A Nonlinear Delay Model for Metabolic Oscillations in Yeast Cells

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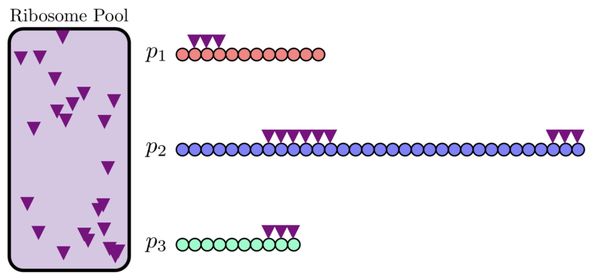
Abstract

We introduce two time-delay models of metabolic oscillations in yeast cells. Our model tests a hypothesis that the oscillations occur as multiple pathways share a limited resource which we equate to the number of available ribosomes. We initially explore a single-protein model with a constraint equation governing the total resource available to the cell. The model is then extended to include three proteins that share a resource pool. Three approaches are considered at constant delay to numerically detect oscillations.

Our results show that certain combinations of total resource available and the time delay, lead to oscillations. We observe that an oscillation region in the parameter space is between regions admitting steady states that correspond to zero and constant production. Similar behavior is found with the three-protein model where all proteins require the same production time. However, a shift in the protein production rates peaks occurs for low available resource suggesting that our model captures the shared resource pool dynamics.

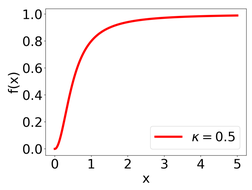
Motivation

Protein synthesis is a critical function for life so it is important to model this process to advance our understanding of biology. A phenomenon has been observed in yeast cell populations under low growth conditions where the protein production oscillates [2].



1-Protein Time Delay Model

- Ribosome Initiation: $\mu(t) = f(p(t))R(t)$
- Hill function: $f(x) = \frac{x^n}{\kappa^n + x^n}$
- $\dot{p}(t) = B\mu(t-\tau) - Dp(t)$
- $R(t) = R_T - A\int_{t-\tau}^{t} \mu(s)ds$ [3]
- $\dot{R}(t) = A(f(p(t-\tau))R(t-\tau) - f(p(t))R(t))$



Single Protein System:

$$\dot{p}(t) = Bf(p(t-\tau))R(t-\tau) - Dp(t),$$
$$\dot{R}(t) = A\left(f(p(t-\tau))R(t-\tau) - f(p(t))\right)R(t))$$

Equilibrium Conditions:

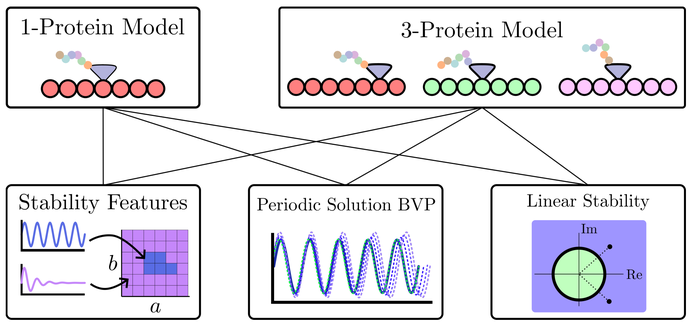
$$(1 + A\tau)p^{*n+1} - \frac{BR_T}{D}p^{*n} + \kappa^n p^* = 0$$

$$R^* = \frac{R_T}{1 + A\tau f(p^*)}$$

$$(p^*, R^*) = (p_{\text{trivial}}, R_{\text{trivial}})$$
$$(p^*, R^*) = (p_{\text{middle}}, R_{\text{middle}})$$
$$(p^*, R^*) = (p_{\text{top}}, R_{\text{top}})$$

Parameter Space Search

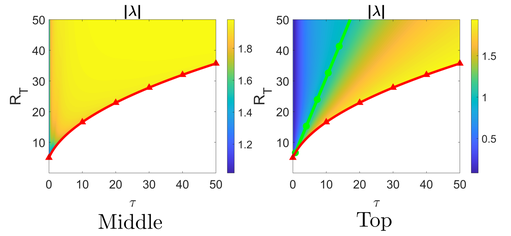
For analysis, we restrict the parameter space to $A = 1$, $B = 2$, $D = 10$, $\kappa = 0.5$, $n = 2$.



1-Protein Linear Stability

Trivial Equilibrium: $(p^*, R^*) = (0, R_T) \rightarrow$ Stable $\forall\ D > 0$

A spectral element approach was used to approximate the dominant eigenvalue of the linearized system about the equilibrium points for combinations of τ and R_T.



