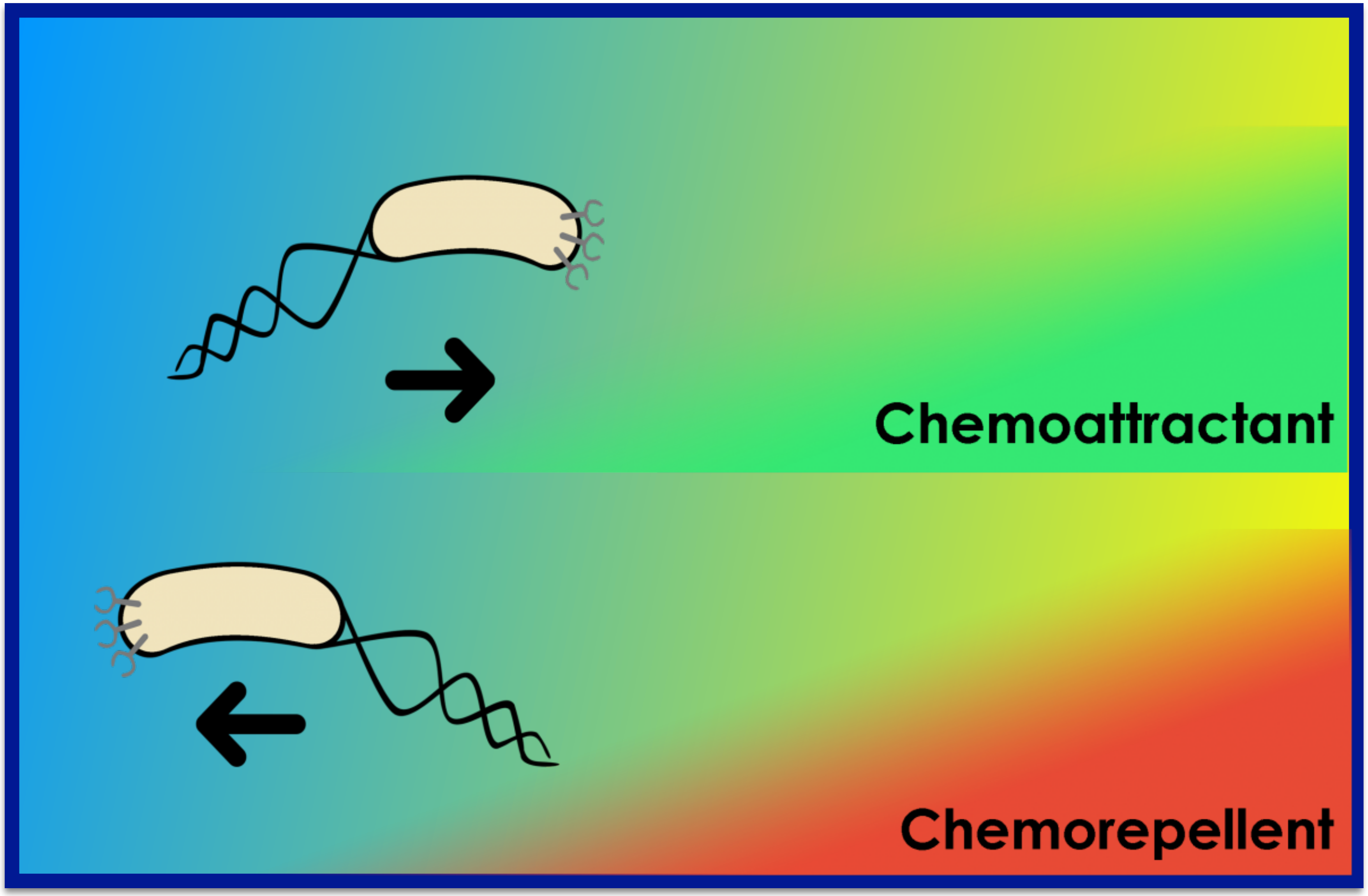
Accuracy Limits to Cellular Sensing



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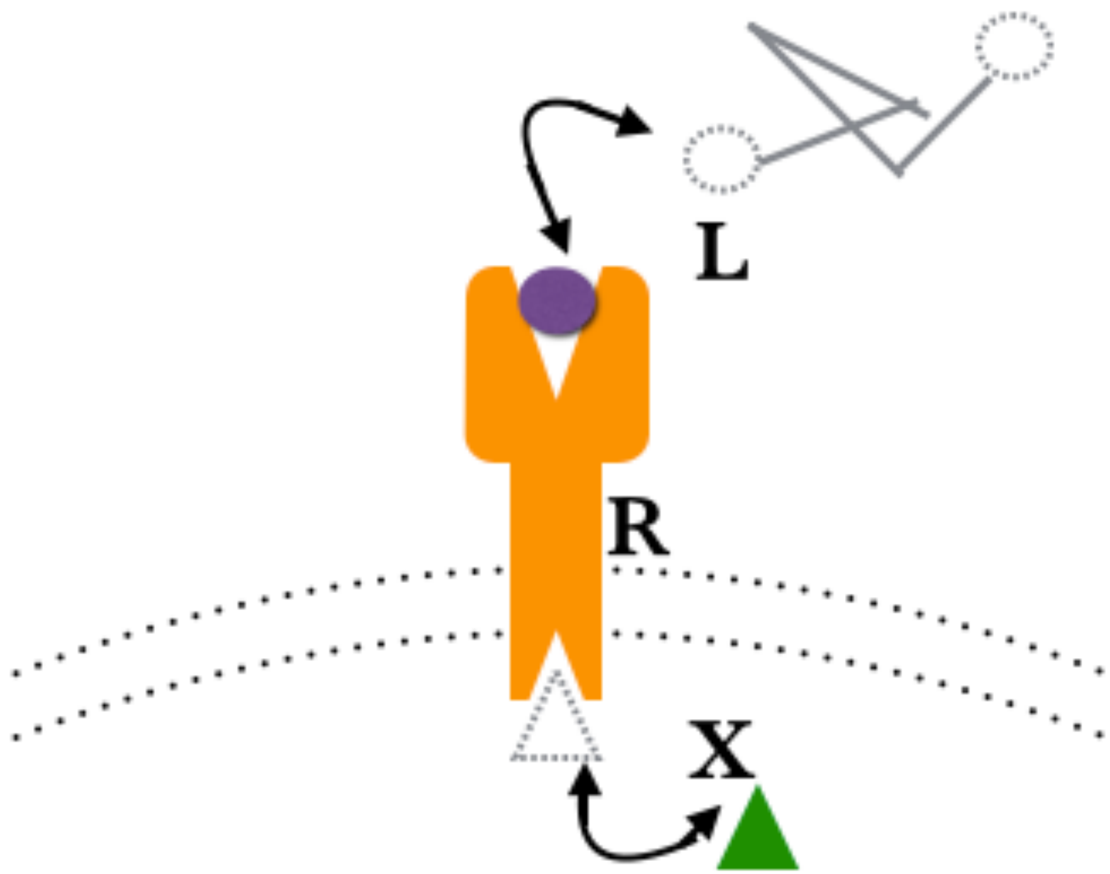
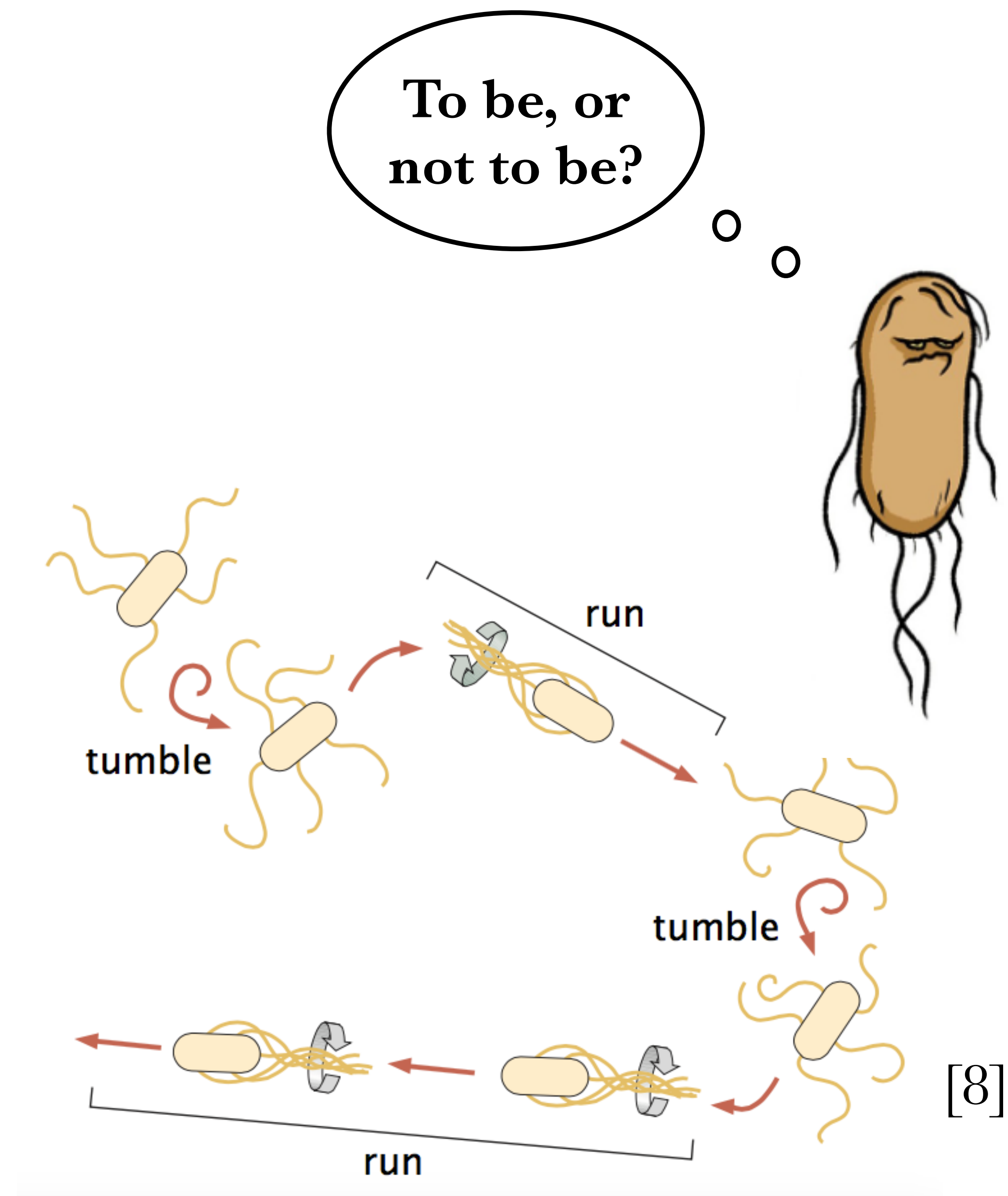
Cellular Sensing

Cells often need to make crucial decisions:

1. Whether to stay or move
2. When to proliferate or differentiate
3. Whether to live or die





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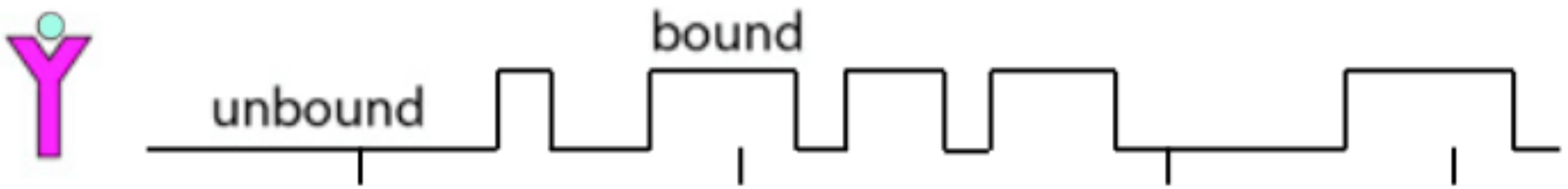
Accuracy is limited

- Cell sensing is inevitably **corrupted by noise**
  - Stochastic **arrival of ligands** by diffusion
  - Stochastic **binding of ligands** to the receptors



[2]

- More 'sensible' for cell to look at mean values (**time averaged**) than instantaneous values of receptor states
  - But **what is the best a cell can do?**

Overview

1. The **Question**

2. Early approaches to the problem:
    - The **Berg-Purcell** limit

3. Limitations of Berg-Purcell approach
    - Inclusion of **intrinsic noise**

4. **Equilibrium sensing** and **its limits**

5. **Non-equilibrium sensing** and **its limits**

Overview

6. Fundamental **resource requirements**

7. Is **non-equilibrium** sensing **always better**?

8. The **optimally designed cell**

9. Performance of cells is nearly optimal:
    - **Two examples**: E. coli & Drosophila

10. **Conclusions**

11. **References**

The Question:
How accurately can cells sense?

