing the conversion of Product from Substrate.
- **Gene B**: Enzyme B is regulated at the translational level, with no Product.
- **Gene C**: Enzyme activity is regulated at the transcriptional level, with no mRNA.
- **Gene D**: No enzyme or mRNA.

**Translation & Transcription**
- mRNA levels are indicated for each gene.
Feedback Inhibition

- end-product of a pathway is capable of inhibiting an earlier (usually the first) step in a biosynthetic pathway
Feedback Inhibition: A reversible and dynamic process

At low end-product concentrations...

Starting substrate
- Enzyme A
- 1st Intermediate
  - Enzyme B
  - 2nd Intermediate
    - Enzyme C
    - 3rd Intermediate
      - Enzyme D
      - End Product

End-product accumulates

As end-products build up within the cell...

Starting substrate
- Enzyme A
- 1st Intermediate
  - Enzyme B
  - 2nd Intermediate
    - Enzyme C
    - 3rd Intermediate
      - Enzyme D
      - End Product

Feedback inhibition

As end-products are used by the cell...

Starting substrate
- Enzyme A
- 1st Intermediate
  - Enzyme B
  - 2nd Intermediate
    - Enzyme C
    - 3rd Intermediate
      - Enzyme D
      - End Product

Synthesis resumes
Mechanics of Feedback Inhibition

- Active site
- End Products
- Catalysis
- Enzyme
- Effector binds
- Conformational change in the active site
- Allosteric site
- Allosteric Effector
- End Products
Regulation by Covalent Modification

- addition or deletion of small organic molecule
  - phosphorylation
  - methylation
  - addition of AMP or ADP
Topic 3

Regulation of Gene Expression
The structure of operons

- **P**: Promoter
- **Gene 1**, **Gene 2**, **Gene 3**: Genes
- **t**: Terminator
- **Regulatory Gene**: Gene that controls transcription
- **Operator (O)**: Sequences that interact with regulatory proteins
- **Regulatory Protein**: (Repressor or Inducer or Corepressor)
- **Effector molecule**: Inducer or Corepressor
Regulation of Transcription: Negative Control

**Previously…**
- looked at regulation of enzyme activity
- very rapid (seconds or less)

**Now…**
- regulation of enzyme synthesis
- relatively slow process (minutes)

**All mechanisms controlling enzyme synthesis are greatly influenced by the cell’s environment**
- presence (or absence) of small molecules
Repression

- Repression
  - enzymes catalyzing the synthesis of a specific end-product are not synthesized if this product is present in the medium
    - enzyme expression is repressed
  - wide-spread phenomenon in bacteria
  - controls many biosynthetic pathways
  - expression is repressed in the presence of the corepressor
    - eg. arginine synthesis
Repression

Legend:
Number of cells
Total protein
Enzymes involved in arginine synthesis

Legend:
Relative increase
Add arginine to medium
Time
Repression: No corepressor
Repression: Add corepressor

Polymerase can’t bind \(\rightarrow\) No transcription

Inactive repressor

Active repressor – corepressor complex
Induction

- Induction
  - the synthesis of an enzyme only when its substrate is present
    - enzyme expression is induced
  - enzymes involved in catabolism of carbon and energy sources are often inducible
  - expression is induced in the presence of an inducer
    - e.g., lactose utilisation
Induction

Add lactose to medium

Legend:
Number of cells
Total protein
β-Galactosidase

Relative increase

Time

Add lactose to medium
Induction: No inducer

RNA Polymerase can’t bind → No transcription

Active repressor
**Induction: Add inducer**

1. **Active repressor**
2. **Inducer**
3. **Repressor / inducer complex (inactive)**
Regulation of Transcription: Positive Control

- Expression under positive control requires the presence of an inducer and an activator protein to induce expression.
- E.g., the maltose regulon.
Positive Control: No inducer

In the absence of the inducer, neither the RNA polymerase or activator protein can bind.

