THE JOURNEY....

GROUP-7

WORKSHOP ON MATHEMATICAL MODELING OF DEVELOPMENT IMSC CHENNAI

17TH MAY, 2024

OUR TEAM

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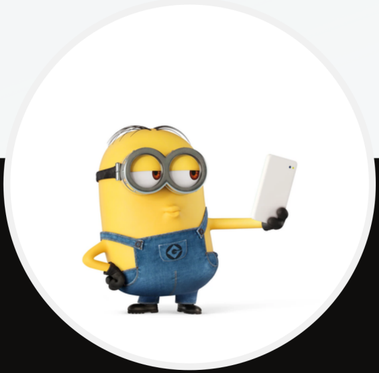
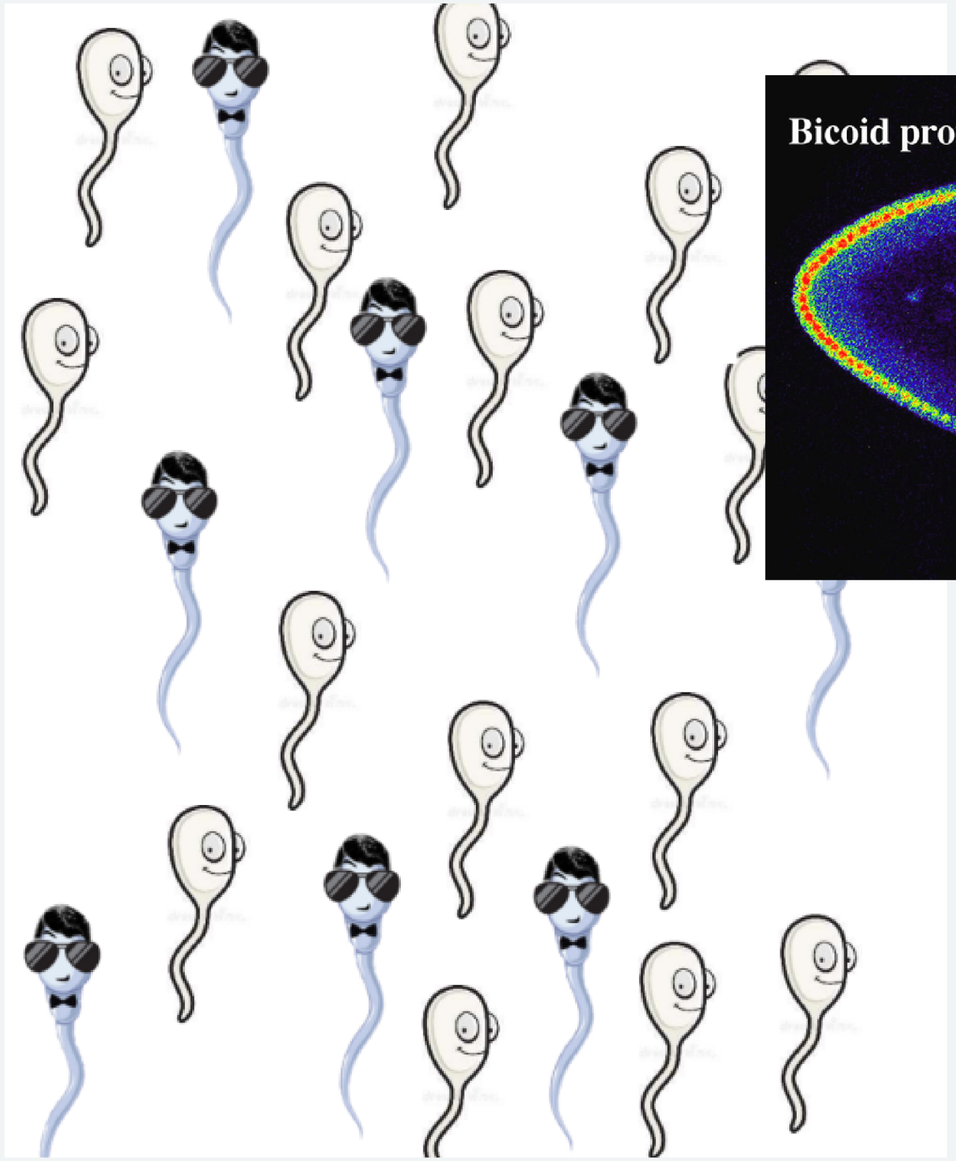
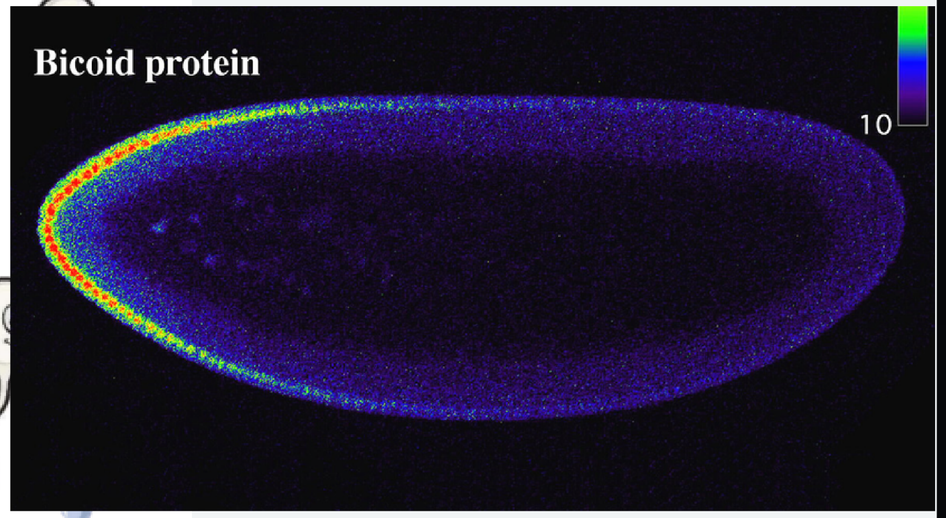
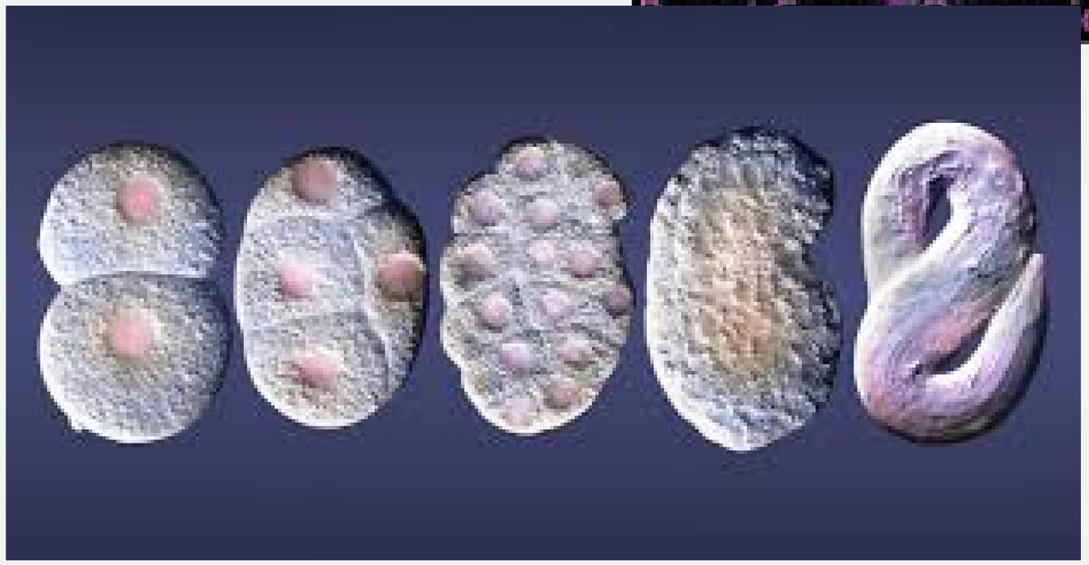


