UNIVERSITY OF PADUA
Department of Information Engineering

Bachelor's Degree in Automation and Systems Engineering

Final Report

A Control Engineering Perspective on Systems Biology: The Role of Molecular Feedback

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ACADEMIC YEAR 2025/2026

THESIS PURPOSES

MODELING

Represent biological circuits in transcription networks as dynamical systems, each one modeled using different differential equations

ANALYSES

Point out different system characteristics and behaviours using Laplace transform, Bode plots and state-space representation

UNDERSTANDING

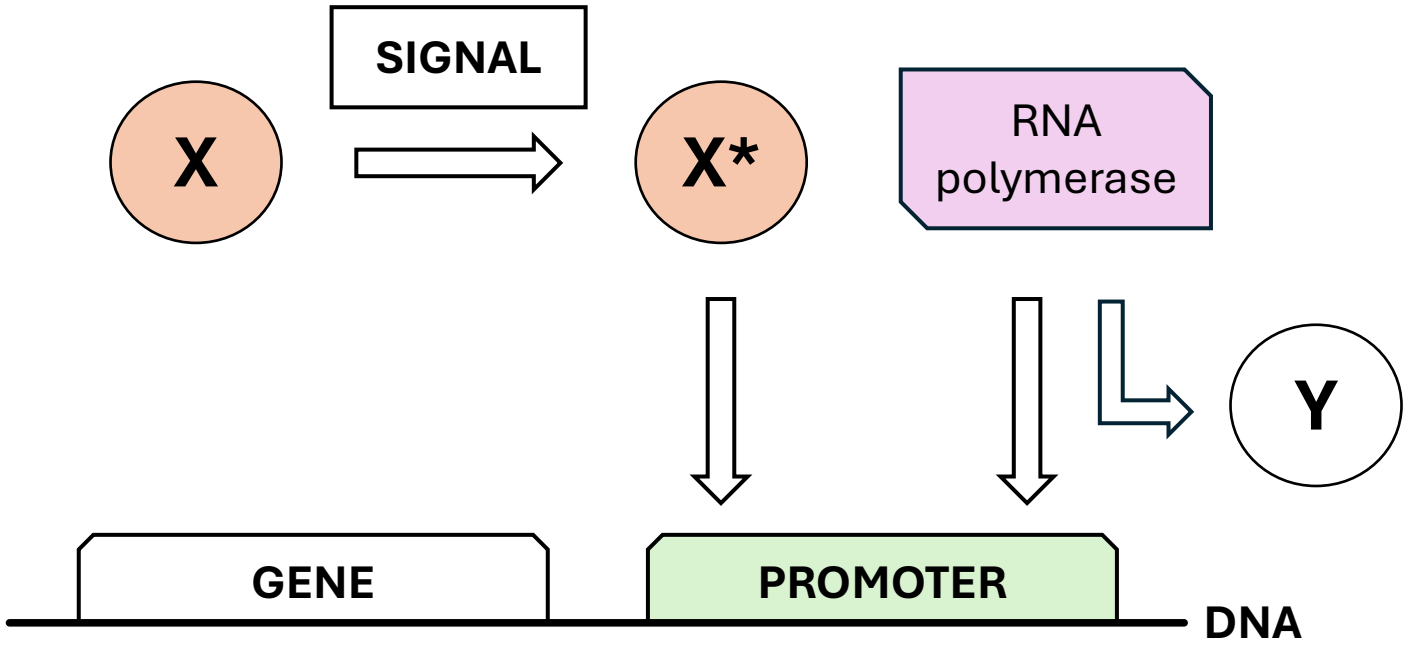
Highlight the strengths of each circuit configuration and the reasons behind evolutionary preservation of certain circuit motifs

PHYSICAL SYSTEM DESCRIPTION

TRANSCRIPTION FACTORS
Proteins involved in changing the production rate of target proteins in the network

PROMOTER
Portion of DNA regulating the production rate of the related protein

RNA POLYMERASE
Protein machine initiating the synthesis of the output protein

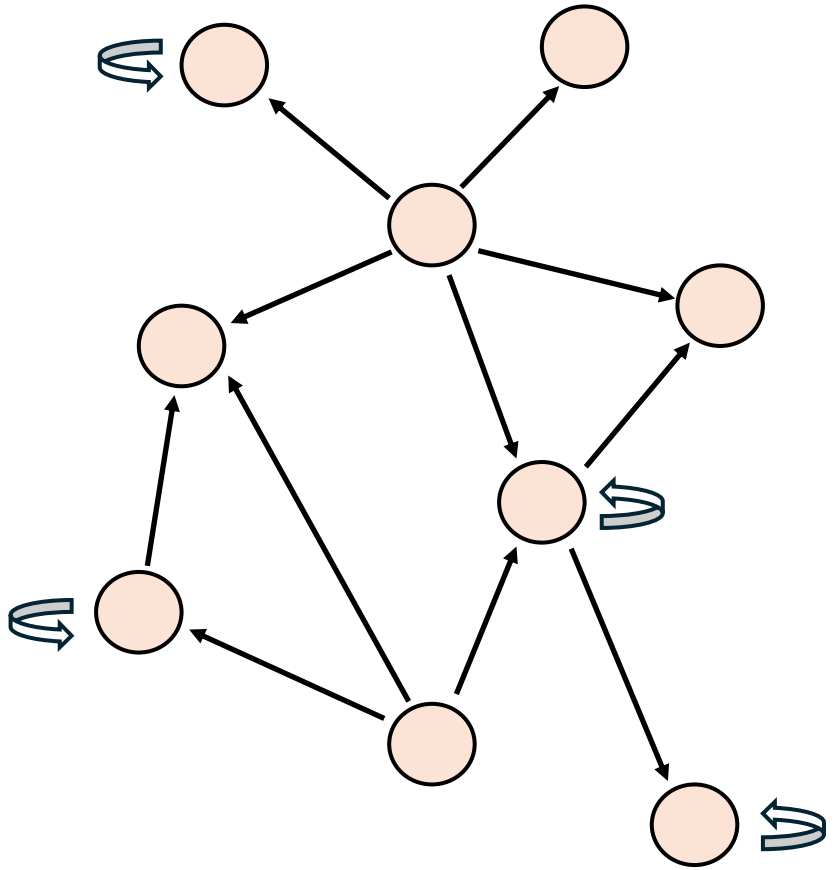


1. The transcription factor activates in response to a signal
2. The active transcription factor binds the promoter, changing its chemical nature
3. This changes the production rate of the corresponding protein

