Signals and receptors 2

The chemotaxis control system

Please sit in row K or forward
RBFD: using the V. fischeri quorum sensing system to treat cancer

LETTER

Synchronized cycles of bacterial lysis for in vivo delivery

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References:
http://dx.doi.org/10.1038/nature18915
http://dx.doi.org/10.1038/nature18930
Topics for this week

• Homework 8 recap
• Receptors and signals example 3: Control of chemotaxis in E. coli
Homework 8 recap

Pathogenic (N16961) strain

vs.

Non-pathogenic strains

2740_80

PS15
## Finding unique genes

<table>
<thead>
<tr>
<th>Genes</th>
<th>vcN16961_vs_vc2740_80</th>
<th>vcN16961_vs_vcPS15</th>
<th>Has homolog?</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP_062585.1 hypothe...</td>
<td>30 21 24 27...</td>
<td>20 21 23 20...</td>
<td>0</td>
</tr>
<tr>
<td>NP_062586.1 flavodo...</td>
<td>28 32 27 28...</td>
<td>37 27 31 30...</td>
<td>1</td>
</tr>
<tr>
<td>NP_062587.1 tRNA mo...</td>
<td>34 36 27 40...</td>
<td>39 31 35 34...</td>
<td>1</td>
</tr>
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<td>NP_062588.1 inner m...</td>
<td>30 39 34 35...</td>
<td>33 30 38 28...</td>
<td>1</td>
</tr>
<tr>
<td>NP_062589.1 hypothe...</td>
<td>21 37 21 26...</td>
<td>26 26 28 26...</td>
<td>0</td>
</tr>
<tr>
<td>NP_062590.1 ribonuc...</td>
<td>27 31 29 29...</td>
<td>28 28 25 26...</td>
<td>1</td>
</tr>
<tr>
<td>NP_062591.1 50S rib...</td>
<td>21 30 23 29...</td>
<td>20 18 23 20...</td>
<td>0</td>
</tr>
<tr>
<td>NP_062592.1 amino a...</td>
<td>29 30 34 31...</td>
<td>36 32 25 22...</td>
<td>1</td>
</tr>
<tr>
<td>NP_062593.1 amino a...</td>
<td>27 27 29 38...</td>
<td>46 34 32 20...</td>
<td>1</td>
</tr>
</tbody>
</table>
islands looks for horizontal transfer events

1, 1, 1, 1, 1, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 1, 0, 1, 0
** Island

chrom 2 344577-356431

- NP_232747.1 hypothetical protein VCA0351 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232749.1 hypothetical protein VCA0353 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232750.2 hypothetical protein VCA0354 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232751.1 hypothetical protein VCA0355 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232752.1 hypothetical protein VCA0356 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232753.1 hypothetical protein VCA0357 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232754.1 plasmid stabilization element ParE [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232756.1 hypothetical protein VCA0361 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232757.1 hypothetical protein VCA0362 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232758.1 hypothetical protein VCA0363 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232759.1 hypothetical protein VCA0364 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232761.1 hypothetical protein VCA0366 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232762.1 hypothetical protein VCA0367 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_232763.1 hypothetical protein VCA0368 [Vibrio cholerae O1 biovar El Tor str. N16961]

** Island

chrom 1 1564152-1573281

- NP_231095.1 RstC protein [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231096.1 RstB1 protein [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231097.1 RstA1 protein [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231098.1 transcriptional repressor RstR [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231100.1 cholera enterotoxin subunit B [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231101.1 cholera enterotoxin subunit A [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231102.1 zona occludens toxin [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231103.1 accessory cholera enterotoxin [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231104.1 hypothetical protein VC1460 [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231105.1 colonization factor [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231106.1 RstB2 protein [Vibrio cholerae O1 biovar El Tor str. N16961]
- NP_231107.1 transcriptional repressor RstR [Vibrio cholerae O1 biovar El Tor str. N16961]
Pathogenic strain

Non-pathogenic strain

RstC, RstB1, RstA1, RstR, CtxB, CtxA, ZOT, VC1459 VC1460, Cep, RstB2, RSTA2, RstR
Topics for this week

- Homework 8 recap
- Receptors and signals example 3: Control of chemotaxis in E. coli
Example: control of chemotaxis in E. coli

- Chemotaxis: move toward or away from chemicals of interest
- Control movement despite Brownian noise
Vibrio also has chemotaxis...
The chemotaxis operon in *E. coli*

Operon for chemotaxis ~10 kb

- cheA
- cheW
- tar
- tap
- cheB
- cheR
- cheY
- cheZ
Bacterial movement: tumbles and runs

Counterclockwise

Run

Clockwise

Tumble
How *E. coli* detects gradients

Could they use detectors at either end of the cell?