Mrinal

IMSc




Bicoid protein
10

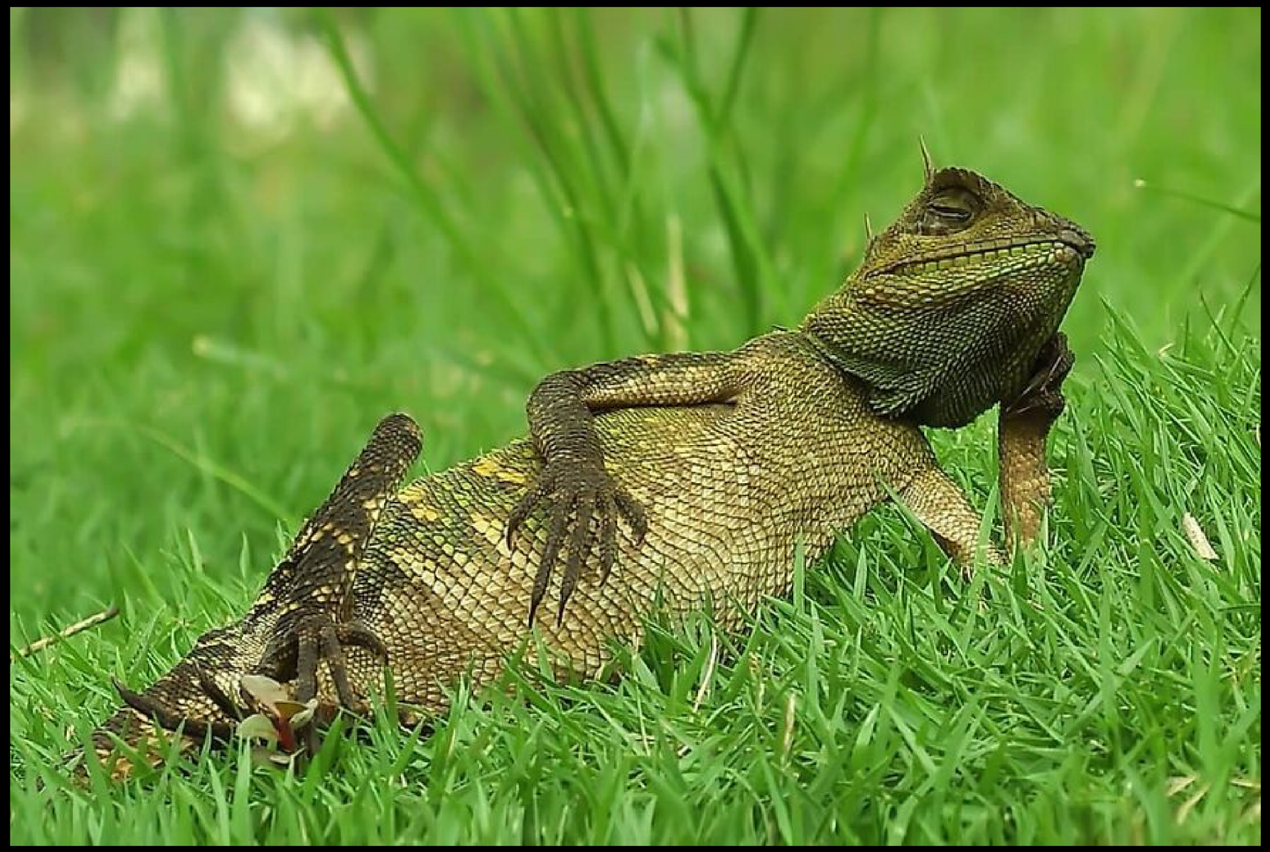


THE BIOLOGICAL QUESTION

https://www.hikariusa.com/wp/blog-post/setting-bearded-dragon-habitat/

- Sex in bearded dragons is determined by sex chromosomes and the temperature at which their eggs are incubated
- <32°C, the offspring from ZZ eggs were all males
- At 36°C, almost all the ZZ individuals were females
- ZZ females themselves lay twice as many eggs as normal ZW females
- ZW lizards are always female.
- If the environment warms significantly, only females may be produced,
- leading to the extinction of the species

Most of the animals are ectothermic

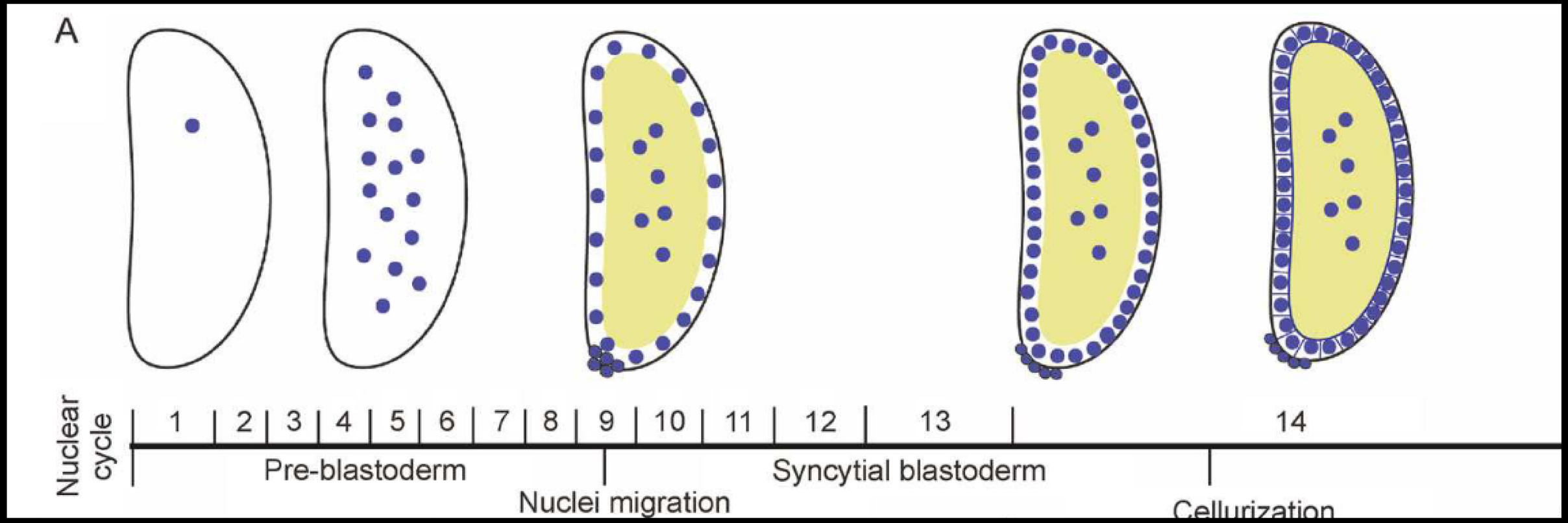


https://en.wikipedia.org/wiki/Sunning_(behaviour)

Some animals like Lizards, crocodiles, terrapins, and snakes routinely use the morning sun to raise their body temperature.

Drosophila is also one of them

Drosophila are ectotherms, and their body temperatures are close to ambient temperature; therefore, flies select a preferred environmental temperature to set their body temperature.



As the temperature increases in certain range,the development time of embryos in the first 13 nuclear cycles shortens from 210 to 110 min

https://doi.org/10.1007/s40484-018-0135-8
https://doi.org/10.1016/j.bpj.2020.08.003

What is effect of the temperature variation the spatial developmental pattern along the AP axis, e.g., the gap gene hb profile?

Experiments (e.g. *Houchmandzadeh, E. Wieschaus, and S. Leibler, 2002)* shows along the AP axis, e.g., the gap gene hb profile, is robust against the temperature perturbation

The gradient formation of bicoid impacts the downstream regulation of genes for spatial developmental pattern formation.

Hypothesis on how temperature interacts with upstream maternal factors:

1. **Temperature-compensation:** The factors involving the formation of gradient formation are fine-tuned to compensate for the effect of temperature.
2. **Temperature-adapted gradients:** Alternatively, some maternal factors might adjust their gradient formation in response to temperature changes. This adaptation could ensure that downstream patterns remain stable despite temperature fluctuations.

Synthesis Diffusion Degradation model

total Bcd concentration (c_{tot}) is given by the reaction-diffusion equation

$$\frac{\partial c_{tot}(x,t)}{\partial t} = D\frac{\partial^2 c_{tot}(x,t)}{\partial x^2} - \frac{c_{tot}(x,t)}{\tau_d} + j_0\delta(x),$$

where D and τ_d represent the diffusion constant and the degradation time of the Bcd protein, respectively. The steady-state solution of the above equation is $c_{tot}(x) = c_0 \times e^{-x/\lambda_{tot}}$, where $c_0 = j_0/\sqrt{D/\tau_d}$, and $\lambda_{tot} = \sqrt{D \times \tau_d}$,

- j_0 = Synthesis rate
- The relationship between temperature and the mean lifetime of a protein can be described using the Arrhenius equation, which is a common model in biochemistry and chemical kinetics: $\tau_d = \tau_{d_0} e^{E_t / RT}$, where E_t is the corresponding activation energy, R is the Universal gas constant in $J/(mol \cdot K)$.