There can be different types of biological signals, either internal or external. Examples are tissue damage, lack of nutriment, cell's aging, etc

BIOLOGICAL CIRCUIT ⟹ One or multiple interacting nodes

TRANSCRIPTION NETWORK ⟹ Set of all circuits implemented in a cell



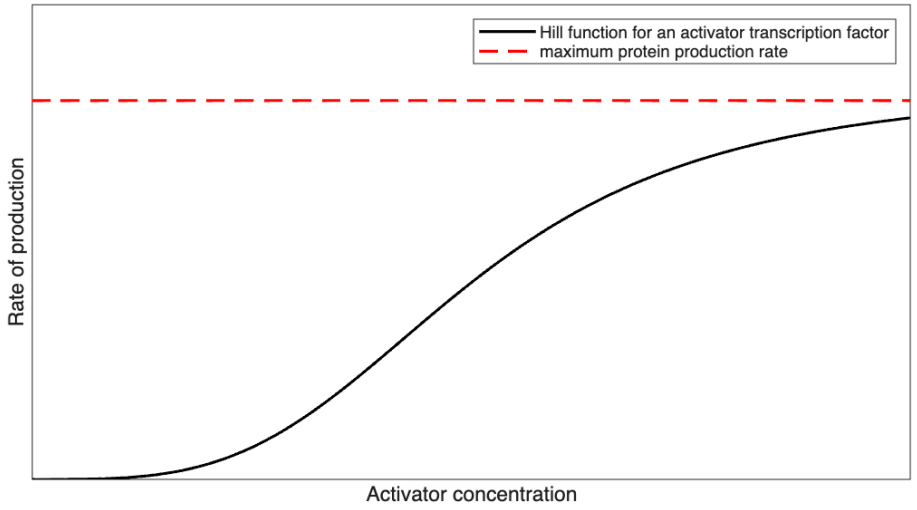
Each arrow in the network represents a function of the output protein production rate with respect to the transcription factor concentration

$$Y_{rate} = f(X^*)$$

HILL FUNCTIONS

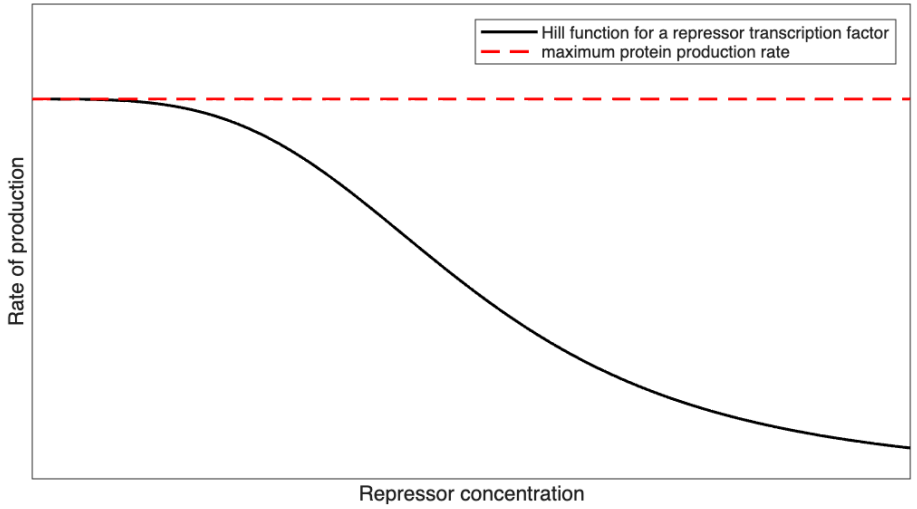
ACTIVATOR

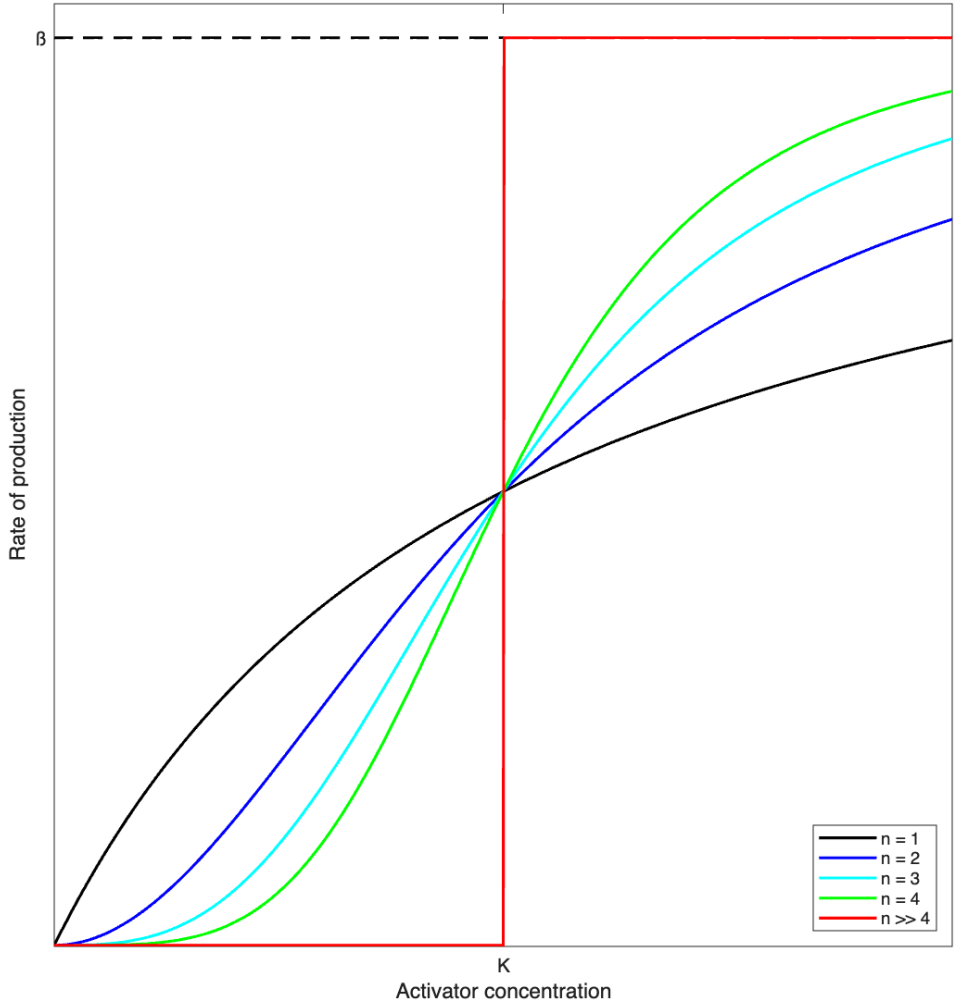
$$Y_{rate} = \beta \frac{X^{*n}}{K^n + X^{*n}}$$