Early approaches to the problem

- First addressed by **H.C. Berg & E.M. Purcell (1977)**

Single receptor:

$$\Delta c/\bar{c} = (\nu/2)^{-\frac{1}{2}}$$
$$\nu = 4Ds\bar{c}(1-\bar{p})T$$

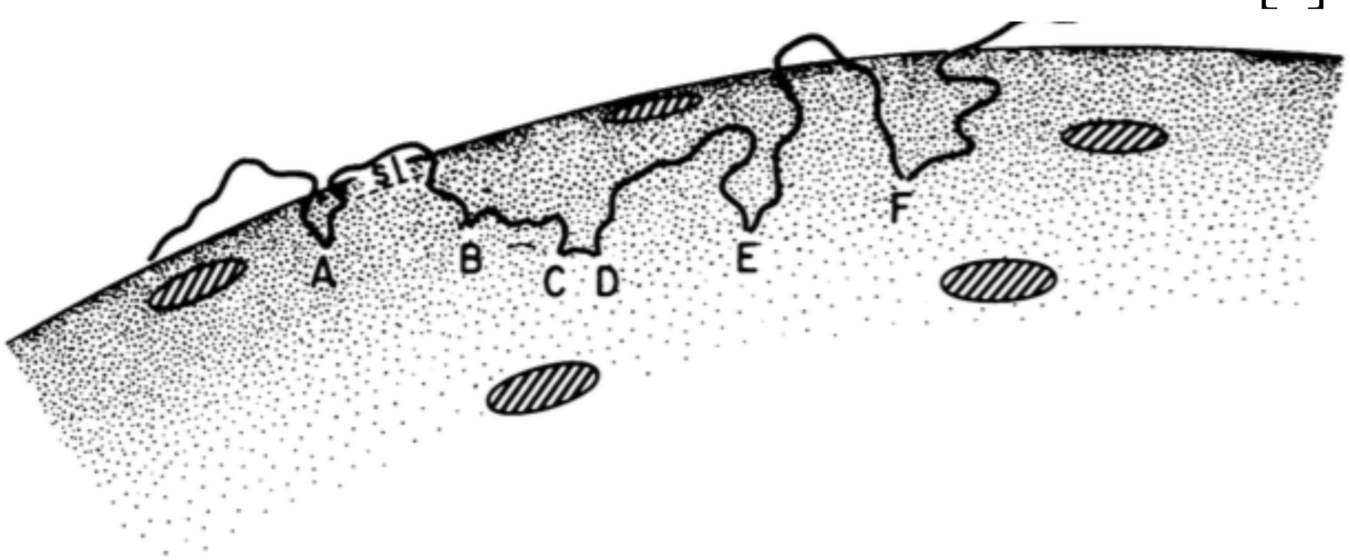
Statistical independence of capture of 'new' molecules by different receptors

N receptors:

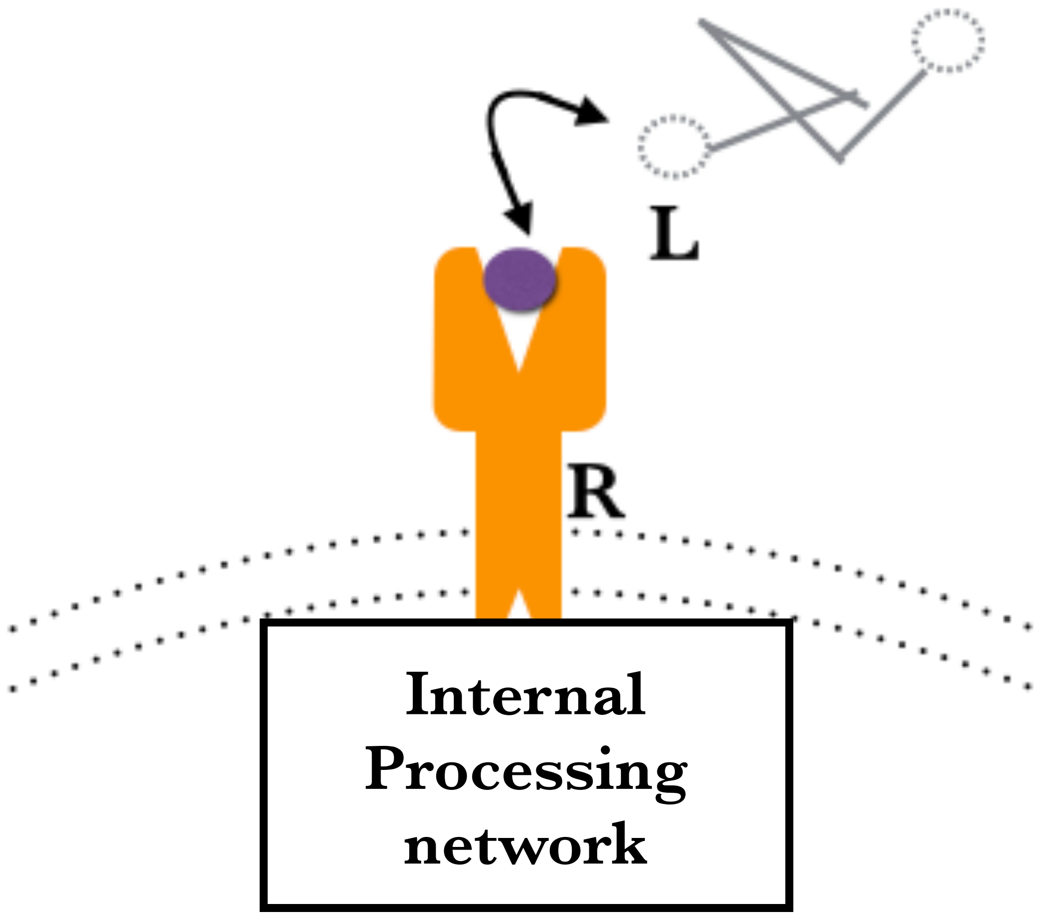
$$\Delta c/\bar{c} = (\nu/2)^{-\frac{1}{2}}$$
$$\nu = \frac{2\pi T D\bar{c}Nsa(1-\bar{p})}{(Ns+\pi a)}$$