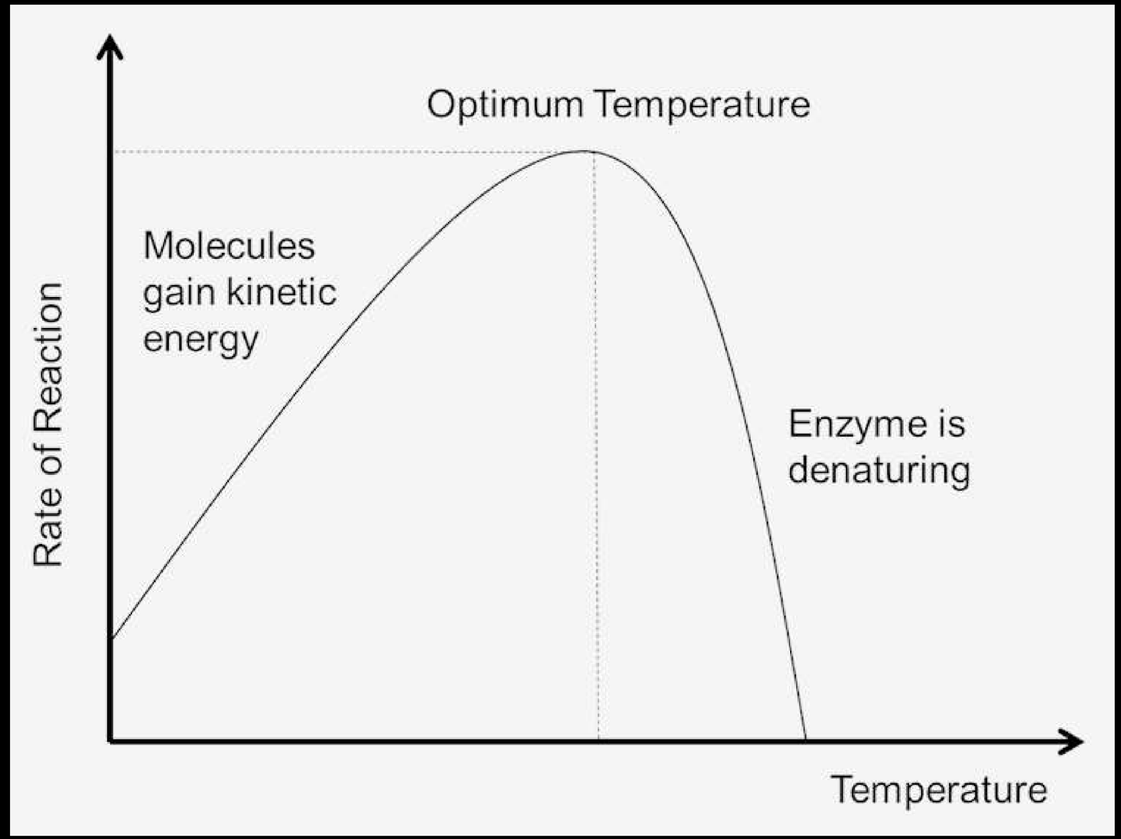
Bicoid gradient formation relevant parameters:

- local production rates of Bcd
- Bcd mobility and transport
- Bcd degradation

All these 3 parameters should be fine-tuned to get the perfect spatial pattern

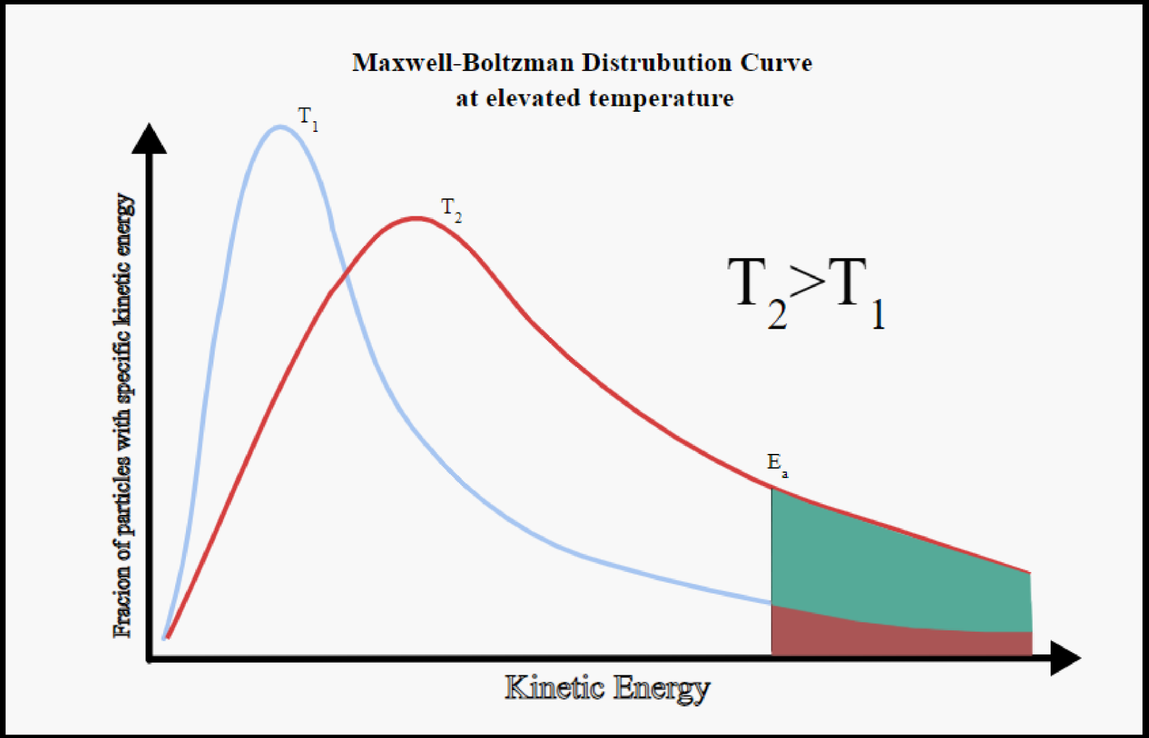
Synthesis

Bcd mRNA (messenger RNA), the blueprint for Bcd protein, is primarily transcribed (copied from DNA) by RNA polymerase II at the anterior end of the embryo.



https://www.creative-enzymes.com/resource/effect-of-temperature-on-enzymatic-reaction_50.html

Effect of temperature on diffusion



Kinetic theory of gases, class 12th, NCERT

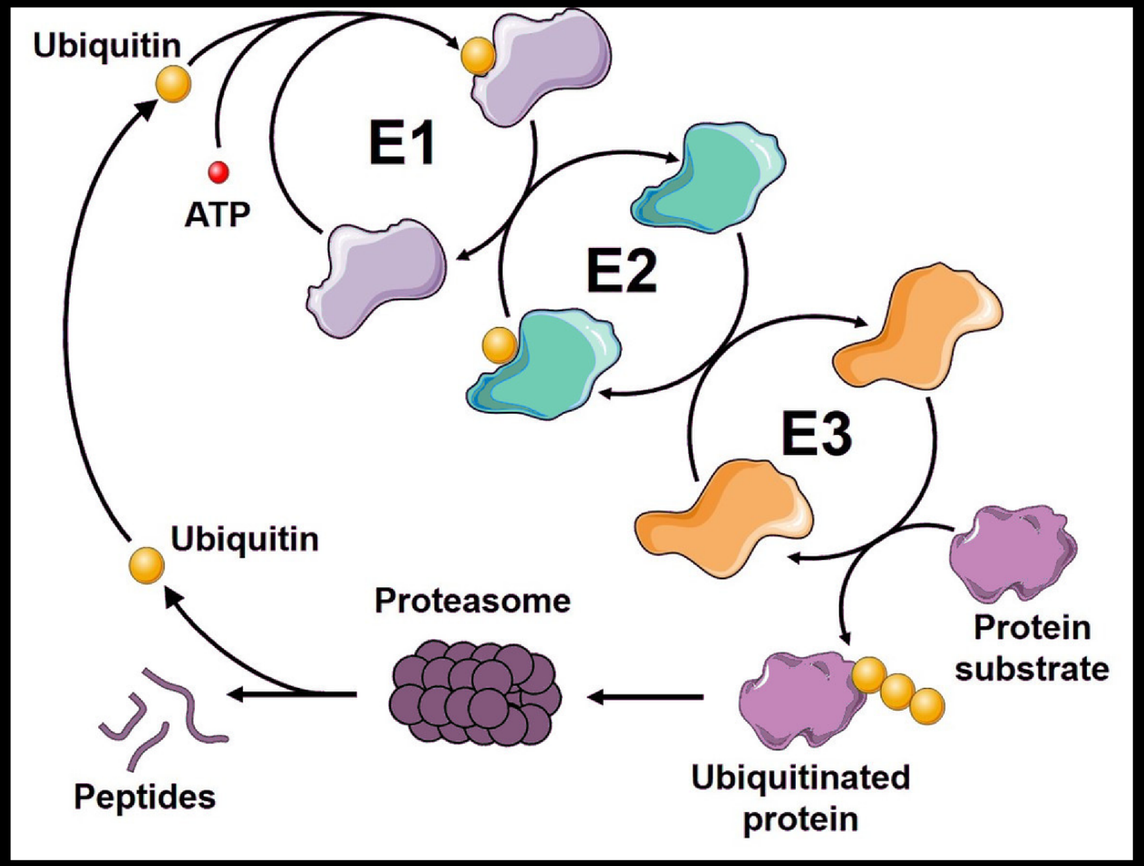
Cell is Crowded

When the temperature increases, the molecules do move faster, but the frequent collisions with other molecules dampen the overall effect of temperature. This means their movement becomes less sensitive to temperature changes compared to the less crowded environment

So in our model, for simplicity, we assumed that the diffusion is insensitive to temperature.