REPRESSOR

$$Y_{rate} = \beta \frac{K^n}{K^n + X^{*n}}$$



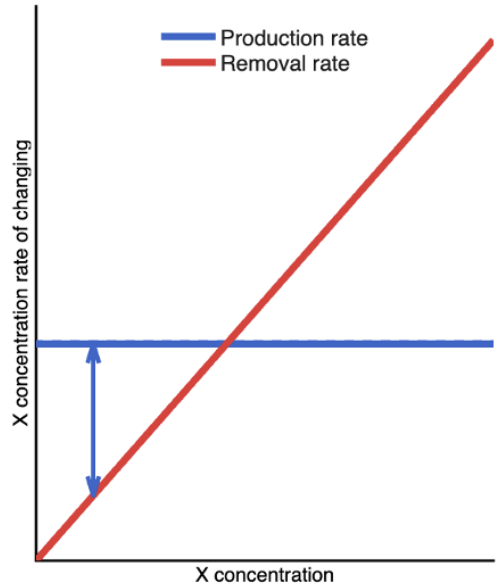


SIMPLE REGULATION

REMOVAL RATE

Protein concentration decrease over time due to dilution and degradation

$$\alpha = \alpha_{deg} + \alpha_{dil}$$



$$\frac{dY}{dt} = f(X^*) - \alpha Y$$

Assumption: either minimal or maximal transcription factor concentration

$$\frac{dY}{dt} = \beta - \alpha Y$$

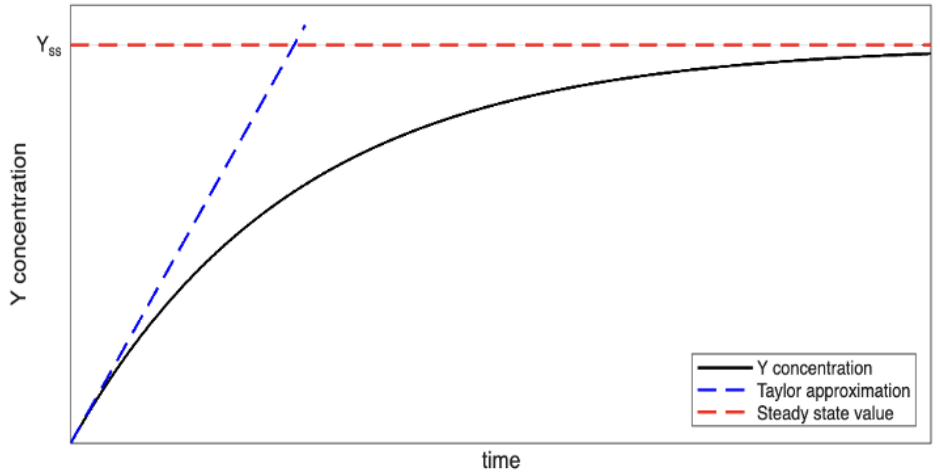
$$W(s) = \frac{Y(s)}{U(s)} = \frac{1}{s+\alpha}$$

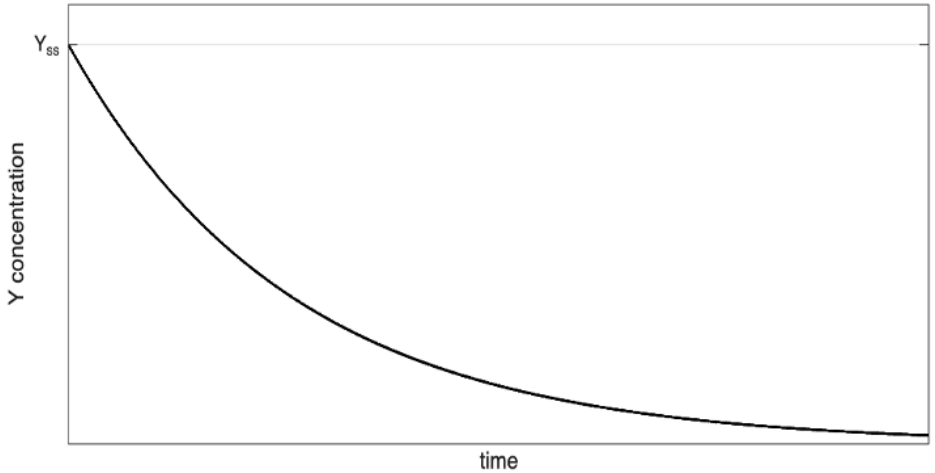
$$Y(s) = \frac{y(0)}{s+\alpha} + \frac{U(s)}{s+\alpha}$$