Where,
D: Diffusion constant of ligands
s : radius of receptor
$\bar{c}$: true concentration of the ligand
$\bar{p}$: probability that receptor is bound
T: integration time
a: radius of the cell
N: number of receptors on the cell

[3]



Going beyond Berg-Purcell



Extrinsic Noise

1. Diffusive Arrival
2. Stochastic Binding

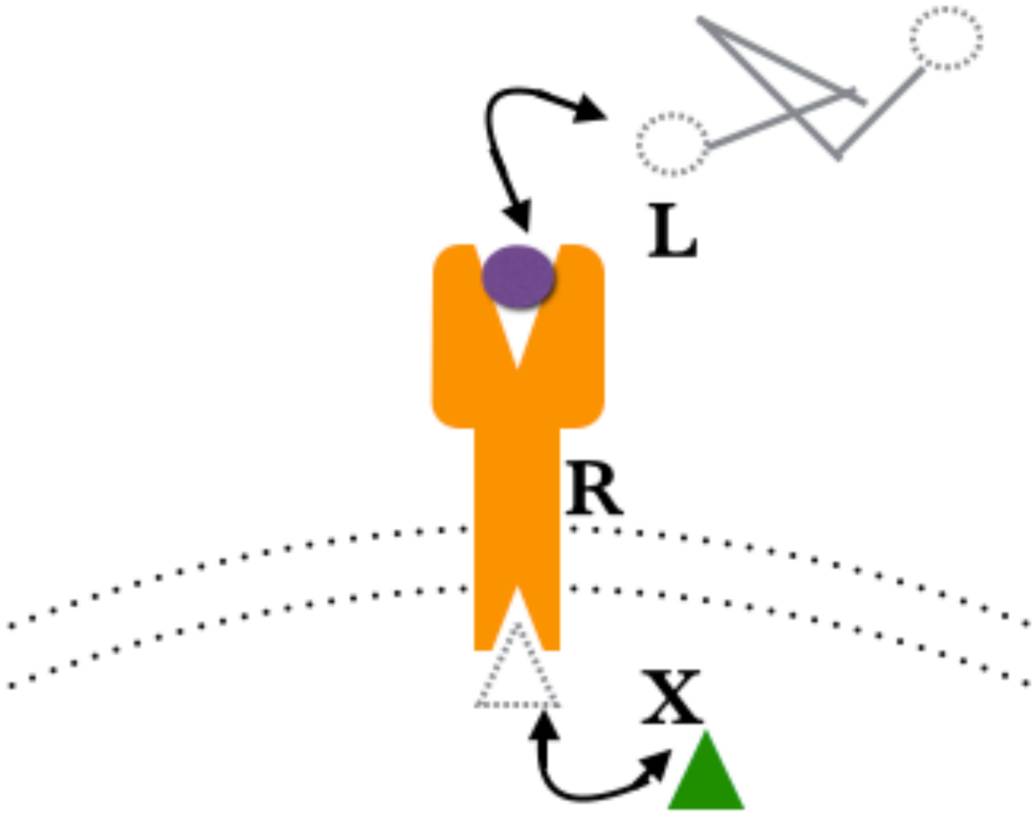
They are correlated in equilibrium sensing networks!

Intrinsic Noise

3. Noise in filtering extrinsic noise and **this can't be ignored**

Limits of Equilibrium Sensing

Let's look at a particular motif



Intuitive explanations: [1]

- In equilibrium, the ligand-receptor binding energy causes the activation of the readout
- Time reversal invariance leads to inevitable 'coupling' between receptor-ligand and receptor-readout reactions

$$R + L \longrightarrow RL + \text{ENERGY}$$

$$\downarrow$$

$$RX + \text{ENERGY} \longrightarrow X + R$$

Accuracy is limited by R_T without readout

By inverting & linearising the **input-output relation**(**X**(**c**)), we get:

$$(\Delta c/c)^2_X = \frac{\sigma_x^2}{c^2(\frac{dX}{dc})^2} = \frac{\sigma_x^2}{(\frac{dX}{d\mu_L})^2}$$

$$K_B T = 1$$
$$\mu_L = \mu_0 + log(C)$$

When receptor state itself is the readout i.e. there's **no time integration**, X=RL, then:

$$\boxed{(\Delta c/c)^2_{RL} = \frac{1}{p(1-p)R_T} \geq \frac{4}{R_T}}$$

Accuracy is limited by R_T even with readout

- Interestingly, employing a **readout molecule** (i.e. time averaging) **doesn't improve** the situation.

- For the **particular motif**, it can be shown that **even with the readout**:

$$(\Delta c/c)^2_X \geq \frac{4}{R_T} \qquad [1]$$

- This is however **not surprising** and is simply a consequence of the **fluctuation-dissipation theorem**!