DOI:10.1038/s41598-018-28833-9

Degradation



Bcd degradation was reported to be proteasome-dependent and regulated by the F-box protein Fates shifted (Fsd)—a specificity factor of the E3 ubiquitin ligase SCF

The Ubiquitination Process involves 3 enzymes. E1 uses ATP energy, E2 and E3 enzymes

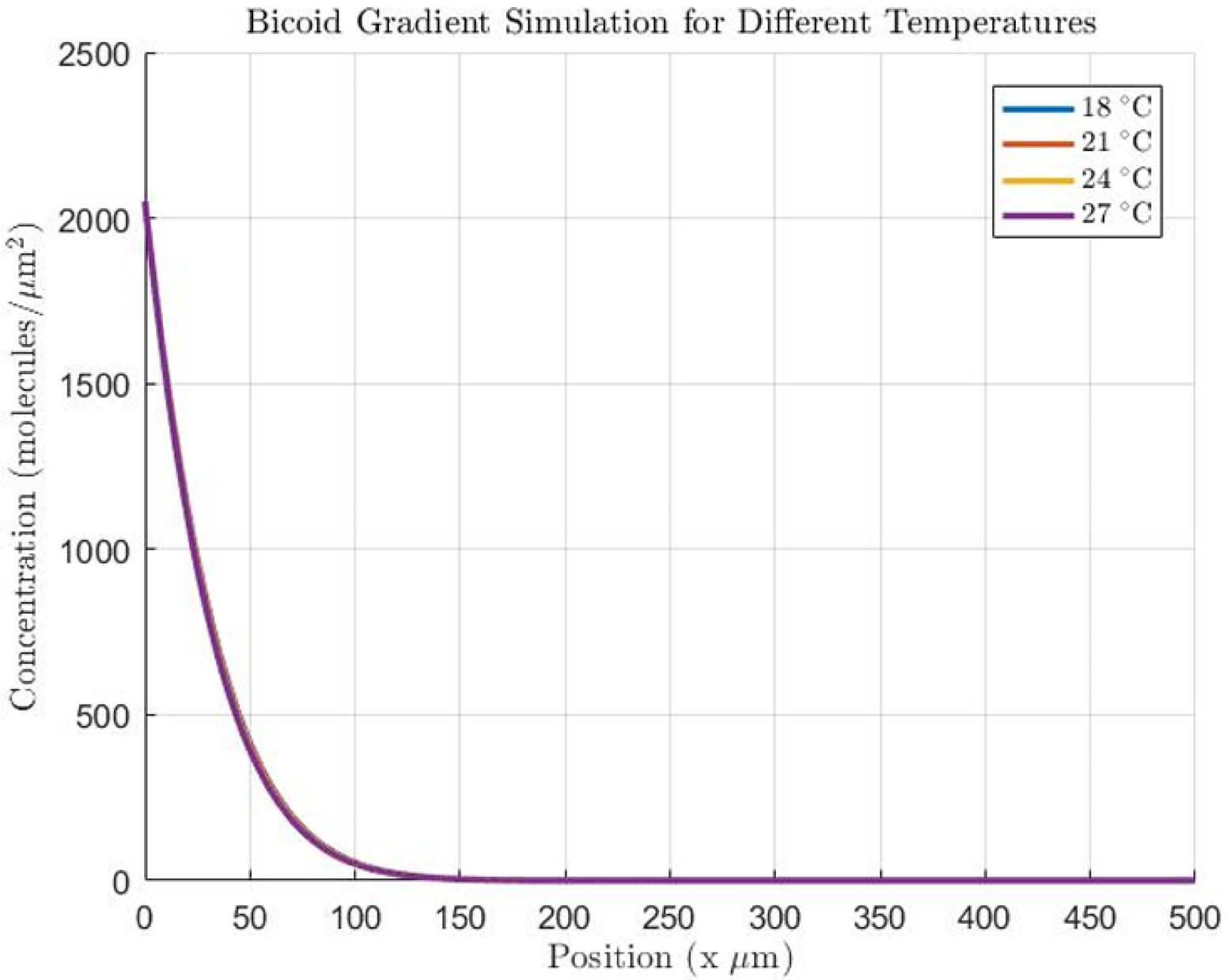
https://www.sdbonline.org/sites/fly/aignfam/protdeg.htm