$$y_{free}(t) = y(0)e^{-\alpha t}$$

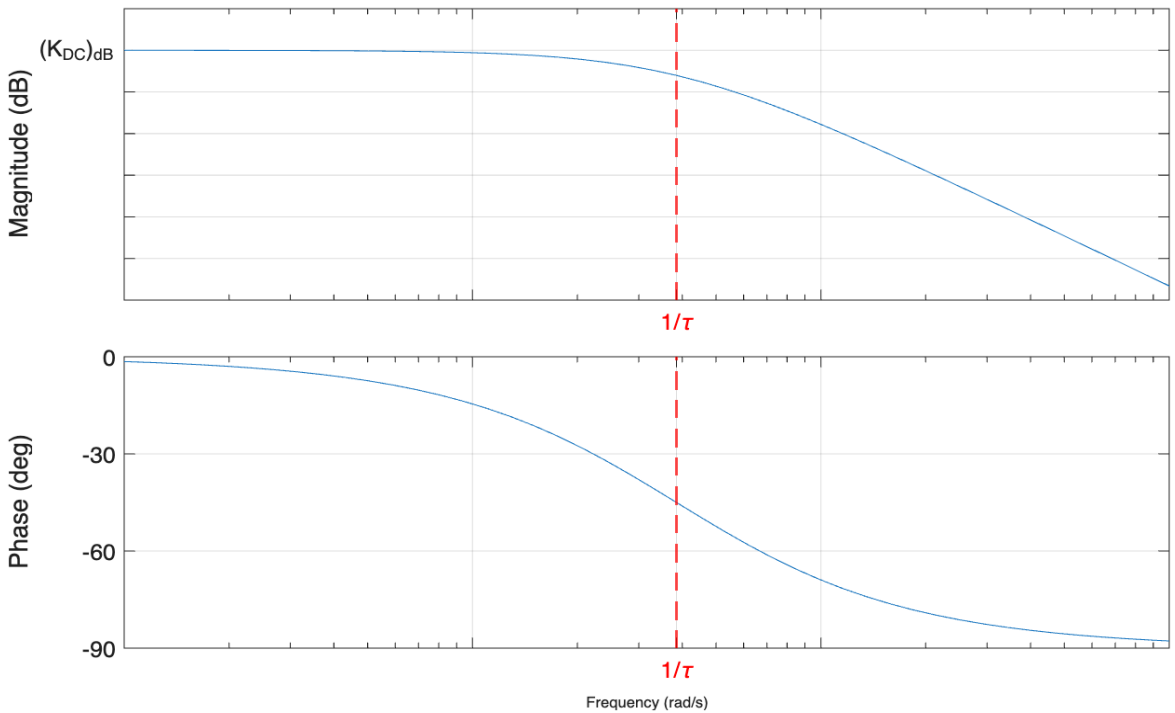
$$y_{forced}(t) = Y_{ss}(1 - e^{-\alpha t})$$

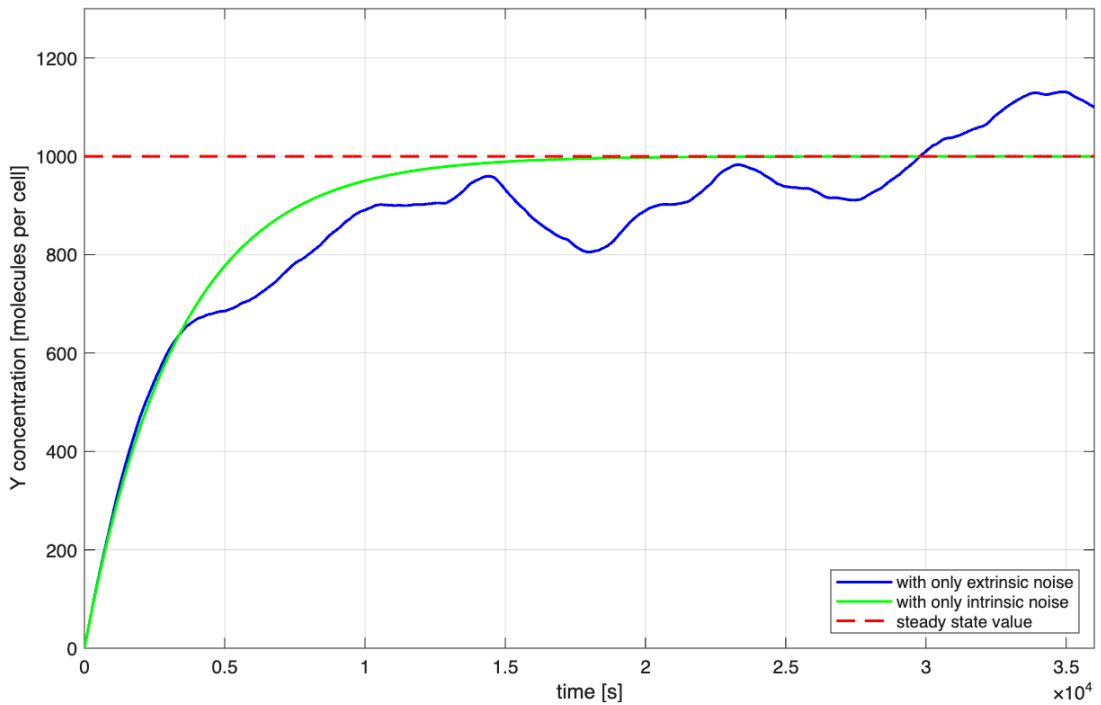
$$y_{forced}(t) \approx \beta t \quad \text{for} \quad t \to 0$$



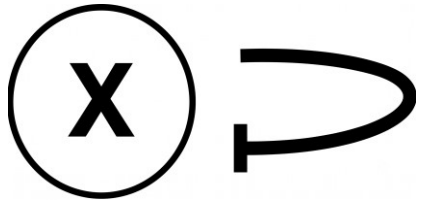


- **INTRINSIC NOISE**
  High frequency noise due to the stochastic nature of chemical reactions
- **EXTRINSIC NOISE**
  Low frequency noise caused by cell – cell variations