Accuracy is limited by R_T for all equilibrium networks

We already saw that,

$$(\Delta c/c)^2_X = \frac{\sigma^2_X}{(\frac{dX}{d\mu_L})^2}$$

From the fluctuation-dissipation theorem:

$$\frac{dX}{d\mu_L} = \sigma^2_{X,RL}$$

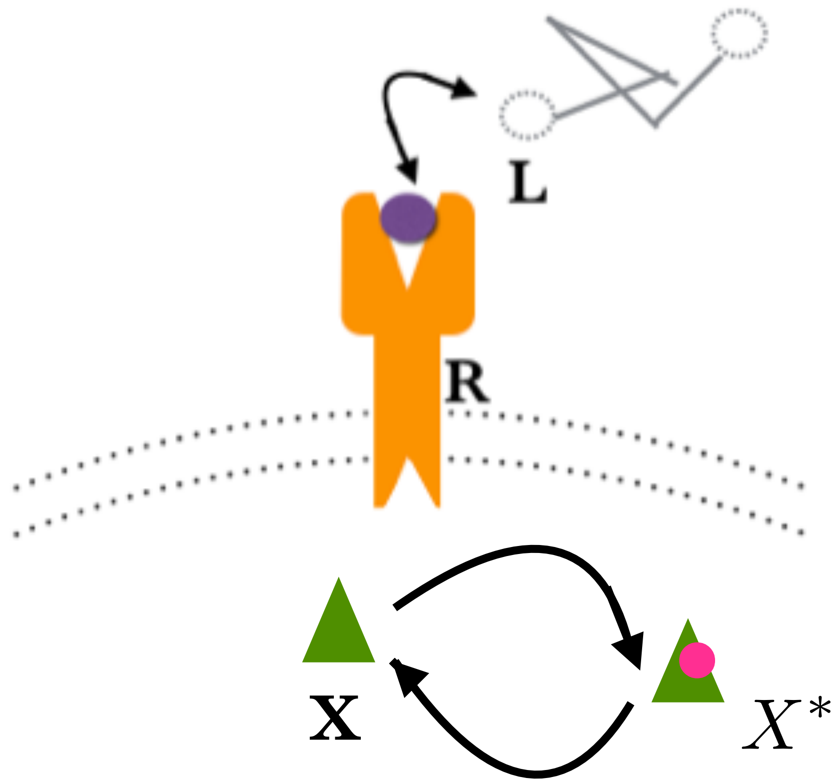
Correlation co-efficient ≤ 1

Popoviciu's inequality

$$(\Delta c/c)^2_X = \frac{\sigma^2_X \sigma^2_{RL}}{(\sigma^2_{X,RL})^2} \cdot (\Delta c/c)^2_{RL} \geq (\Delta c/c)^2_{RL} \geq 4/R^2_T\,!$$

Limits of Non-equilibrium Sensing

Non-equilibrium Sensing



$RL + X \longrightarrow X^* + RL$

- Extrinsic and intrinsic noise become **uncorrelated**
- The precision is no longer solely limited by the number of receptors R_T
- The **number of readout molecules**(X_T), the **energy dissipated**(w) and the **integration time**(τ_r) also become important

$$(\Delta c/c)^2 \geq MAX(\frac{4}{R_T(1+\tau_r/\tau_c)}, \frac{4}{X_T}, \frac{4}{w})$$

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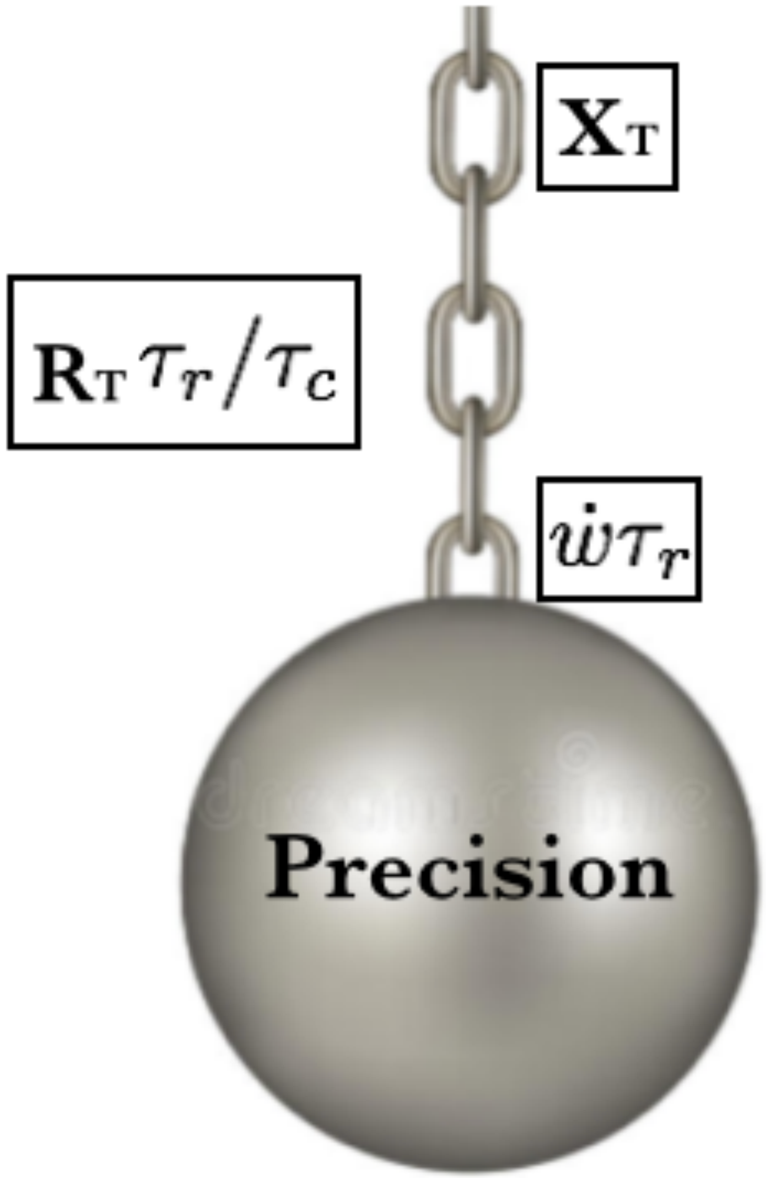
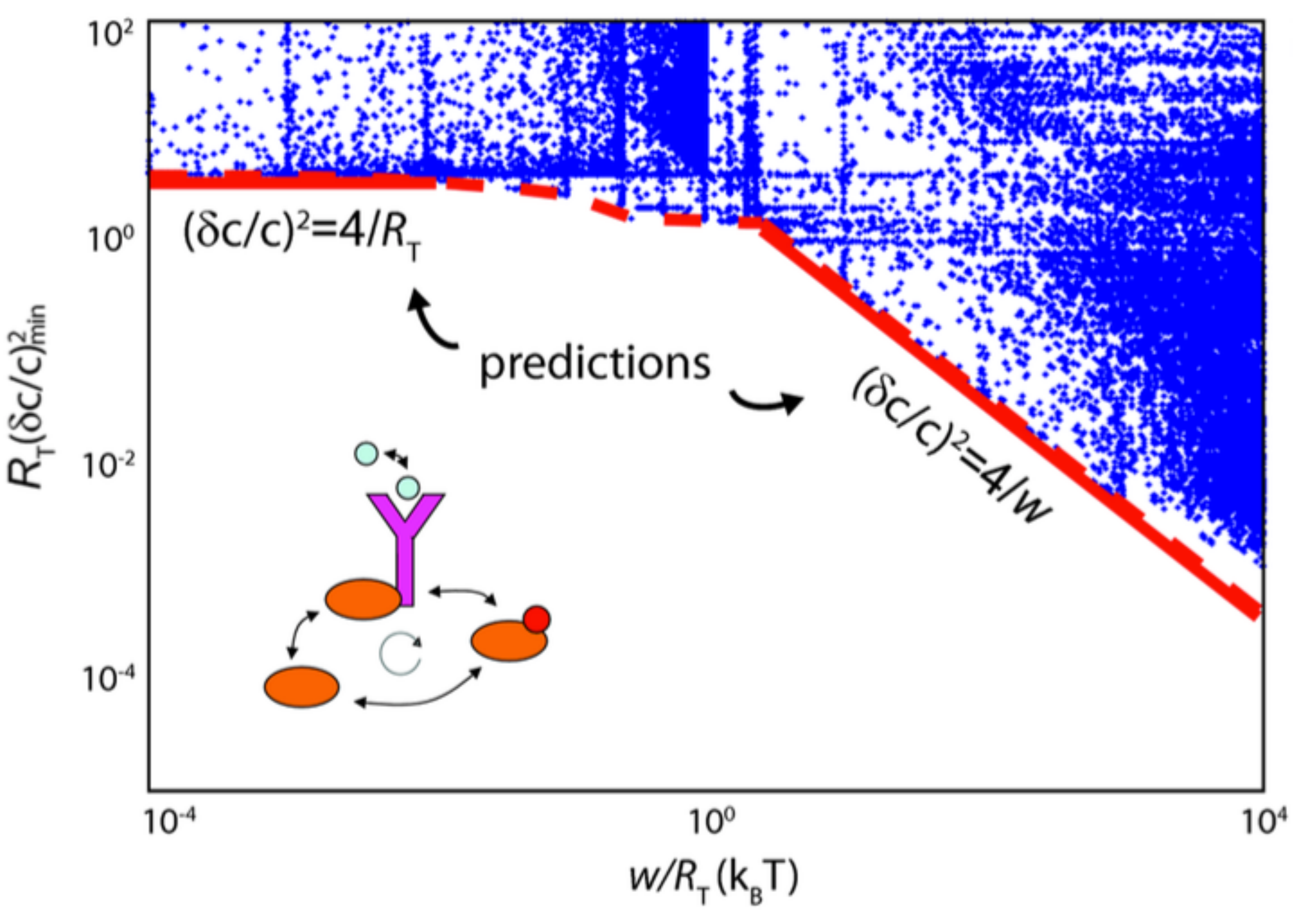
Fundamental Resource Classes