Simulation 1: Only the Degradation rate changes

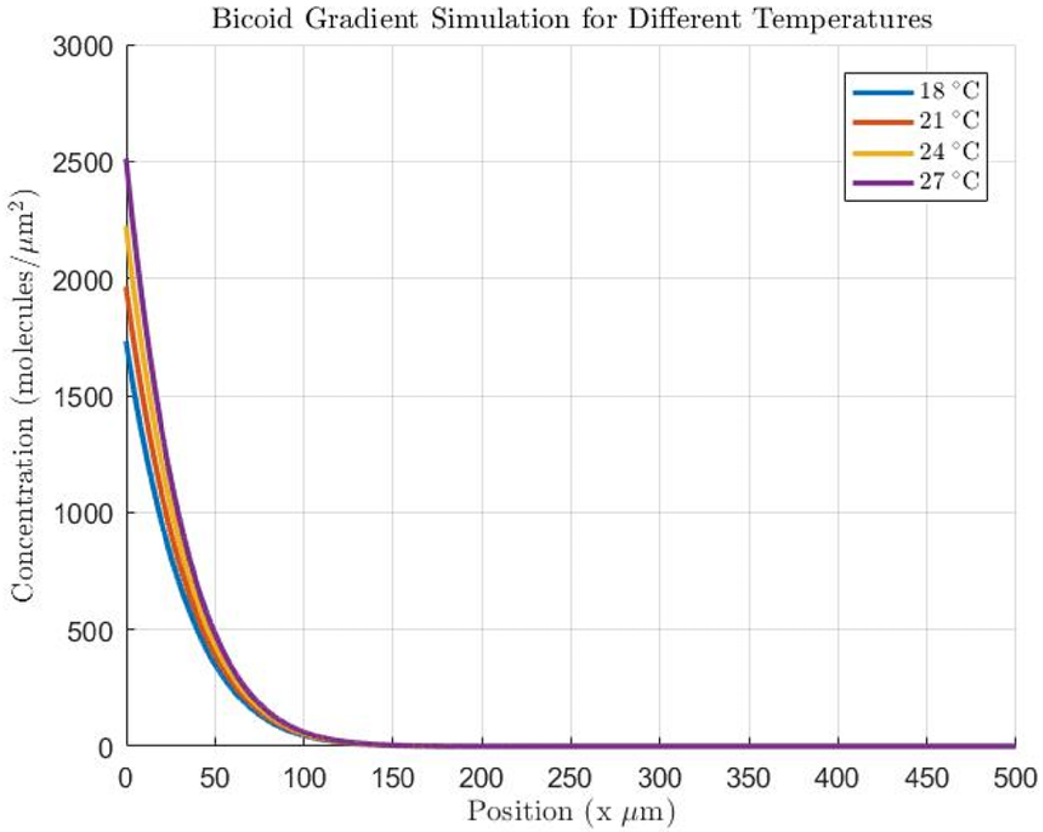
- Based on the previous measurements, $D = 3.60 \mu m^2 / s$, and $t_d = 34\ min$ and $E_t = 5*10^4$ J/mol, $j_0 = 4.1$ molecules/ $\mu m^2 .s$ at 25 Degree C. *(Di Talia, S., and E. F. Wieschaus. 2012., Drocco, J. A., O. Grimm, ., E. Wieschaus. 2011.)*
- From this data, we can find τ_{d_0}.
- For simplicity, we are considering constant source for all temperature.
- We are taking the Diffusion coefficient to be constant for all temperature because of cell crowding.

```
function bicoid_gradient_simulation_multiple
    % Temperatures in Celsius
    temperatures = [18, 21, 24, 27];
    T_kelvin = temperatures + 273.15; % Convert to Kelvin

    % Given synthesis rate at 25°C (used as a constant source term)
    S0_25C = 4.1; % molecules/?m²/s
    Ea_synthesis = 30e3; % Activation energy for synthesis in J/mol
    % Given mean lifetime at 25°C
    A_25C = 34 * 60; % mean lifetime in seconds
    Ea_decay = 50e3; % Activation energy for decay in J/mol
    R = 8.314; % Universal gas constant in J/(mol·K)
    T_25C = 298.15; % Temperature in Kelvin (25°C)

    % Calculate A (Pre-exponential factor for decay) based on the data at 25°C
    A = A_25C / exp(Ea_decay / (R * T_25C));

    % Calculate S0 (Pre-exponential factor for synthesis) based on the data at 25°C
    S0 = S0_25C / exp(-Ea_synthesis / (R * T_25C));

    % Parameters
    D = 3.6; % Diffusion coefficient (?m²/s)
    L = 500; % Length of the spatial domain (?m)
    dx = 0.1; % Spatial step size (?m)
    dt = 0.01; % Initial time step size (s)
    total_time = 500; % Total simulation time (s)

    % Ensure stability condition for the diffusion equation
    if D * dt / dx^2 >= 0.5
        dt = 0.5 * dx^2 / D;
        disp(['Adjusted dt for stability: ', num2str(dt)]);
    end

    % Number of spatial steps
    N = round(L / dx);

    % Initialize matrix to store concentrations for different temperatures
    concentrations = zeros(N, length(T_kelvin));
    concentrations_raw = zeros(N, length(T_kelvin)); % Store raw concentrations

    % Loop through each temperature
    for j = 1:length(T_kelvin)
        T = T_kelvin(j);

        % Derived parameters
        tau = A * exp(Ea_decay / (R * T)); % Temperature-dependent mean lifetime (s)
        S = S0 * exp(-Ea_synthesis / (R * T)); % Temperature-dependent synthesis rate
        num_steps = round(total_time / dt); % Number of time steps

        % Initial conditions
        C = zeros(N, 1); % Concentration array

        % Time-stepping loop
        for t = 1:num_steps
            % Calculate new concentration values
            C_new = C;
            for i = 2:N-1
                C_new(i) = C(i) + D * dt / dx^2 * (C(i+1) - 2*C(i) + C(i-1)) - (1/tau) *
t * C(i);

            end

            % Boundary condition at x = 0 (constant source term)
            C_new(1) = C_new(1) + S * dt;

            % Update concentration values
            C = C_new;
        end

        % Normalize the concentration values (taking both max and min into account)
        C_normalized = (C - min(C)) / (max(C) - min(C));

        % Store the normalized and raw concentrations for this temperature
        concentrations(:, j) = C_normalized;
        concentrations_raw(:, j) = C;
    end

    % Spatial positions
    x = (0:N-1) * dx;
```

```
    % Plotting the normalized concentrations
    figure;
    hold on;
    colors = lines(length(T_kelvin)); % Get distinct colors for each line
    for j = 1:length(T_kelvin)
        plot(x, concentrations(:, j), 'LineWidth', 2, 'Color', colors(j, :));
    end
    hold off;
    xlabel('Position (x $\mu$m)', 'Interpreter', 'latex');
    ylabel('Normalized Concentration', 'Interpreter', 'latex');
    title('Bicoid Gradient Simulation for Different Temperatures', 'Interpreter', 'latex')
;
    legend(arrayfun(@(T) [num2str(T - 273.15) ' $^\circ$C'], T_kelvin, 'UniformOutput', fa
lse), 'Interpreter', 'latex');
    grid on;

    % Plotting the raw concentrations
    figure;
    hold on;
    for j = 1:length(T_kelvin)
        plot(x, concentrations_raw(:, j), 'LineWidth', 2, 'Color', colors(j, :));
    end
    hold off;
    xlabel('Position (x $\mu$m)', 'Interpreter', 'latex');
    ylabel('Concentration (molecules/$\mu$m$^2$)', 'Interpreter', 'latex');
    title('Bicoid Gradient Simulation for Different Temperatures', 'Interpreter', 'latex')
;
    legend(arrayfun(@(T) [num2str(T - 273.15) ' $^\circ$C'], T_kelvin, 'UniformOutput', fa
lse), 'Interpreter', 'latex');
    grid on;
end
```



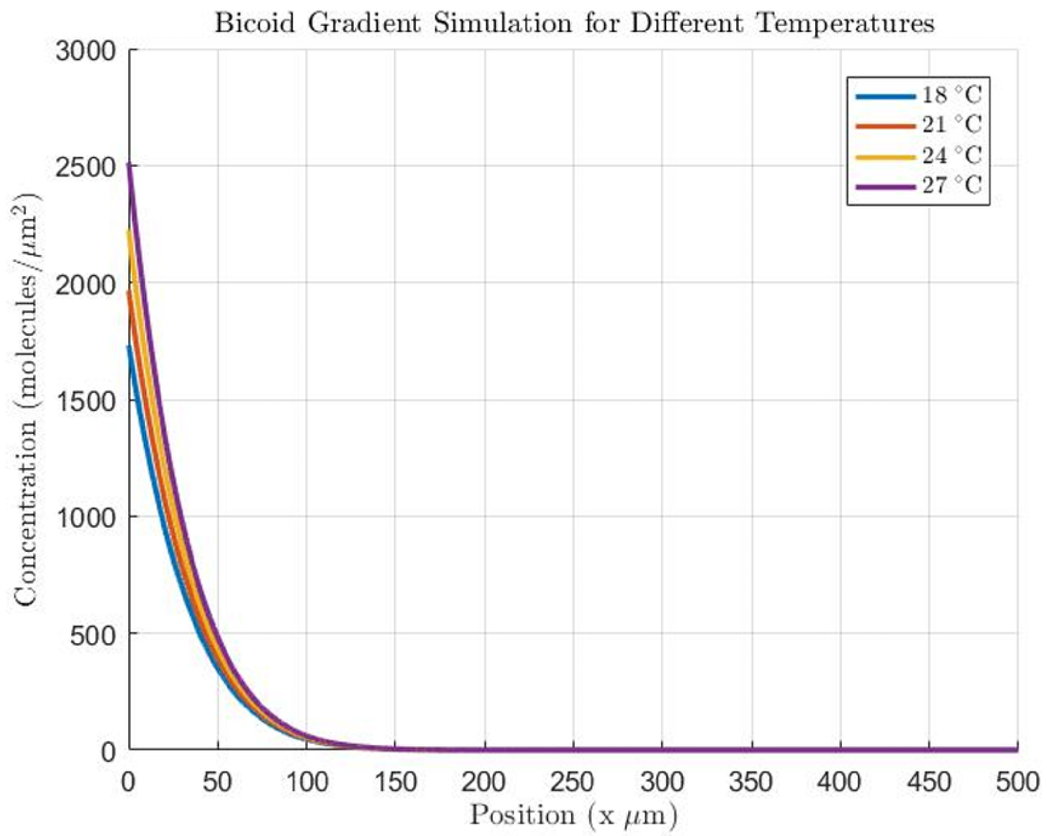
- Observe that there is no significant change with the change in temperature.
- However, we have not considered the change in the synthesis rate



Simulation 2: Considering Synthesis rate varies with temperature

- Calculated the value of the pre-factor j_{s_0} by using the data of j_0 = **4.1 molecules/ μm^2 .s** at 25 Degree C. (*(Di Talia, S., and E. F. Wieschaus. 2012.; Drocco, J. A., O. Grimm, ., E. Wieschaus. 2011.; Hongcun Zhu, Yeping Cui, Chunxiong Luo, and Feng Liu, 2020)*)

- The graph shows that the concentration is varying for a position at different temperature
- However, the bicoid concentration should remain conserved with varying temperatures for spatial developmental patterns to remain the same.
- Probable reasons for this discrepancy:
  - Diffusion also varies significantly with temperature.
  - The active process may involve the propagation of the bicoid.
  - Constant source: the enzyme's optimal temperature is not considered.