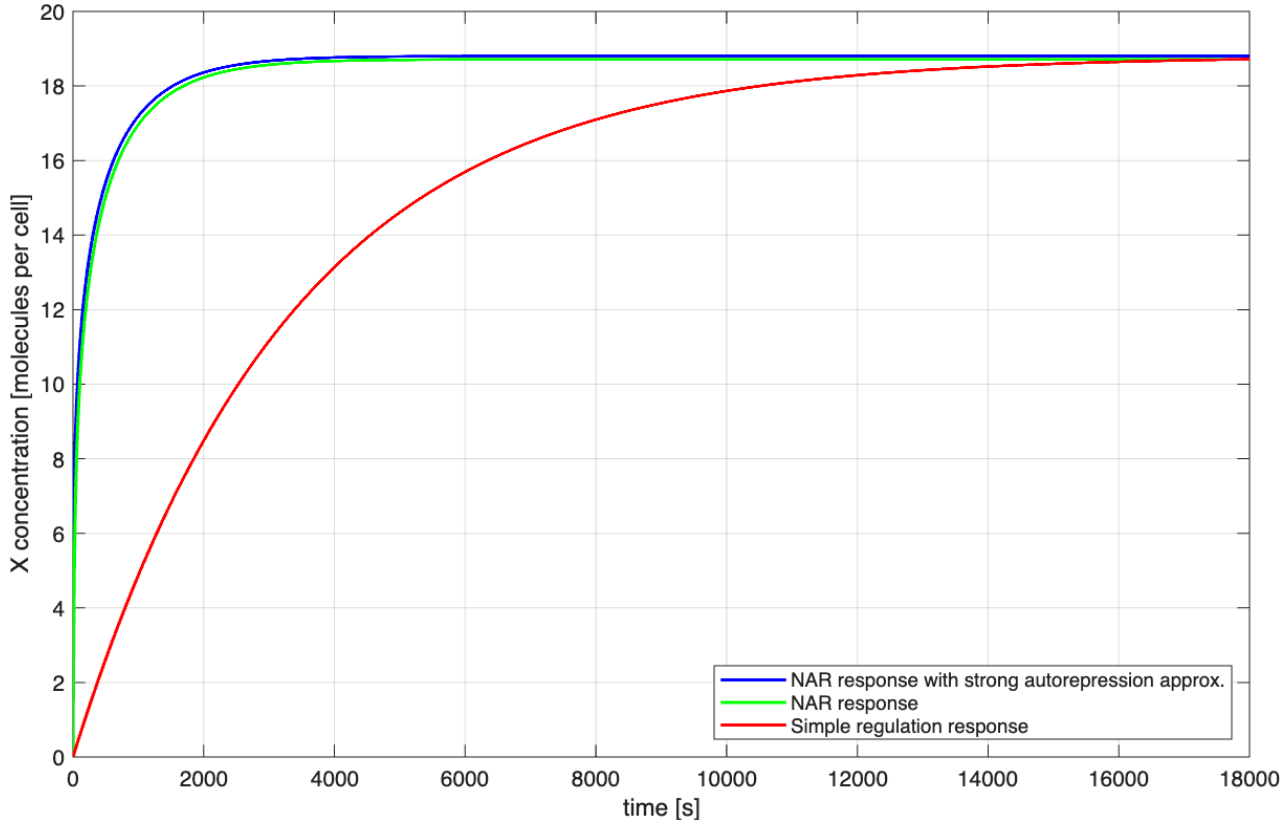




NEGATIVE AUTOREGULATION



$$\frac{dX}{dt} = \frac{\beta}{1+\left(\frac{X}{K}\right)^n} - \alpha X \approx \frac{\beta}{\left(\frac{X}{K}\right)^n} - \alpha X \Longrightarrow X(t) = X_{ss}\left(1 - e^{-(n+1)\alpha t}\right)^{\frac{1}{n+1}}$$



ROBUSTNESS TO PRODUCTION RATE VARIATIONS

$$PS(X_{ss},\beta) = \frac{\triangle X_{ss}}{X_{ss}}\left(\frac{\triangle \beta}{\beta}\right)^{-1} = \frac{\beta}{X_{ss}}\frac{dX_{ss}}{d\beta}$$

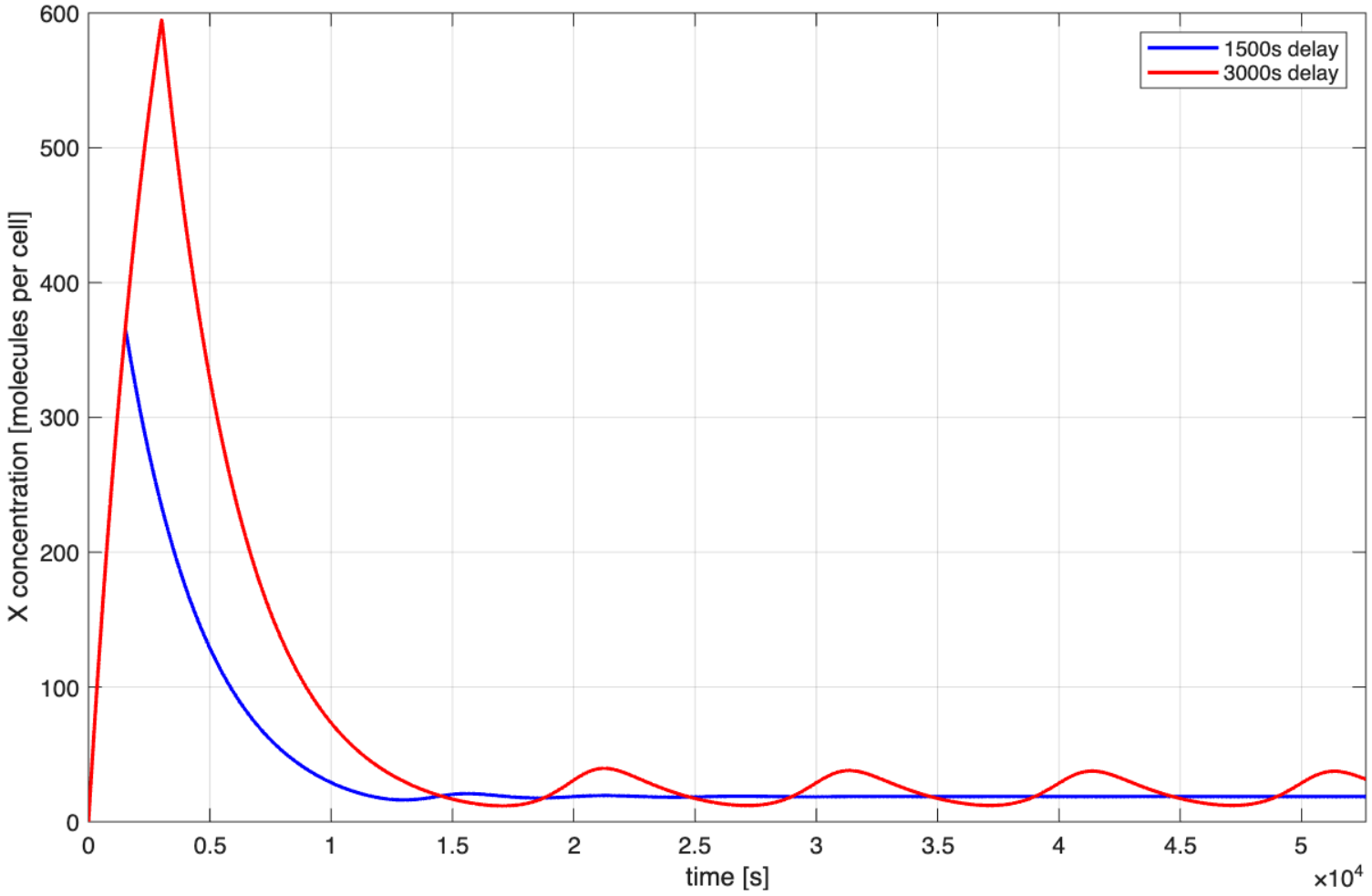
$$PS_{NAR}(X_{ss},\beta) = \frac{\beta}{X_{ss}}\frac{dX_{ss}}{d\beta} = \frac{1}{n+1}$$