Polymerase can’t bind → No transcription
Positive control: Add inducer
Control of Transcription Termination

- General features
  - RNA polymerase pauses
  - secondary structures form in the mRNA
  - transcription is interfered with
  - RNA polymerase is ejected from the transcription bubble
  - transcription ceases

- eg. attenuation
Control of Translation

- Post-transcriptional regulation
- Regulation usually involves preventing translation initiation
Topic 3a: Global Control, Signal Transduction and Two-component Systems
Global Control

- regulation of many genes simultaneously in response to environmental stimuli

<table>
<thead>
<tr>
<th>System</th>
<th>Signal</th>
<th>Regulator</th>
<th>Regulator</th>
<th># of genes regulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic respiration</td>
<td>Presence of $O_2$</td>
<td>Repressor</td>
<td>ArcA</td>
<td>50+</td>
</tr>
<tr>
<td>Anaerobic respiration</td>
<td>Lack of $O_2$</td>
<td>Activator</td>
<td>FNR</td>
<td>70</td>
</tr>
<tr>
<td>Heat Shock</td>
<td>Temperature</td>
<td>Alternative $\sigma$</td>
<td>$\sigma^{32}$</td>
<td>36</td>
</tr>
<tr>
<td>SOS response</td>
<td>DNA damage</td>
<td>Repressor</td>
<td>LexA</td>
<td>20+</td>
</tr>
<tr>
<td>Catabolite repression</td>
<td>cAMP concentrations</td>
<td>Activator</td>
<td>CAP</td>
<td>300+</td>
</tr>
</tbody>
</table>
Catabolite Repression

- synthesis of a variety of unrelated enzymes is repressed when cells are grown in medium that contains a preferred energy source
- can lead to diauxic growth

Medium contain both glucose and lactose

Relative cell density

Glucose exhausted

Growth on lactose

Relative β-galactosidase levels

Time
How does Catabolite Repression Work?

- control of transcription by an activator protein
  - binding of RNA polymerase only occurs if the catabolite activator protein (CAP) has first bound

- CAP is an allosteric protein
  - to bind to DNA, CAP must have bound cAMP

- cAMP is synthesised from ATP
  - adenylate cyclase
How does Catabolite Repression Work?

- Glucose inhibits cAMP formation
  - ↑ glucose in the cell, ↓ cAMP
    - RNA polymerase does not bind to promoter
      - no expression of repressed genes
- Furthermore…
  - each operon that CAP controls is also under the control of a specific regulatory protein
    - eg. lac operon is under the control of Lacl
- Bottom line: as long as glucose is present, catabolite repression prevents expression from all other catabolic operons
How does Catabolite Repression Work?

- If glucose is absent, expression of alternative catabolic operons is possible if the correct alternative substrate is available.
- Eg. If lactose is present, it will induce the expression of lactose metabolising enzymes.
- If both high glucose and lactose are present, the global regulation by CAP will over-ride the possible induction of any alternative metabolic pathway enzymes.
Quorum Sensing

- regulatory pathways that are controlled in response to cell density within their population
  - ability to sense organisms of the same species
- sensing is done via acylated homoserine lactone (AHL)
- AHL is inducer
  - combine with activator proteins
Signal Transduction

● Bacteria respond to a wide variety of environmental fluctuations
  ● must be able to receive signal from the environment and transmit them to a specific target

● Some act directly via entering the cell
  ● effector molecules

● Some do not act directly
  ● detected by a sensory protein
  ● signal is transmitted through cellular processes to the rest of the regulatory machinery
Two-Component Systems

- Involve two different proteins
  - specific sensor protein
  - response regulator protein

- Sensor protein
  - kinase
  - autophosphorylate in response to environmental signal

- Regulator protein
  - phosphoryl group is transferred to regulator
  - phosphorylated regulator bind to DNA and regulates transcription
Two-Component Systems

Environmental signal

Sensor kinase

Cell Membrane

RNA Polymerase

Response regulator

Gene 1  Gene 2  Gene 3  t
Two-Component Systems

Cell Membrane

Autophosphorylation (+ATP)