Future prospect

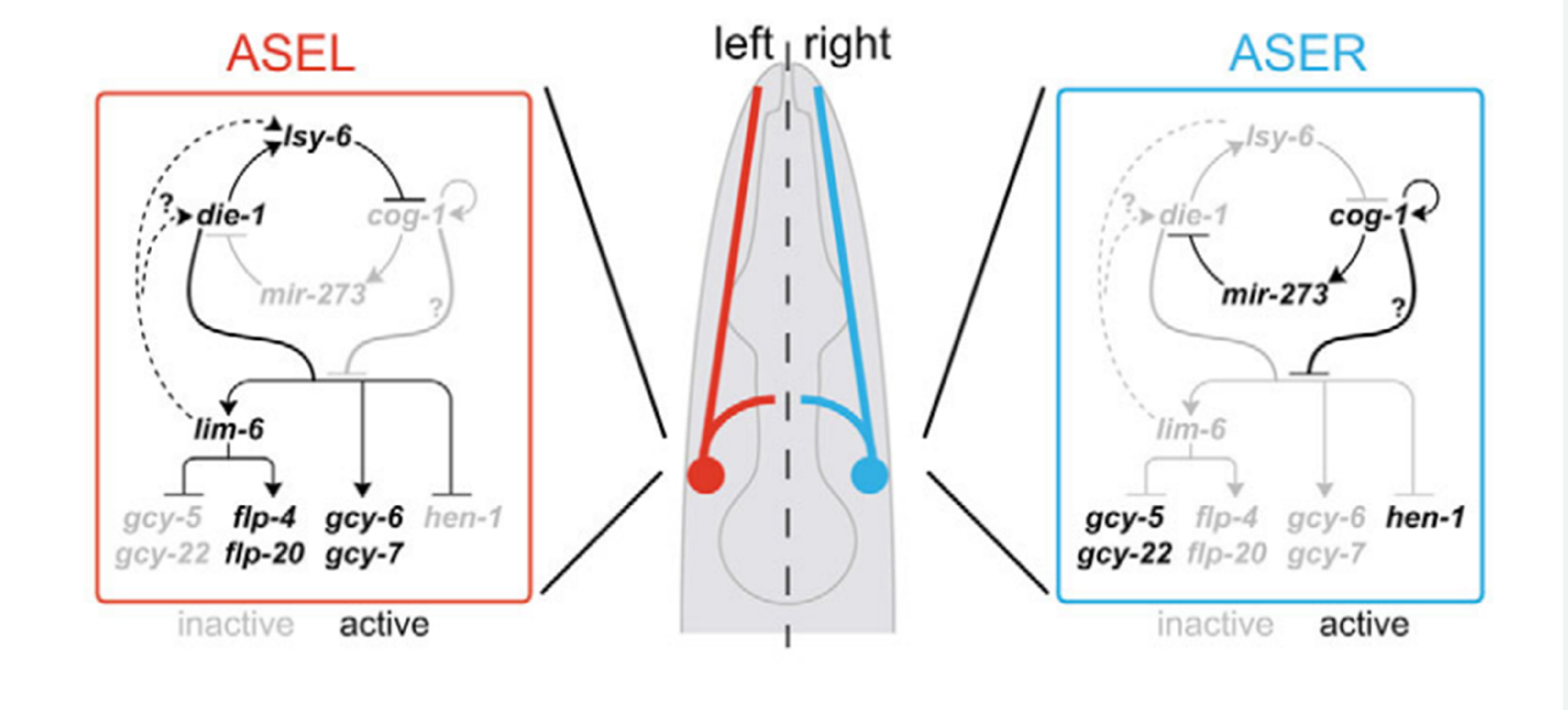
- To include the biological activity of enzymes, how their efficiency changes with temperature
- Consider the change in the length of the larva.
- To study dynamics of downstream genes

REFERENCES

- Kerrie A Smyth, John M Belote, The Dominant Temperature-Sensitive Lethal DTS7 of Drosophila melanogaster Encodes an Altered 20S Proteasome β-Type Subunit, Genetics, Volume 151, Issue 1, 1 January 1999, Pages 211–220, Add a littl
- Durrieu L, Kirrmaier D, Schneidt T, et al. Bicoid gradient formation mechanism and dynamics revealed by protein lifetime analysis. Mol Syst Biol. 2018;14(9):e8355. Published 2018 Sep 4. doi:10.15252/msb.20188355
- Zhu H, Cui Y, Luo C, Liu F. Quantifying Temperature Compensation of Bicoid Gradients with a Fast T-Tunable Microfluidic Device. Biophys J. 2020;119(6):1193-1203. doi:10.1016/j.bpj.2020.08.003
- Little SC, Tkačik G, Kneeland TB, Wieschaus EF, Gregor T (2011) The Formation of the Bicoid Morphogen Gradient Requires Protein Movement from Anteriorly Localized mRNA. PLOS Biology 9(3): e1000596. https://doi.org/10.1371/journal.pbio.1000596
- Nat Cell Biol. 2011 January ; 13(1): 22–29. doi:10.1038/ncb2141. DOI: 10.1371/journal.pbio.1000596 · Source: PubMed
- Liu J, He F, Ma J. Morphogen gradient formation and action: insights from studying Bicoid protein degradation. Fly (Austin). 2011;5(3):242-246. doi:10.4161/fly.5.3.15837
- Reaction and diffusion thermodynamics explain optimal temperatures of biochemical reactions.

End-time anxieties can lead to good ideas

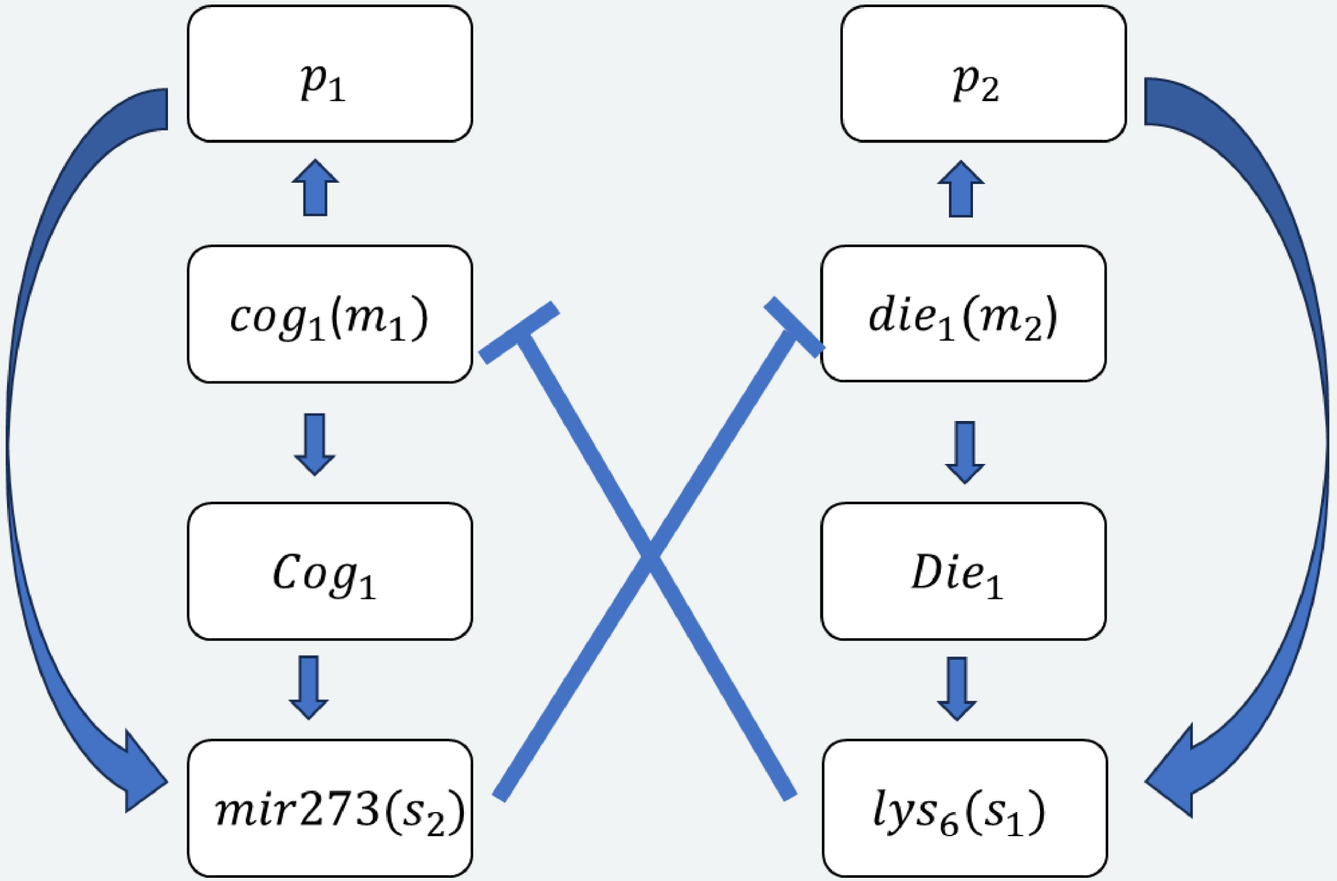
Neuronal cell fate decision in *Caenorhabditis elegans*



- ✓ Johnston Jr, Robert J., and Oliver Hobert. "A novel C. elegans zinc finger transcription factor, lsy-2, required for the cell type-specific expression of the lsy-6 microRNA." (2005): 5451-5460.