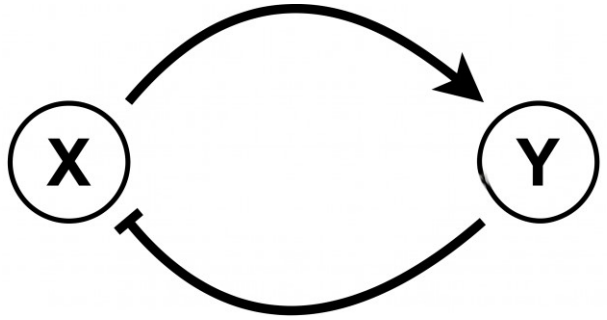
$$PS_{SR}(X_{ss},\beta) = \frac{\beta}{X_{ss}}\frac{dX_{ss}}{d\beta} = 1$$

OSCILLATORY MODES

Oscillations can arise in the presence of a sufficient time delayed NAR

$$W(s) = \frac{1}{s + (e^{-sT}|\gamma| + \alpha)}$$
$$= \frac{\frac{1}{s+\alpha}}{1 + \frac{e^{-sT}|\gamma|}{s+\alpha}}$$
$$= \frac{\frac{1}{s+\alpha}}{1 + L(s)}$$





$$\begin{cases} \frac{dX}{dt} = f(Y) - \alpha_1 X \\ \frac{dY}{dt} = g(X) - \alpha_2 Y \end{cases}$$

- X and Y concentration values represent the system state vector
- Overdamped oscillations thanks to removal rate

$$\begin{pmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \end{pmatrix} = J \begin{pmatrix} X \\ Y \end{pmatrix}$$

$$J = \begin{bmatrix} -\alpha_1 & \frac{df}{dY} \\ \frac{dg}{dX} & -\alpha_2 \end{bmatrix}\Bigg|_{eq} = \begin{bmatrix} -\alpha_1 & -k_1 \\ k_2 & -\alpha_2 \end{bmatrix}$$

$$\lambda_{1,2} = \frac{-(\alpha_1 + \alpha_2) \pm \sqrt{(\alpha_1 - \alpha_2)^2 - 4k_1 k_2}}{2}$$

CONDITION FOR OSCILLATIONS

$$(\alpha_1 - \alpha_2)^2 - 4k_1 k_2 < 0$$

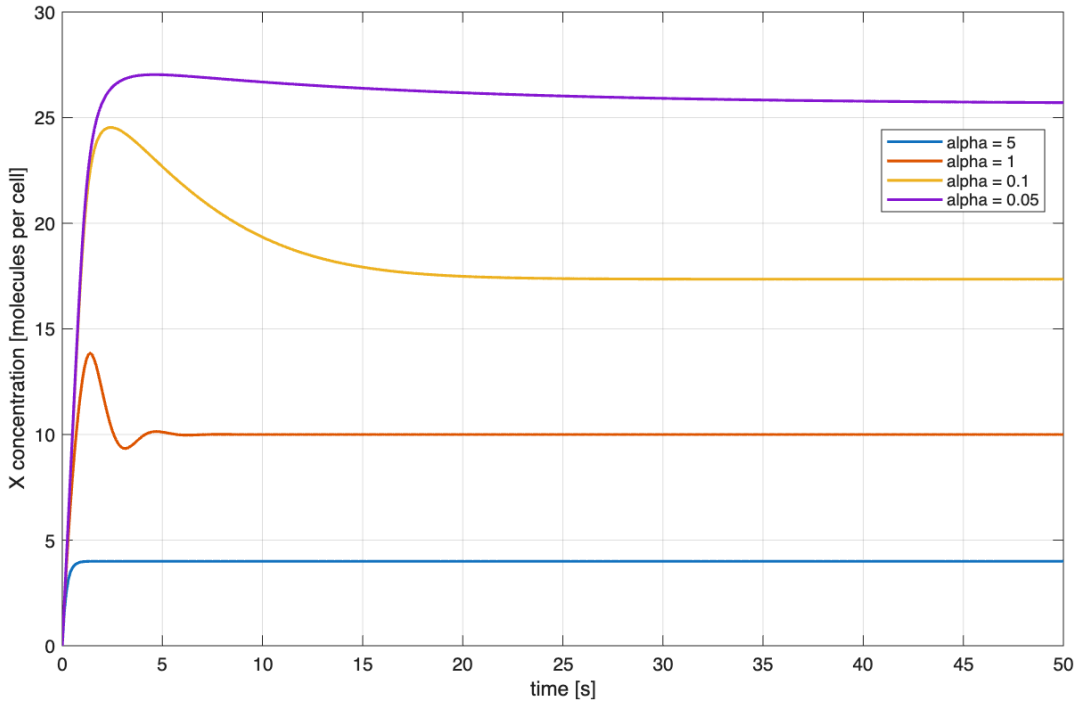
- Similar timescales: $\alpha_1 \approx \alpha_2$
- Strong feedback, hence high hill coefficients