- Precision is bounded by the **weakest link** in the chain
- Trade-offs **within** a resource class is possible

  e.g. Energy-speed-accuracy trade-off in case of adaptation has already been predicted and observed [7]

Equilibrium or Non-equilibrium?



- **Non-equilibrium** sensing results in greater accuracy than **equilibrium sensing**, only when:
    1. There is at least **one readout molecule per receptor**
    2. Amount of **energy dissipated** during the integration time is **at least 1K_BT per receptor**.

Optimal Design

- Since precision is limited by the scarcest resource, for an **optimally designed cell:**

$$R_T \tau_r / \tau_c \approx X_T \approx w$$

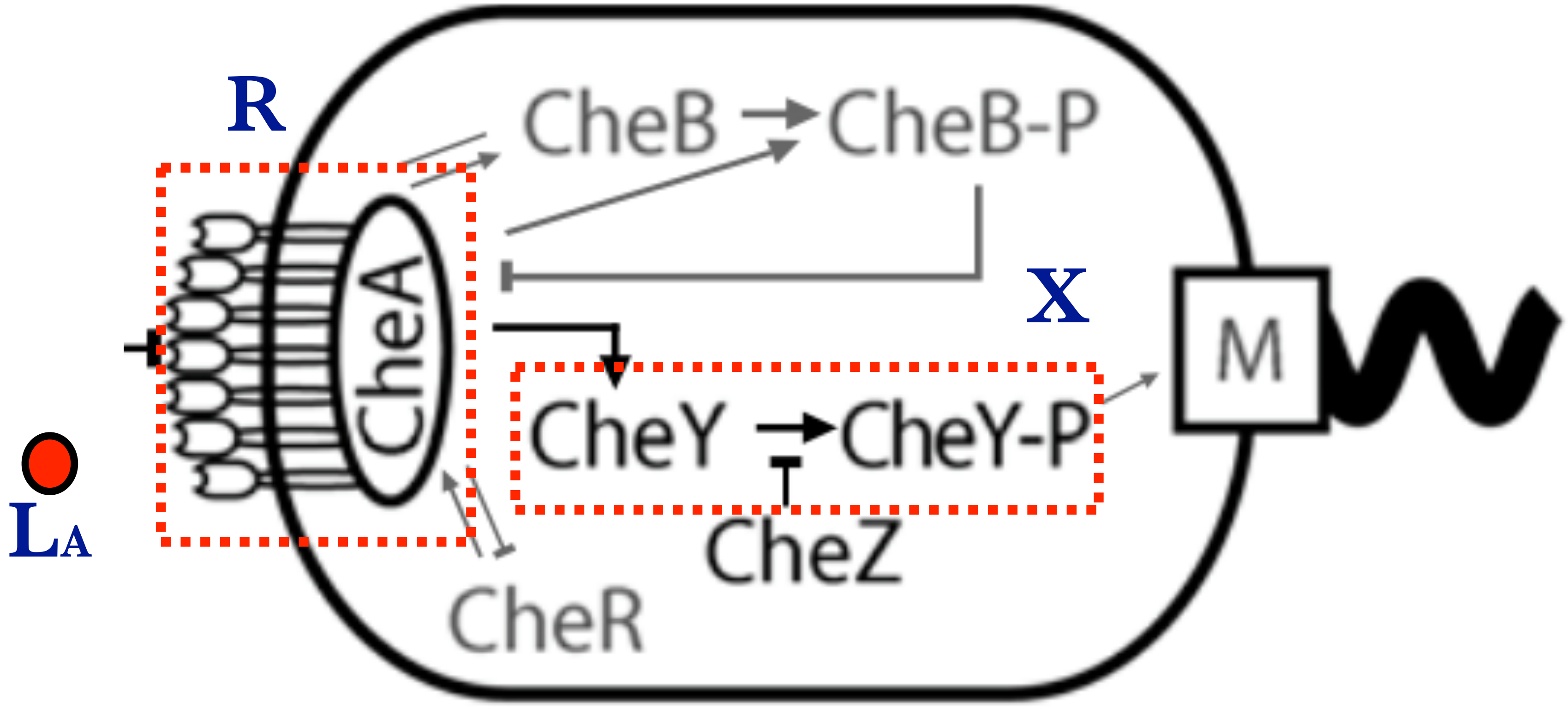
- This is such that no resource is wasted and it's regardless of how cheap producing that resource is.