Internal Gene regulatory network

miRNA	$lys_6(s_1)$	$mir273(s_2)$
Transcription Factor	Die_1	Cog_1
mRNA	$die_1(m_2)$	$cog_1(m_1)$
Protein	p_2	p_1



Mathematical Modelling

miRNA	$lys_6(s_1)$	$mir273(s_2)$
mRNA	$die_1(m_2)$	$cog_1(m_1)$
Protein	p_2	p_1

$$\frac{d[m_1]}{dt} = \alpha m_1 - \mu_1[m_1][s_1] + \mu_2[c_1] - k_m[\mathrm{m_1}]$$

$$\frac{d[s_1]}{dt} = \alpha s_1 + \frac{a_1[p_2]}{a_2 + [p_2]} - \mu_1[m_1][s_1] + \mu_2[c_1] + \mathrm{k_1}\,[c_1] - k_s[\mathrm{s_1}]$$

$$\frac{d[c_1]}{dt} = \mu_1[m_1][s_1] - \mu_2[c_1] - \mathrm{k_1}\,[c_1] - k_c[c_1]$$

$$\frac{d[p_1]}{dt} = \alpha p_1[m_1] - k_p[p_1]$$

$$\frac{d[m_2]}{dt} = \alpha m_2 - \mu_2[m_2][s_2] + \mu_2[c_1] - k_m[\mathrm{m_2}]$$

$$\frac{d[s_2]}{dt} = \alpha s_2 + \frac{a_1[p_1]}{a_2 + [p_1]} - \mu_1[m_2][s_2] + \mu_2[c_2] + \mathrm{k_2}\,[c_2] - k_s[\mathrm{s_2}]$$

$$\frac{d[c_2]}{dt} = \mu_1[m_2][s_2] - \mu_2[c_2] - \mathrm{k_1}\,[c_2] - k_c[c_2]$$

$$\frac{d[p_2]}{dt} = \alpha p_2[m_2] - k_p[p_2]$$

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```
Clear[gammam1, gammam2, am1, am2, as1, as2, gammas1, gammas2, ap1, ap2, gammap1, gammap2,
  mu1, mu2, k1, k2, tau1, tau2, dc1, dc2, d1, c1, d2, c2, y1, y2, p1, p2, r1, dp1, dp2, leak, n];
gammam1 = gammam2 = 0.2; am1 = am2 = 15; as1 = as2 = 1; gammas1 = gammas2 = 0.08; ap1 = ap2 = 0.1;
gammap1 = gammap2 = 0.08; t1 = t2 = 20; r1 = r2 = 40; mu1 = 0.2; mu2 = 0.001; k1 = k2 = 0.1;
tau1 = tau2 = 0.2;
Solve[{am1 - mu1 * m1 * s1 + mu2 * c1 - gammam1 * m1 == 0,
  as1 + (t1 * p2)/(r1 + p2) - mu1 * m1 * s1 + mu2 * c1 + k1 * c1 - gammas1 * s1 == 0, mu1 * m1 * s1 - mu2 * c1 - k1 * c1 - tau1 * c1 == 0,
  ap1 * m1 - gammap1 * p1 == 0, am2 - mu1 * m2 * s2 + mu2 * c2 - gammam2 * m2 == 0,
  as2 + (t2 * p1)/(r2 + p1) - mu1 * m2 * s2 + mu2 * c2 + k2 * c2 - gammas2 * s2 == 0, mu1 * m2 * s2 - mu2 * c2 - k2 * c2 - tau2 * c2 == 0,
  ap2 * m2 - gammap2 * p2 == 0}, {s1, c1, p1, m1, m2, s2, c2, p2}]
```