- 900 molecules per cell volume
- 901 molecules per cell volume
- 902 molecules per cell volume

Poisson distribution for concentration measurements
How *E. coli* detects gradients

- Comparing concentration changes over time
- If concentration of attractant growing, less likely to tumble
- Biased random walk
Responding to an attractant: the aspartate receptor kinase complex

Receptor kinase exists in two states: active and inactive

Active receptor kinase (A)  
Inactive receptor kinase (I)

Active form increases cell's probability of tumbling

Binding domain of aspartate receptor in \textit{E. coli} [2ASR_A]
The connection between receptor and tumbling: a phosphorylation based signaling cascade

CheY-P interacts with motor:
• ↑motor probability turn clockwise
• ↑cell prob tumble
**Active and inactive forms in equilibrium**

The value of $K_{eq}$ determines the concentration of active receptor kinase and baseline tumbling frequency.
The connection between attractant binding and tumbling

Attractant binding shifts equilibrium to favor inactive form
CheY

$K_{eq}$

Baseline level of clockwise turns & tumbling

Less autophosphorylation / phosphorylation of cheY

$K_{eq_{bound}}$

↓ clockwise turns
↓ tumbling
Responding to an attractant signal

<table>
<thead>
<tr>
<th>Location of signal</th>
<th>High [Aspartic acid]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change to the receptor</td>
<td></td>
</tr>
<tr>
<td>Response to the signal</td>
<td></td>
</tr>
</tbody>
</table>
Responding to an attractant signal

<table>
<thead>
<tr>
<th></th>
<th>High [Aspartic acid]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location of signal</td>
<td>Outside plasma membrane</td>
</tr>
<tr>
<td>Change to the receptor</td>
<td>Change shape and do less phosphorylation</td>
</tr>
<tr>
<td>Response to the signal</td>
<td>↘ probability of clockwise rotation/tumbling</td>
</tr>
</tbody>
</table>
An experiment to consider

- E coli in a petri dish
- After a few minutes we add attractant uniformly to dish
- What happens to tumble frequency curve over time?
Sensory adaptation is a fundamental property of sensory systems

- Allow for other molecules to affect tumbling frequency
- Take advantage of full dynamic range of tumbling frequencies
Methylation is the molecular basis of adaptation

Active methylated receptor kinase (A)

Inactive methylated receptor kinase (I)

Methyl group

H

C

H

Un-methylated receptor kinase is always inactive.

Inactive un-methylated receptor kinase (U)
A simple model of adaptation in chemotaxis

- Active methylated receptor kinase (A)
- Inactive methylated receptor kinase (I)
- Inactive un-methylated receptor kinase (U)
- De-methylation enzyme (CheB)
- Methylation enzyme (CheR)
Inter-conversions between states: the equilibrium process

Active methylated receptor kinase (A)  
Inactive methylated receptor kinase (I)

Timescale: fractions of a second
Inter-conversions between states: demethylation

Rate varies with substrate concentration.

Timescale: minutes

Inactive un-methylated receptor kinase (U)

De-methylation enzyme

CheB
Inter-conversions between states: methylation

Rate is constant, independent of substrate concentration.

Timescale: minutes
Adaptation experiment with simple model

Starting value $A$

Starting value $U$

Starting value $I$

$K_{eq}$

Fast

Tumbling frequency

Time
Moments after attractant was added

Starting value A

$K_{eqbound}$

Fast

Starting value I

Starting value U

Tumbling frequency

Time
Minutes after attractant was added

Starting value $A$

$K_{eq\text{bound}}$

Fast

Starting value $I$

Starting value $U$

Tumbling frequency

Time
A long time after attractant was added: new steady state
1. Indicate the concentrations of the three receptor-kinase states during the course of our adaptation experiment. Use a 0-12 integer scale where 12 is high concentration. For this question assume:

<table>
<thead>
<tr>
<th></th>
<th>Starting values</th>
<th>Moments after attractant added</th>
<th>Minutes after attractant added</th>
<th>A long time after attractant added</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U</td>
<td></td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Indicate the corresponding rate for the following

<table>
<thead>
<tr>
<th></th>
<th>Methylation</th>
<th>De-methylation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Slow</td>
<td>Medium</td>
<td>Slow</td>
</tr>
<tr>
<td>Very slow</td>
<td>Medium</td>
<td>Slow</td>
</tr>
<tr>
<td></td>
<td>Slow</td>
<td>Slow</td>
</tr>
<tr>
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<td>Very slow</td>
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\[ K_{eq} = 1 \quad K_{eq_{bound}} = 0.5 \]
1. Indicate the concentrations of the three receptor-kinase states during the course of our adaptation experiment. Use a 0-12 integer scale where 12 is high concentration. For this question assume:

\[ K_{eq} = 1 \quad K_{eqbound} = 0.5 \]

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<tbody>
<tr>
<td>A</td>
<td>6</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>I</td>
<td>6</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
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<td>8</td>
<td>8</td>
<td>5</td>
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<table>
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<th>Medium</th>
<th>Medium</th>
<th>Medium</th>
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</tr>
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<tbody>
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<td>Very slow</td>
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</table>

**Worksheet**

(Rip it off from the back of your packet)

**Name:**
This model is simplified

- Doesn't model multiple methylations
- Assumes only methylated receptor active
Sensory adaptation is a fundamental property of sensory systems.

What are some examples of adaptation in human sensory systems?
Hand in your worksheet please!

(and be sure you put your name on it)