Two Real Examples

E.coli Sensing Network

L can be either an attractant ($\mathbf{L_A}$) or a repellent ($\mathbf{L_R}$).

e.g. sugars are attractants while metal ions are repellents.



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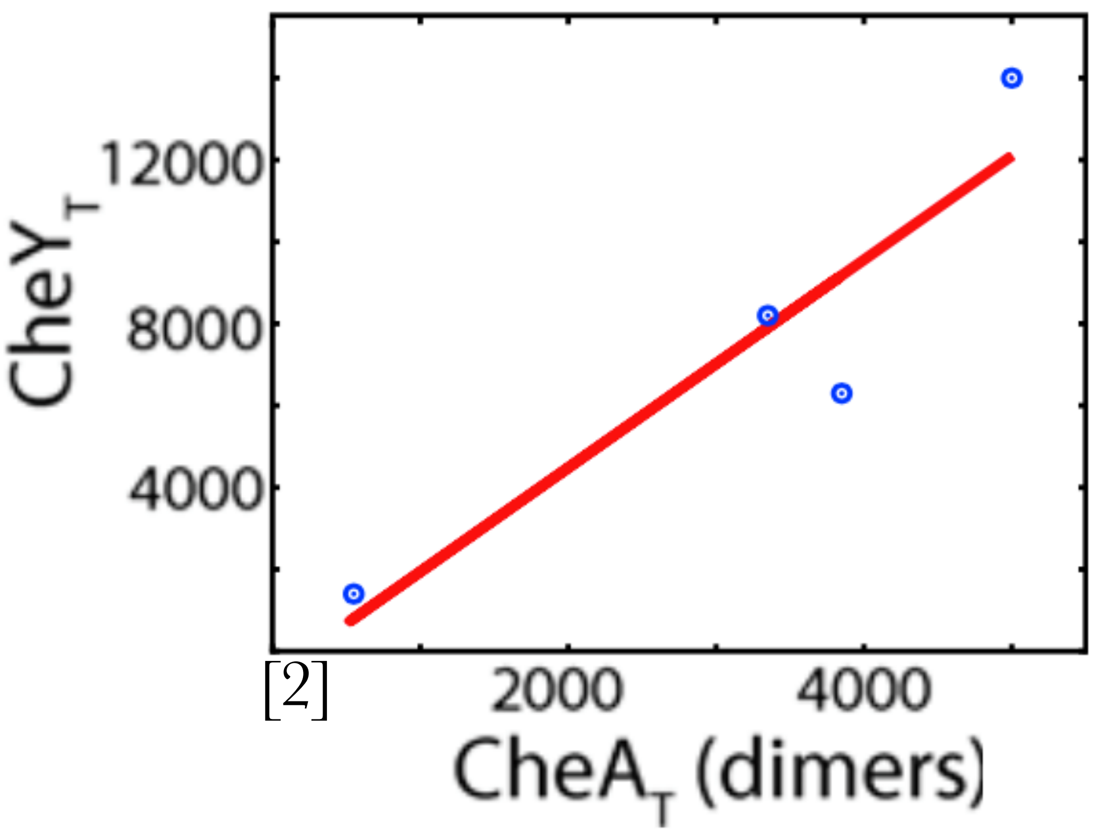
Receptors can be of 4-5 types and each cell has around 1000 receptors.

Is E.coli sensing optimal?

If there is a **selective pressure** for optimal sensing, we should expect organisms to employ optimal sensing strategies



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- If so, $\mathbf{X_T}$ (CheY), should scale **linearly** with $\mathbf{R_T}$ (receptor–CheA complexes) with slope $\boldsymbol{\tau r / \tau c}$
- Best fit to data has **slope ≈ 3** and thus $\boldsymbol{\tau r / \tau c \approx 3}$.
- Now, $\boldsymbol{\tau r \approx 100}$ **ms and** $\boldsymbol{\tau c \approx 10}$ **ms** (estimated from the measured receptor–ligand dissociation constant and association rate) i.e $\boldsymbol{\tau r / \tau c \approx 10}$

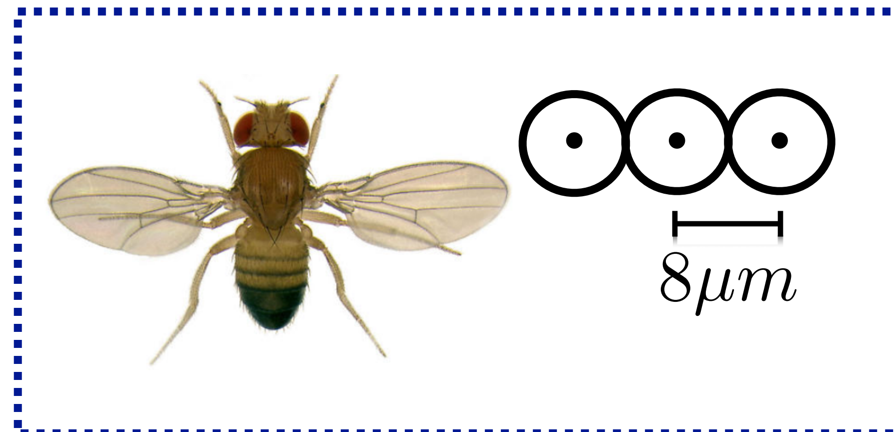
Prediction and observation have the same order of magnitude.

