D.6 Understanding the Hill equation

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February 2025

Abstract

In this study, we analyze the Hill equation and explore how variations in its parameters maximum reaction rate(V_{max}), Hill coefficient(h) and substrate concentration at half the maximal activity (K_{half}) affects the shape of the graph created by our equation. By generating plots for each parameter while keeping the others constant, we find that a higher V_{max} causes our maximum reaction rate to increase. With a higher h, hill coefficient, We also reach the maximum reaction rate at much lower concentrations, whereas with a higher K_{half} it takes higher substrate concentrations to reach maximum reaction rate. These insights help us predict the system's behavior with given initial conditions. Additionally, we also analyze the substrate concentration over time using the Forward Euler method to highlight the dynamic between the reaction rate curves and time evolution graphs.

Introduction

The Hill equation is a general functional form that can be used to describe cooperativity in the rate of an enzyme or in the activity of a transcription factor. The Hill equation takes the form of:

$$\nu = \frac{V_{\max}[S]^h}{K_{1/2}^h + [S]^h}$$

where:

- ν is the reaction rate or activity of the enzyme.

- $V_{\max}$ represents the maximum reaction rate, which occurs when all enzyme binding sites are saturated with substrate.
- $[S]$ is the substrate concentration.
- h is the Hill coefficient, which signifies the degree of cooperativity in substrate binding:
- $K_{1/2}$ is the substrate concentration at which the reaction rate reaches half of $V_{\max}$.

In this study, we computationally explore the impact of these parameters on the Hill equation by generating plots and modeling substrate concentration dynamics over time.

Figure 1 and 2 show the code in MATLAB we wrote to simulate and generate our graphs. Figure 1 generates graph of reaction rate vs substrate concentration and Figure 2 generates graph of substrate concentration vs time.

```
V_max = 5;
K_half = 20;
h = 1;
h_two = 2;
h_three = 10;

S_values = linspace(0,100,101);
v_values = zeros(1, 101);
v_values_two = zeros(1, 101);
v_values_three = zeros(1, 101);

function v = hill_equation(V_max, h, K_half, S)
    v = V_max * S ^ h / (K_half + S ^ h);
end

for i = 1:101
    v_values(i) = hill_equation(V_max, h, K_half, S_values(i));
    v_values_two(i) = hill_equation(V_max, h_two, K_half, S_values(i));
    v_values_three(i) = hill_equation(V_max, h_three, K_half, S_values(i));
end

figure;
hold on;
plot(S_values, v_values, 'b');
plot(S_values, v_values_two, 'r');
plot(S_values, v_values_three, 'g');
xlabel('Substrate concentration(mM)');
ylabel('Rate(mM/s)');
title('Vary h');
legend('h = 1', 'h = 2', 'h = 10');
```

Figure 1: Code used to plot rate vs substrate concentration

```
V_max = 20;
K_half = 50;
h = 4;


init_S = 100;
step_size = 0.01; % Step size
num_steps = 10/step_size;
S_values = zeros(1, num_steps + 1); % Protein amounts
S_values(1) = init_S;
t_values = zeros(1, num_steps + 1);
t = 0;

function v = hill_equation(V_max, h, K_half, S)
    v = V_max * S ^ h / (K_half + S ^ h);
end


for i = 1:num_steps
    t = t + step_size;
    S_values(i+1) = S_values(i) + hill_equation(V_max, h, K_half, S_values(i)) * step_size;
    t_values(i+1) = t;
end

figure;
hold on;
plot(t_values, S_values, 'b');
xlabel('Time(sec)');
ylabel('Substrate concentration(mM)');
title('Substrate concentration over time');
legend('V_{max} = 20, h = 2, K_{half} = 50');
```

Figure 2: Code used to plot substrate concentration over time

Results and Discussion

To visualize how the parameters of the Hill equation impact its shape, we plot the equation with varying parameters. Below, Figures 3, 4, and 5 show simulations over a range of [S] = 0 to 100 mM each with a single varying parameter.