```
{{c1 → 8.9967, c2 → 49.0915, m1 → 61.505, m2 → 1.36279, p1 → 76.8812, p2 → 1.70349,
  s2 → 54.2144, s1 → 0.220145}, {c1 → 38.558, c2 → 38.558, m1 → 17.163, m2 → 17.163,
  p1 → 21.4538, p2 → 21.4538, s2 → 3.38109, s1 → 3.38109}, {c1 → 49.0915, c2 → 8.9967,
  m1 → 1.36279, m2 → 61.505, p1 → 1.70349, p2 → 76.8812, s2 → 0.220145, s1 → 54.2144},
 {c1 → 50.4264, c2 → 50.4264, m1 → -0.639549, m2 → -0.639549, p1 → -0.799437,
  p2 → -0.799437, s2 → -118.664, s1 → -118.664}, {c1 → 137.75, c2 → 137.75, m1 → -131.625,
  m2 → -131.625, p1 → -164.532, p2 → -164.532, s2 → -1.57503, s1 → -1.57503}}
```

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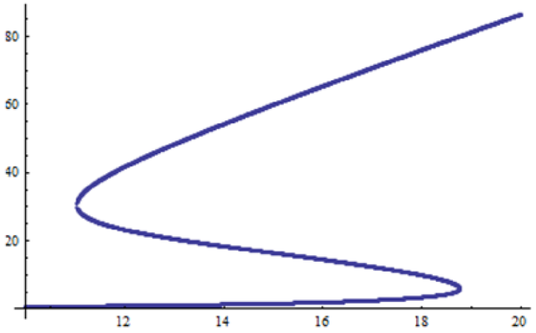
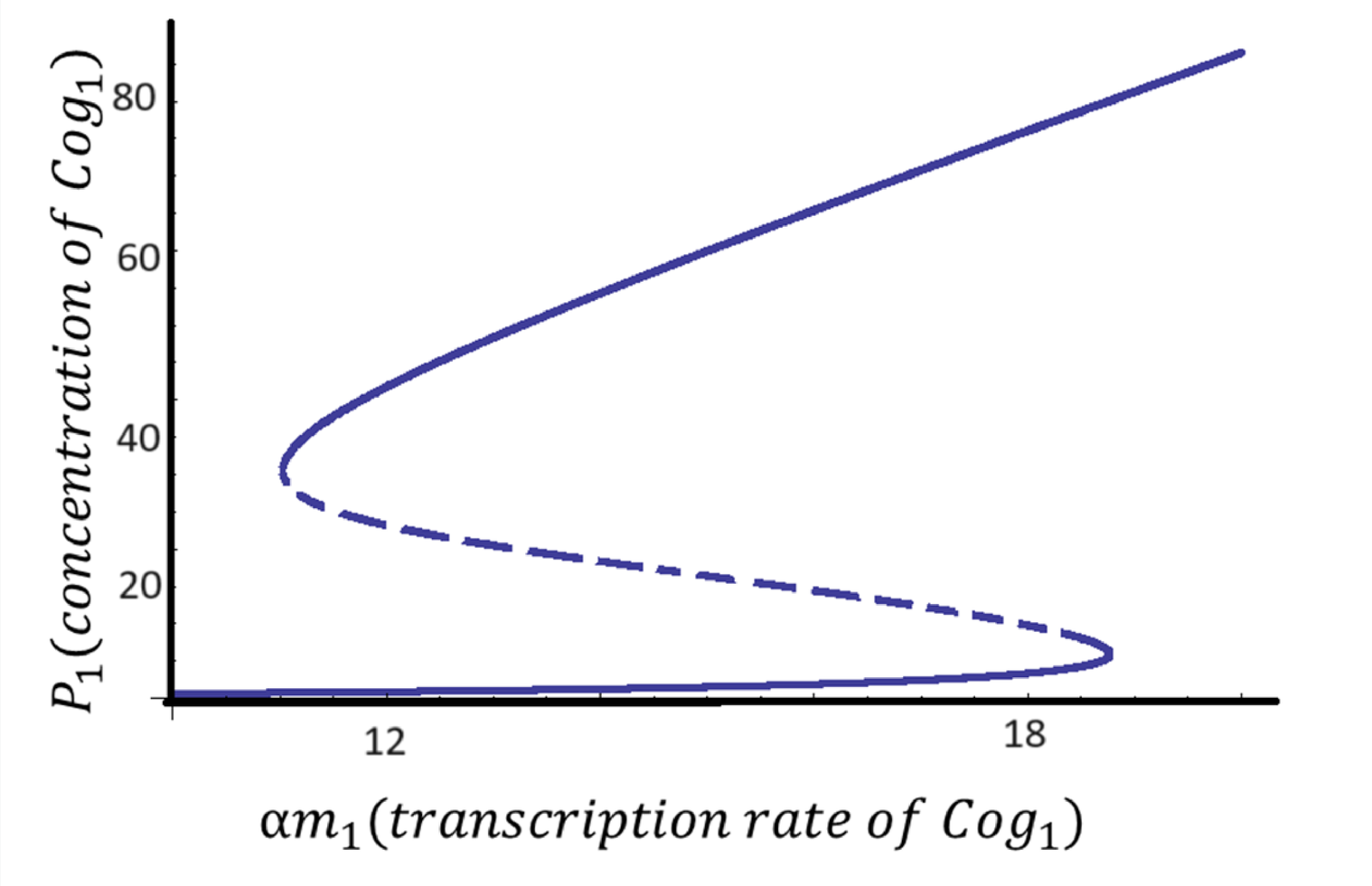
```
Clear[gammam1, gammam2, am1, am2, as1, as2, gammas1, gammas2, ap1, ap2, gammap1, gammap2, mu1, mu2, k1, k2, tau1, tau2, dc1, dc2, d1, c1, d2, c2, y1, y2, p1, p2, r1, dp1, dp2, leak, n];
stmp9 = OpenWrite["tog_1.dat", FormatType → OutputForm];
gammam1 = gammam2 = 0.25; am2 = 15; as1 = as2 = 1; gammas1 = gammas2 = 0.08; ap1 = ap2 = 0.1; gammap1 = gammap2 = 0.08; t1 = t2 = 20; r1 = r2 = 35; mu1 = 0.2; mu2 = 0.001; k1 = k2 = 0.1; tau1 = tau2 = 0.15;
Do[
 {S = NSolve[{am1 - mu1 * m1 * s1 + mu2 * c1 - gammam1 * m1 == 0, as1 + t1 * p2 / (r1 + p2) - mu1 * m1 * s1 + mu2 * c1 + k1 * c1 - gammas1 * s1 == 0, mu1 * m1 * s1 - mu2 * c1 - k1 * c1 - tau1 * c1 == 0, ap1 * m1 - gammap1 * p1 == 0, am2 - mu1 * m2 * s2 + mu2 * c2 - gammam2 * m2 == 0,
     as2 + t2 * p1 / (r2 + p1) - mu1 * m2 * s2 + mu2 * c2 + k2 * c2 - gammas2 * s2 == 0, mu1 * m2 * s2 - mu2 * c2 - k2 * c2 - tau2 * c2 == 0, ap2 * m2 - gammap2 * p2 == 0}, {s1, c1, p1, m1, m2, s2, c2, p2}];
  x1 = p1 /. S[[1]];
  x2 = p1 /. S[[2]];
  x3 = p1 /. S[[3]];
  x4 = p1 /. S[[4]];
  x5 = p1 /. S[[5]];
  z1 = p2 /. S[[1]];
  z2 = p2 /. S[[2]];
  z3 = p2 /. S[[3]];
  z4 = p2 /. S[[4]];
  z5 = p2 /. S[[5]];
  If[Im[x1] == 0 && x1 ≥ 0 && Im[z1] == 0 && z1 ≥ 0, {Write[stmp9, am1, " ", x1]}];
  If[Im[x2] == 0 && x2 ≥ 0 && Im[z2] == 0 && z2 ≥ 0, {Write[stmp9, am1, " ", x2]}];
  If[Im[x3] == 0 && x3 ≥ 0 && Im[z3] == 0 && z3 ≥ 0, {Write[stmp9, am1, " ", x3]}];
  If[Im[x4] == 0 && x4 ≥ 0 && Im[z4] == 0 && z4 ≥ 0, {Write[stmp9, am1, " ", x4]}];
  If[Im[x5] == 0 && x5 ≥ 0 && Im[z5] == 0 && z5 ≥ 0, {Write[stmp9, am1, " ", x5]}];
 }, {am1, 10, 20, 1}];
Close[stmp9];
data1 = Import["tog_1.dat"]
```

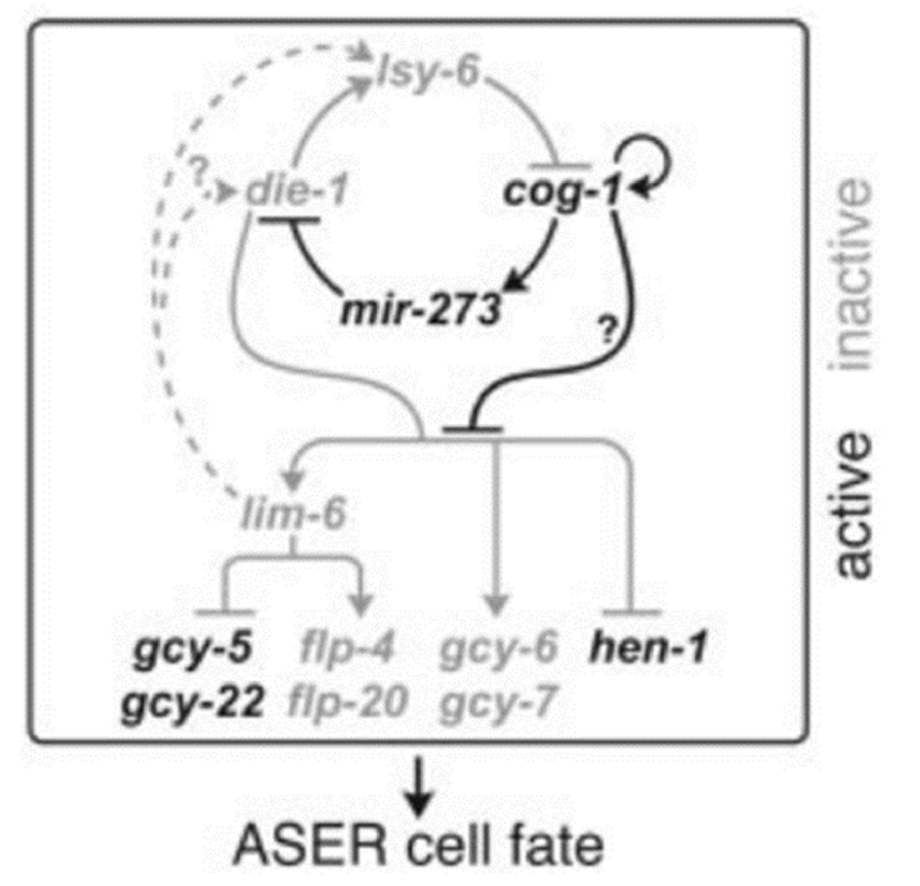
```
{{10, 0.619926}, {11, 0.738888}, {12, 41.6876}, {12, 0.88015}, {12, 23.2101}, {13, 48.2995}, {13, 1.05109}, {13, 20.5094}, {14, 54.2382}, {14, 1.26305}, {14, 18.3801},
 {15, 59.877}, {15, 1.53467}, {15, 16.4228}, {16, 65.3471}, {16, 1.89985}, {16, 14.4632}, {17, 70.7104}, {17, 2.43119}, {17, 12.3556}, {18, 76.001}, {18, 3.34636}, {18, 9.835}, {19, 81.2394}, {20, 86.4388}}
```

```
i1 = ListPlot[data1]
```



Bistability in cog-1 redirects cell fate decision-making





References

1. Johnston Jr, Robert J., et al. "MicroRNAs acting in a double-negative feedback loop to control a neuronal cell fate decision. " Proceedings of the National Academy of Sciences 102.35 (2005): 12449-12454.

2. Johnston Jr, Robert J., and Oliver Hobert. "A novel C. elegans zinc finger transcription factor, lsy-2, required for the cell type-specific expression of the lsy-6 microRNA." (2005): 5451-5460.

3. Hobert, Oliver. "Development of left/right asymmetry in the Caenorhabditis elegans nervous system: from zygote to postmitotic neuron." genesis 52.6 (2014): 528-543.

THANK YOU