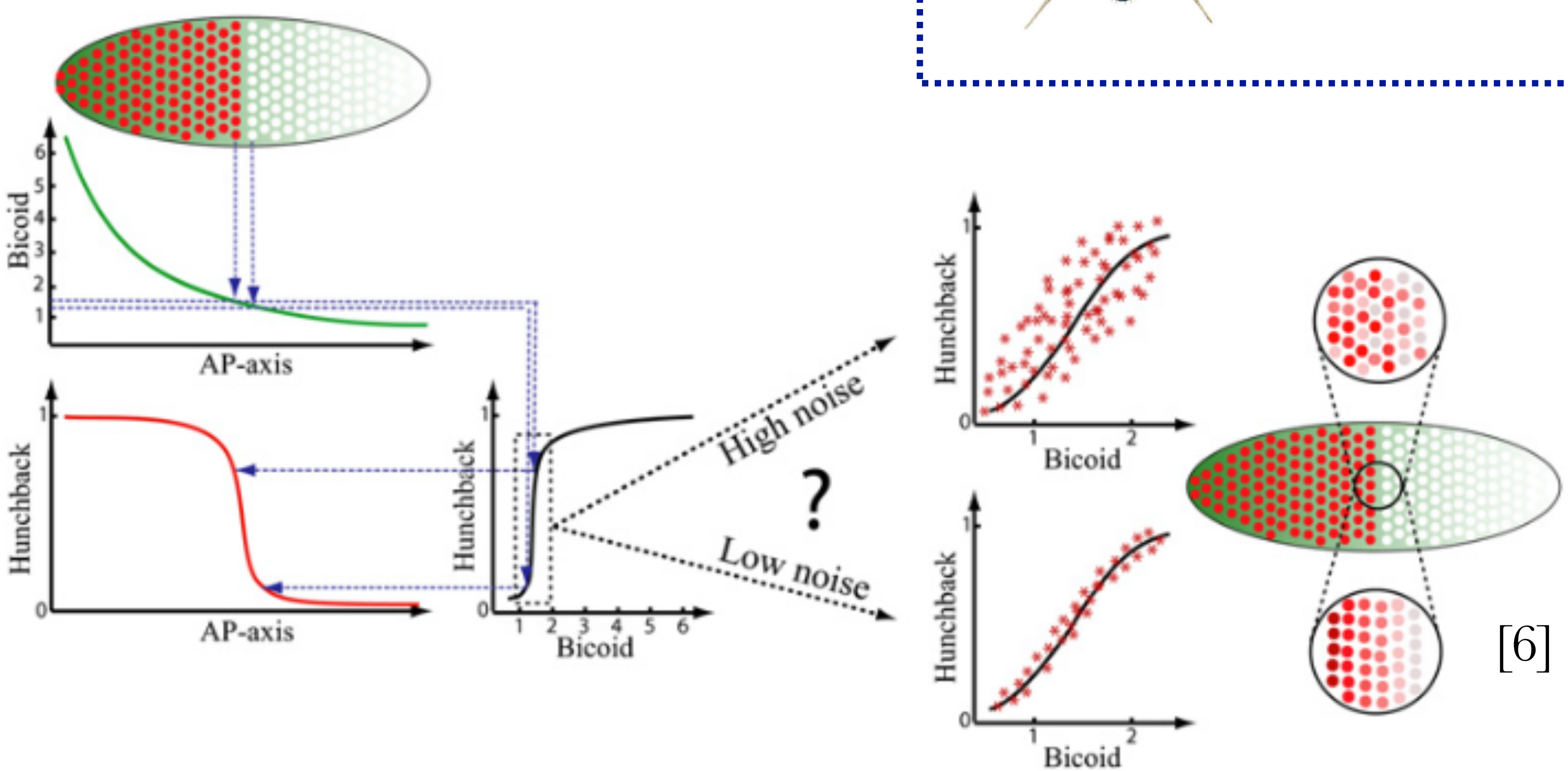
What about Drosophila?

- 2-3 hrs after fertilisation**, neighbouring cells adopt distinct fates** (different gene expression patterns) **i.e.** $\Delta c/c$ **must be ~10%**

$$c(x) = c_0 e^{-x/\lambda}, \lambda = 100\mu m$$

$$\Delta c/c = \Delta x/\lambda \approx 0.1$$





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Drosophila development is also quite precise & reproducible

Two possible explanations: → Each step is **noisy** / Each step is **precise**

Errors arise due to:

- Concentration difference between neighbours
- Random arrival of Bicoid molecules
- Noise in readout by Hb activation
- Non-reproducibility of Bi concentration profiles

In each case, it is established through experiments that $\Delta c/c$ ~ **10%**

Conclusion: Embryo is **not** faced with noisy i/p and readout mechanisms…**response approaches limits set by physical principles**.

Conclusions

- Cells **sense** to make **crucial decisions**
- **Precision is limited** due to stochastic nature of sensing
- In **equilibrium**, precision is limited by **number of receptors** and even **time averaging doesn't help**
- **Non equilibrium** sensing is **not solely limited** by **number of receptors** and **time averaging helps**
- **Non-equilibrium** sensing is more **costly** (requires resources) and is more **beneficial only if 1K_BT energy per receptor is invested**

Conclusions

- **Resources** required for **non-equilibrium** sensing are like 'links in a chain'-they **cannot compensate for one another**

- **Optimally sensing cell** must use **same amount of each resource**(=quantity of scarcest resource present) to avoid wastage

- **Biological organisms** have **evolved to sense very precisely** and their **precision** is perhaps **only limited by physical principles.**

References

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[6] T. Gregor et al. Probing the limits to positional information(2007)

[7] G. Lan et al. The energy–speed–accuracy trade-off in sensory adaptation(2012)

[8] Rob Phillips et al. Physical Biology of the Cell (2nd Edition)-Garland Science (2012)

Thank you for your attention!