In Figure 3 we plot the Hill equation with h = 1, h = 2, h = 10 while keeping $K_{half} = 20$ mM and $V_{max} = 5$ mM/s for all 3 lines. Hill coefficient is a measure of the degree of "cooperativity" of binding. As such, the higher the coefficient, the stronger the binding cooperativity, which leads to an increased rate of reaction. This is reflected in our graph where as h increases, the curve becomes steeper and we reach maximum reaction rate at lower a substrate concentration.

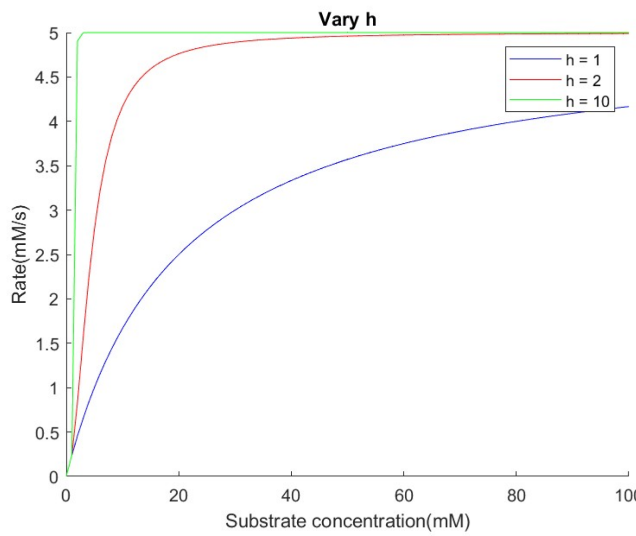

Figure 3: Varying hill coefficient, h

In figure 4, we graph 3 lines with varying K_{half}, substrate concentration at which the reaction reaches half its maximal activity. We keep V_{max} = 5 mM/s and h = 2 for each graph. As K_{half} increases, the curve shifts rightward, meaning a higher substrate concentration is required to reach a given reaction rate.

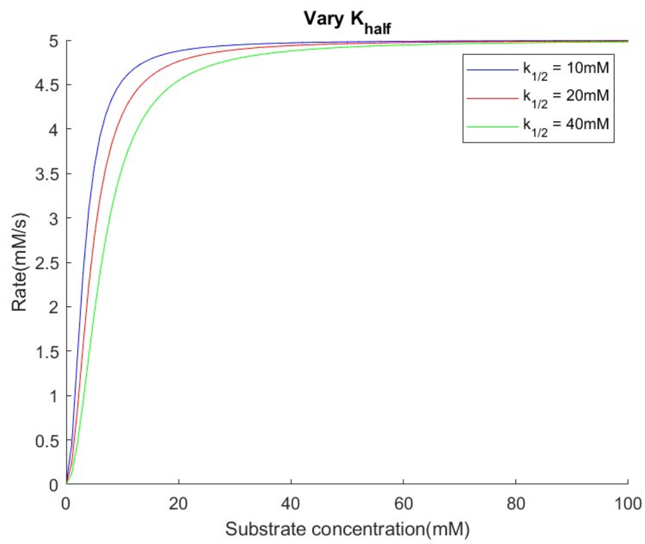

Figure 4: Varying half concentration, K_{half}

In figure 5, we graph 3 lines with varying V_{max}, the maximal activity rate. We keep K_{half} = 20 mM and h = 2 for all 3 lines. The results in Figure 3 demonstrate that increasing V_{max} increases the ceiling for the maximum rate. This alters the curve but does not change the substrate concentration at which half maximal activity occurs.