The natural frequency of the system, and consequently the oscillation frequency, depends on both removal and production terms:

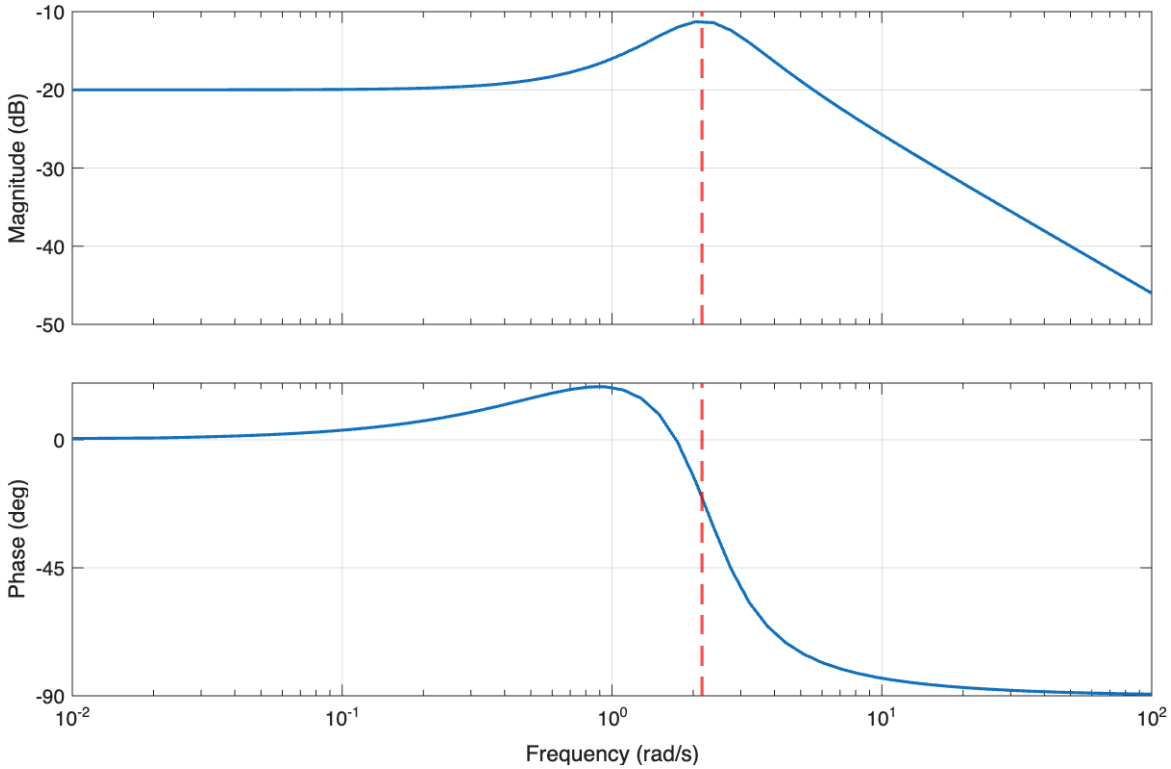
$$\omega_n = \sqrt{\alpha_1 \alpha_2 + k_1 k_2}$$

$$\begin{cases} \begin{pmatrix} \frac{dX}{dt} \\ \frac{dY}{dt} \end{pmatrix} = A \begin{pmatrix} X \\ Y \end{pmatrix} + Bu \\ y = C \begin{pmatrix} X \\ Y \end{pmatrix} + Du \end{cases} \qquad A = J \qquad B = \begin{bmatrix} 1 \\ 1 + \left(\frac{Y_{ss}}{K}\right) \\ 0 \end{bmatrix} \qquad C = \begin{bmatrix} 1 \\ 0 \end{bmatrix} \qquad D = 0$$