RNA Polymerase

Gene 1  Gene 2  Gene 3  t
Two-Component Systems

Cell Membrane

Gene 1
Gene 2
Gene 3

RNA Polymerase

P
O

t
Two-Component Systems

Cell Membrane

RNA Polymerase

Gene 1   Gene 2   Gene 3   t
Two-Component Systems

Cell Membrane

RNA Polymerase

Phosphatase

Gene 1

Gene 2

Gene 3

P

O

Gene 1

Gene 2

Gene 3

Gene 3

Gene 1

Gene 2

Gene 3

Gene 3

Gene 3

Gene 1

Gene 2

Gene 3

Gene 3

Gene 3

Gene 1

Gene 2

Gene 3

Gene 3

Gene 1

Gene 2

Gene 3

Gene 3
Two-Component Systems

RNA Polymerase

Cell Membrane

Gene 1

Gene 2

Gene 3

P O Gene 1 Gene 2 Gene 3 t
## Two-Component Systems

<table>
<thead>
<tr>
<th>System</th>
<th>Environmental Signal</th>
<th>Sensor Kinase</th>
<th>Response Regulator</th>
<th>Activity of regulator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arc system</td>
<td>$O_2$</td>
<td>ArcB</td>
<td>ArcA</td>
<td>Repressor / Activator</td>
</tr>
<tr>
<td>Nitrogen utilisation (Ntr)</td>
<td>$NH_4^+$</td>
<td>NR$_{II}$</td>
<td>NR$_I$ (glnL)</td>
<td>Activator</td>
</tr>
<tr>
<td>Pho regulon</td>
<td>$P_i$</td>
<td>PhoR</td>
<td>PhoB</td>
<td>Activator</td>
</tr>
<tr>
<td>Porin regulation</td>
<td>Osmotic pressure</td>
<td>EnvZ</td>
<td>OmpR</td>
<td>Activator / Repressor</td>
</tr>
</tbody>
</table>
Topic 4
Specific Examples
Histidine Biosynthesis

ATP phosphoribosyltransferase is an allosteric enzyme.

Histidine does not resemble either the substrate or product of the first reaction.

Histidine is the effector molecule.
Aspartate Amino Acid Family

- Aspartate family of amino acids
  - lysine
  - threonine
  - methionine
  - isoleucine
- Synthesized via diaminopimelic acid pathway
- Humans cannot synthesize lysine
  - must obtain from diet
- Commercially produced also for feed stocks
E. coli

- L-Aspartate
  - L-Aspartyl phosphate
    - L-Aspartyl semialdehyde
      - 2,3-dihydrodipicolinate
        - L-Lysine
        - meso-2,6-Diaminopimelate
          - L-Threonine
            - L-Methionine
            - L-Isoleucine
      - L-Homoserine phosphate
        - L-Homoserine
          - L-Lysine
  - L-Homoserine dehydrogenase
E. coli: Repression

- L-Aspartate
- L-Aspartyl phosphate
- L-Aspartyl semialdehyde
- 2,3-dihydrodipicolinate
- meso-2,6-Diaminopimelate
- L-Lysine
- L-Homoserine
- L-Homoserine phosphate
- L-Threonine
- L-Methionine
- L-Isoleucine
E. coli: Feedback Inhibition

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

meso-2,6-Diaminopimelate

L-Lysine

L-Homoserine

L-Homoserine phosphate

L-Threonine

L-Methionine

L-Isoleucine
E. coli: Regulation

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E. coli: Regulation

A Complex Mess of Feedback Inhibition, Repression, and bifunctional isozymes

- L-Aspartate
- L-Aspartyl phosphate
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- 2,3-dihydrodipicolinate
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- L-Lysine
- L-Methionine
- L-Homoserine
- phosphate
- L-Threonine
- L-Isoleucine
- L-Homoserine

2,3-d: 2,3-dihydrodipicolinate
E. coli versus C. glutamicum

L-Aspartate → L-Aspartyl phosphate → L-Aspartyl semialdehyde

L-Aspartyl semialdehyde → 2,3-dihydrodipicolinate
2,3-dihydrodipicolinate → meso-2,6-Diaminopimelate → L-Lysine

L-Aspartyl semialdehyde → L-Homoserine
L-Homoserine → L-Homoserine phosphate → L-Methionine
L-Methionine → L-Threonine
L-Threonine → L-Isoleucine

Other metabolites:
- L-Methionine
- L-Lysine
- L-Threonine
- L-Isoleucine
**E. coli** versus **C. glutamicum**