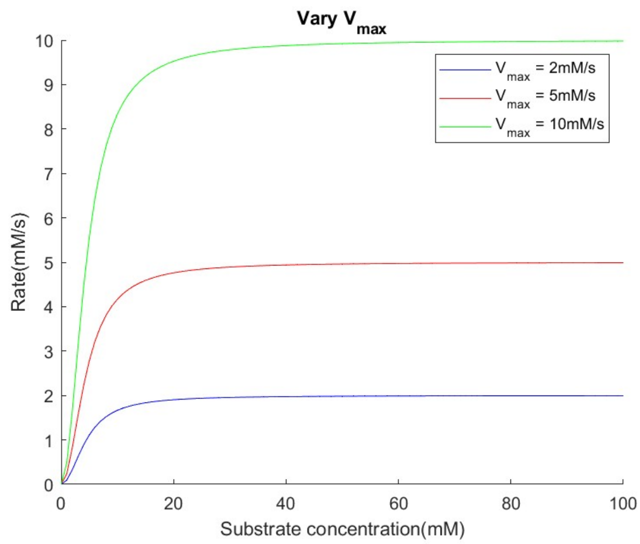

Figure 5: Varying max reaction rate, V_{max}

Based on the observations made in Figure 3, 4 and 5 we can predict that a plot of the hill equation with h = 4, V_{max} = 20 mM/s and K_{half} = 50 mM, we will get a graph with a maximal activity rate of 20 mM/s. Even though both h and K_{half} have an impact on the rate at which we reach the maximum activity, h clearly has a stronger affect so we can expect the slope of our graph to be steep. Figure 6 is a sketch of our expected graph.

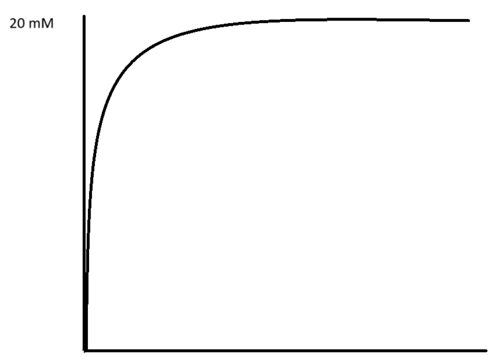

Figure 6: Sketch of our prediction

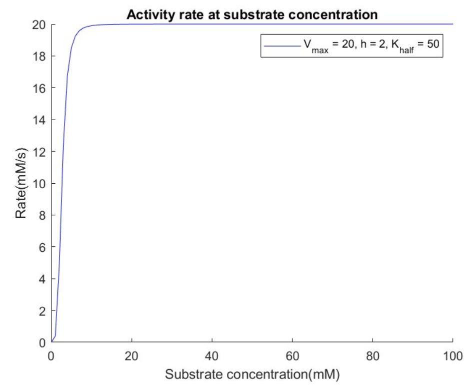

Figure 7: h = 4, V_{max} = 20 mM/s, K_{half} = 50 mM

Figure 7 shows the result of running a simulation with the above parameters which supports our sketch of the expected graph.

In Figure 8, we model the change in substrate concentration over time using the Forward Euler algorithm. Unlike the previous graphs where we we plot the reaction rate as a function of substrate concentration, this graph shows the total substrate concentration over a 10 second period with a time step of .01s, starting concentration of 100 mM and model parameters of h = 4, V_{max} = 20 mM/s, K_{half} = 50 mM.

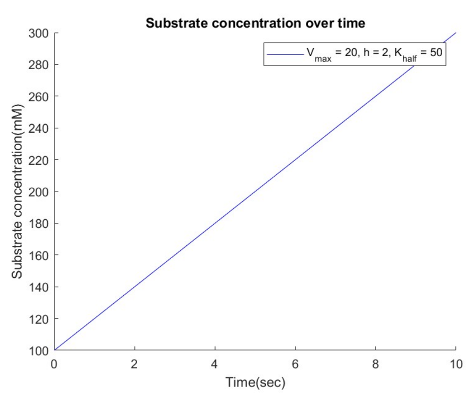

Figure 8: Concentration vs Time graph calculated using Forward Euler

This plot is different from our previous plot as this one shows the total substrate concentration as we move in time whereas the other graphs shows the rate of reaction at various substrate concentrations.

Conclusion

By computationally simulating the hill equation with varying parameters, we reveal that: Increasing V_{max} raises the upper limit of our equation's reaction rate, increasing h improves cooperativity which increases reaction rate at lower substrate concentrations and finally increasing K_{half} increases the substrate concentration required to reach a given rate. Overall our finding show the importance of the Hill equation in understanding cooperative binding and enzyme reaction. Further studies could be done on more complex models to also evaluate their effectiveness in simulating ezymatic reactions.