Bifurcations

Hopf:
$R_T \approx 2.6449\tau + 4.6323$

Saddle Node:
$R_T = \sqrt{25(1+\tau)}$

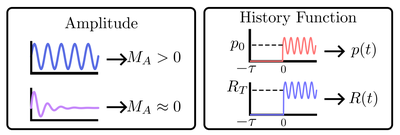
Numerical Simulations

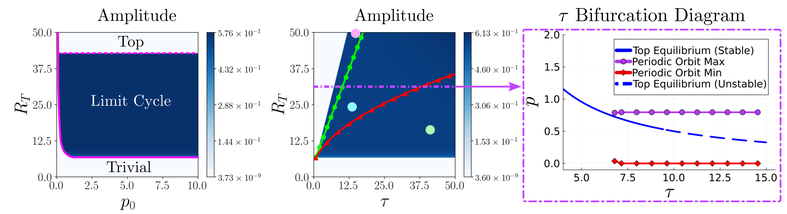
History Function [2]

$p(\theta) = 0,\ R(\theta) = 0\ \forall\ \theta \in [\tau, 0)$
At $t = 0 \rightarrow p(0) = p_0,\ R_0 = R_T$

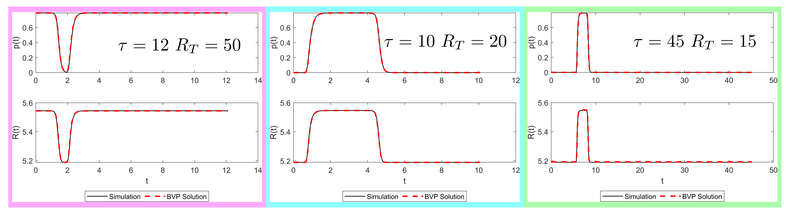
Amplitude Feature

$M_A = \sum_{i=1}^{n} \frac{1}{2}(\max(x_i(t)) - \min(x_i(t)))$





Periodic Solutions



3-Protein System

Model:

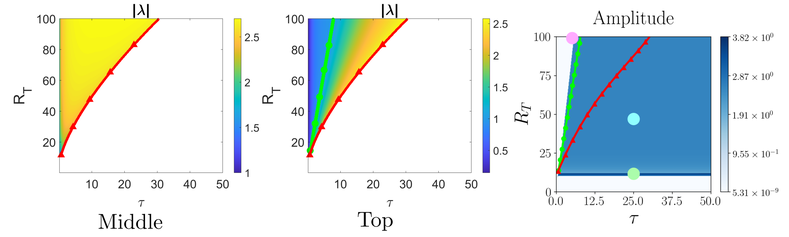
$$\dot{p_1}(t) = B_1 f(p_2(t-\tau_1))f(p_3(t-\tau_1))R(t-\tau_1) - D_1 p_1,$$
$$\dot{p_2}(t) = B_2 f(p_1(t-\tau_2))R(t-\tau_2) - D_2 p_2,$$
$$\dot{p_3}(t) = B_3 f(p_1(t-\tau_3))R(t-\tau_3) - D_3 p_3,$$
$$\dot{R}(t) = A(\mu_1(t-\tau_1) + \mu_2(t-\tau_2) + \mu_2(t-\tau_3) - \mu_1(t) - 2\mu_2(t)),$$

$$R_T = R(t) + A\left(\int_{t-\tau_1}^{t} f(p_2(s))f(p_3(s))R(s)ds + \int_{t-\tau_2}^{t} f(p_1(s))R(s)ds + \int_{t-\tau_3}^{t} f(p_1(s))R(s)ds\right).$$

3-Protein Linear Stability

Trivial Equilibrium: $(p_1^*, p_2^*, p_3^*, R^*) = (0, 0, 0, R_T) \rightarrow$ Stable $\forall\ D_1, D_2, D_3 > 0$

We restrict the delays to $\tau_1 = \tau_2 = \tau_3 = \tau$ and set all growth and decay rates to be equal to the values from the single protein system.



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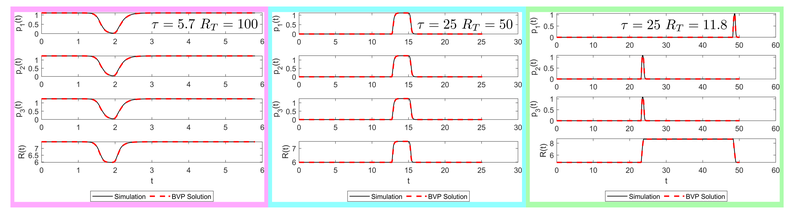

Conclusion

1. For low production time and sufficient resource, protein production is constant.
2. For insufficient resource, no production occurs.
3. Between the steady states, oscillations occur in the protein production rate.
4. Low total resource results in a temporal shift occurs in the protein production rate which could be a more efficient use of shared resources.

References

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