- **L-Aspartate**
  - **L-Aspartyl phosphate**
  - **L-Aspartyl semialdehyde**
    - **2,3-dihydrodipicolinate**
      - **meso-2,6-Diaminopimelate**
        - **L-Lysine**
    - **L-Homoserine**
      - **L-Homoserine phosphate**
        - **L-Threonine**
          - **L-Methionine**
            - **L-Isoleucine**
  - **L-Homoserine**
    - **L-Methionine**
      - **L-Isoleucine**

One single aspartakinase
E. coli versus C. glutamicum

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

meso-2,6-Diaminopimelate

L-Lysine

L-Homoserine

L-Homoserine phosphate

L-Threonine

L-Methionine

L-Isoleucine

One homoserine dehydrogenase that is not an aspartakinase
C. glutamicum

L-Aspartate → L-Aspartyl phosphate → L-Aspartyl semialdehyde → 2,3-dihydrodipicolinate

Single step replaces 4

2,3-dihydrodipicolinate → meso-2,6-Diaminopimelate → L-Lysine

L-Homoserine → L-Homoserine phosphate → L-Threonine

L-Methionine → L-Isoleucine

L-Threonine
E. coli: Repression

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

meso-2,6-Diaminopimelate

L-Lysine

L-Homoserine

L-Homoserine phosphate

L-Methionine

L-Threonine

L-Isoleucine
C. glutamicum: Repression

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

deso-2,6-Diaminopimelate

L-Lysine

L-Homoserine

L-Homoserine phosphate

L-Threonine

L-Methionine

L-Isoleucine
E. coli: Feedback Inhibition

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

meso-2,6-Diaminopimelate

L-Lysine

L-Homoserine

L-Homoserine phosphate

L-Threonine

L-Methionine

L-Isoleucine
**C. glutamicum**: Feedback Inhibition

- L-Aspartate
- L-Aspartyl phosphate
- L-Aspartyl semialdehyde
- 2,3-dihydrodipicolinate
- *meso*-2,6-Diaminopimelate
- L-Lysine
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- L-Homoserine phosphate
- L-Threonine
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- L-Lysine
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- L-Isoleucine
E. coli

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C. glutamicum

- L-Aspartate
  - Aspartakinase
  - L-Aspartyl phosphate
  - L-Aspartyl semialdehyde
    - Homoserine dehydrogenase
      - 2,3-dihydrodipicolinate
        - meso-2,6-Diaminopimelate
          - L-Lysine
            - L-Threonine
              - L-Methionine
                - L-Isoleucine
C. glutamicum

- Only 3 steps are under regulation
  - regulate the branch points
- Will only consider lysine production vs the production of the other 3
  - i.e. regulation of the branch point controlled by homoserine dehydrogenase
  - also need to examine the regulation of aspartakinase activity
Regulation Summary: Lysine

- Flow of L-aspartate semialdehyde is controlled by
  - threonine (feedback inhibition)
  - methionine (repression)
  - isoleucine (to a lesser extent)

- Excess threonine / methionine
  - reduce homoserine dehydrogenase activity
  - L-aspartate semialdehyde flows into the lysine-producing pathway
  - lysine accumulates
L-Aspartate \approx \text{Methionine} \approx \text{Threonine} \approx \text{Isoleucine}

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

\text{meso-2,6-Diaminopimelate}

L-Lysine

L-Methionine

L-Threonine

L-Isoleucine
High threonine, High lysine

- L-Lysine
- L-Threonine
- L-Isoleucine
- L-Methionine
- L-Homoserine
- 2,3-dihydrodipicolinate
- meso-2,6-Diaminopimelate
- L-Lysine

Both required for inhibition

↑↑ Methionine
↑↑ Threonine
↑↑ Isoleucine
↓↓ Methionine
↓↓ Threonine
↓↓ Isoleucine
High threonine, Low lysine

L-Aspartate

L-Aspartyl phosphate

L-Aspartyl semialdehyde

2,3-dihydrodipicolinate

meso-2,6-Diaminopimelate

L-Lysine

↓ Lysine

↑ Lysine

L-Methionine

↑↑ Methionine

↑↑ Threonine

↑↑ Isoleucine

L-Threonine

L-Isoleucine

↓ Methionine

↓ Threonine

↓ Isoleucine
Low threonine, High lysine

- **L-Aspartate**
- **L-Aspartyl phosphate**
- **L-Aspartyl semialdehyde**
- **2,3-dihydrodipicolinate**
- **meso-2,6-Diaminopimelate**
- **L-Lysine**
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- **L-Isoleucine**
- **L-Methionine**
- **L-Homoserine phosphate**
- **L-Homoserine dehydrogenase**

**↑↑ Lysine**

**↓ Methionine**
**↓ Threonine**
**↓ Isoleucine**

**↑↑ Homoserine dehydrogenase**

**↓ Lysine**

**↑ Methionine**
**↑ Threonine**
**↑ Isoleucine**
Industrial Application

- *Corynebacterium glutamicum* (along with strains of *Brevibacterium*) are used for the commercial production of lysine
- Require mutations in single genes to get over-producing strains
  - homoserine dehydrogenase
  - aspartokinase feedback inhibition mechanism
The *lac* Operon

- genes responsible for lactose utilization
- lactose = glucose + galactose
- in the absence of glucose

![Diagram of the lac Operon]

- lac repressor
- β-galactosidase
- β-galactoside permease
- β-galactoside transacetylase
High glucose, High lactose

- Glucose levels are high
  - cAMP levels are low
  - cAMP-CAP levels are low
- Lactose is present
- 2% of induced activity
No glucose, low lactose

- no glucose
  - high cAMP
  - cAMP-CAP
- low lactose
  - little (or no) inducer
  - inducer is allolactose
  - conversion from lactose by $\beta$-galactosidase
No glucose, low lactose

Because there is no glucose, cAMP-CAP can form

No Inducer. LacI binds preventing transcription (though there is a very low level)
No glucose, High lactose

- no glucose
  - high cAMP
  - cAMP-CAP
- high lactose
  - lactose is converted to allolactose by β-galactosidase
  - inducer is present
  - bind to repressor
- Transcription
No glucose, High lactose

Because there is no glucose, cAMP-CAP can form cAMP-CAP bound to CAP binding site
Repressor not bound to operator
RNA polymerase binds
β-galactosidase

β-galactosidase

Lactose

β-galactosidase

Allolactose (inducer)

Inducer binds to repressor. Complex cannot bind to operator
In Summary

- **Low glucose, Low lactose**
  - cAMP-CAP → polymerase can bind
  - no lactose → no inducer → repressor binds
  - no transcription

- **High glucose, Low lactose**
  - no cAMP-CAP → polymerase can’t bind
  - no lactose → no inducer → repressor binds
  - no transcription
In Summary

- **High glucose, High lactose**
  - inducer present $\rightarrow$ repressor can’t bind
  - no cAMP-CAP $\rightarrow$ polymerase can’t bind
  - no transcription

- **Low glucose, High lactose**
  - cAMP-CAP $\rightarrow$ polymerase can bind
  - inducer present $\rightarrow$ repressor can’t bind
  - Transcription!!
The \textit{trp} operon

- Tryptophan synthesis is under the control of
  - repression
  - attenuation
The *trp* operon

- Tryptophan synthesis is under the control of
  - Repression
    - Similar to LacI induction in Lac operon
    - TrpR repressor binds to the operator region only when tryptophan is present
  - Attenuation
    - Extra regulatory mechanism
The *trp* Attenuator

- **PO**: Start point of transcription
- **trpL**: Initiator codon
- **trpE**: First region capable of forming secondary structure
- **trpD**: Second region capable of forming secondary structure
- **trpC**: Third region capable of forming secondary structure
- **trpB**: Fourth region capable of forming secondary structure
- **trpA**: Stop codon

4 regions capable of forming secondary structures

Two tryptophan (W) codons

Transcription terminator
High tryptophan

Region 1

Terminator forms and transcription stops
Low tryptophan

Low trp ribosome stalls

2 binds with 3
Terminator can’t form. Transcription
Summary

- **High tryptophan**
  - tryptophan not needed
  - ribosome passes through two trp codons in leader peptide
  - transcription terminator forms (region 3-4)
  - transcription stops

- **Low tryptophan**
  - tryptophan required
  - ribosome stalls at trp codons in leader peptide
  - region 2 interacts with region 3
  - terminator cannot form
  - transcription continues
Learning Exercises

- Review this material thoroughly
- Answer all questions for this module
Next Week…

- Revision Modules 1, 2 and 3
- Attempt questions from these modules
- Other questions will be given and answered in this session