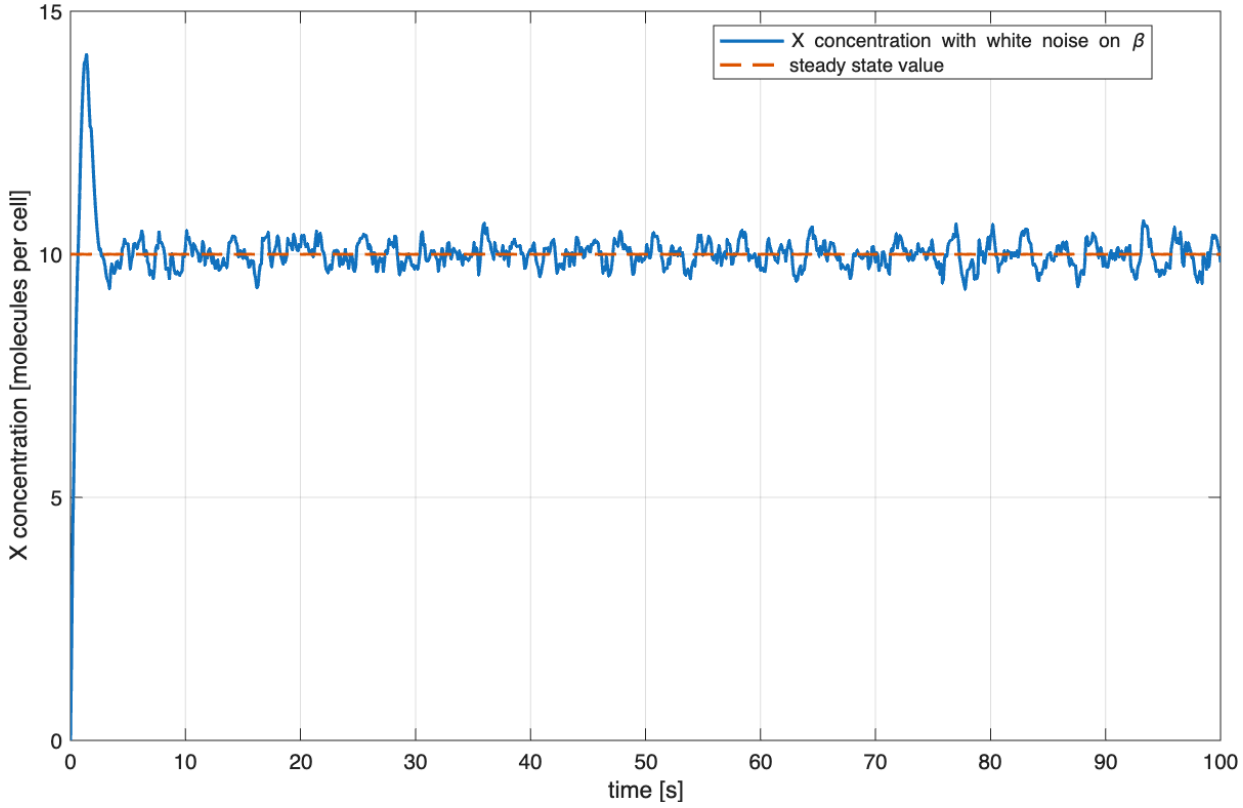
Different behaviors for various X removal rates (constant Y removal rate, equal to 0.1)



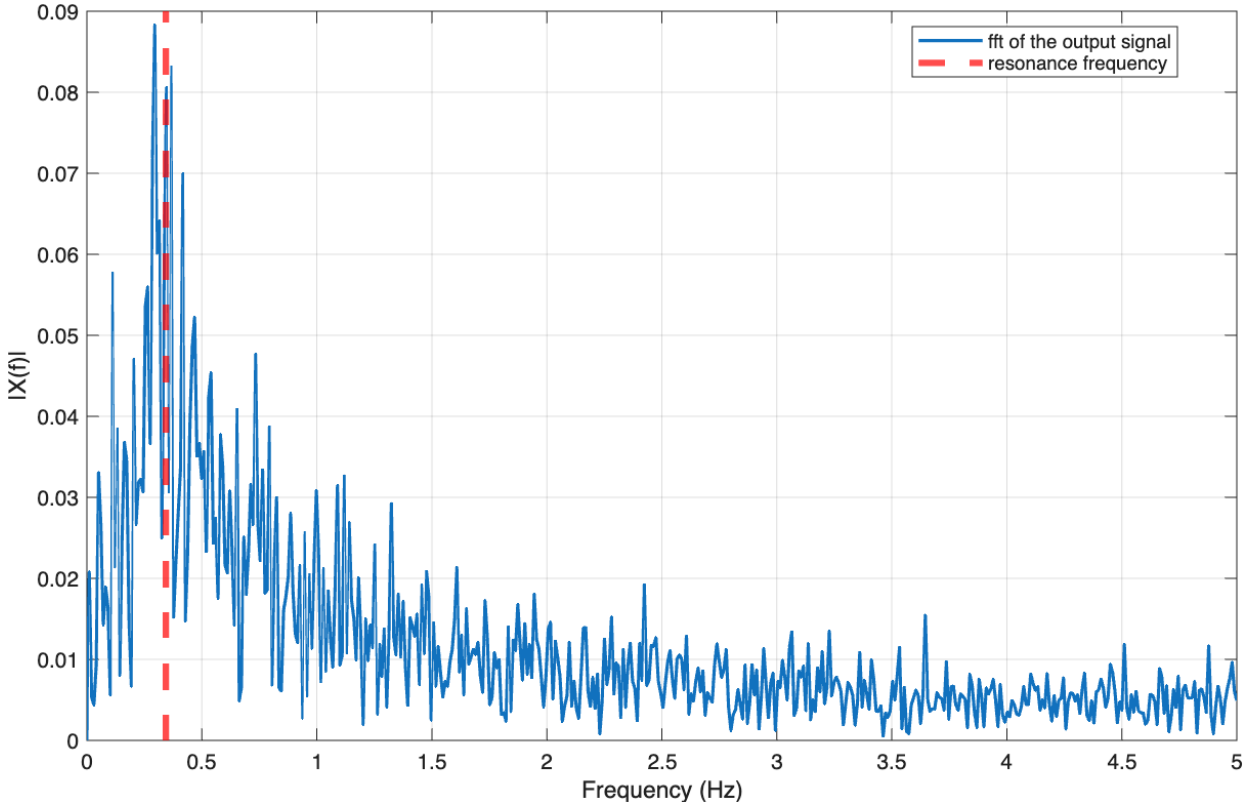
Bode plot of $W(s) = C(sI - A)^{-1}B + D$



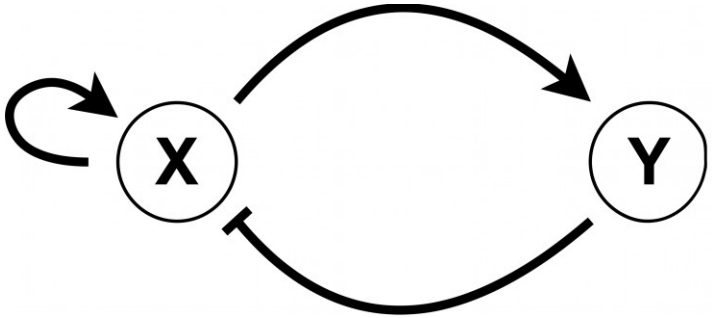
Noise-induced oscillations on two-node circuit



Fourier transform of the output response



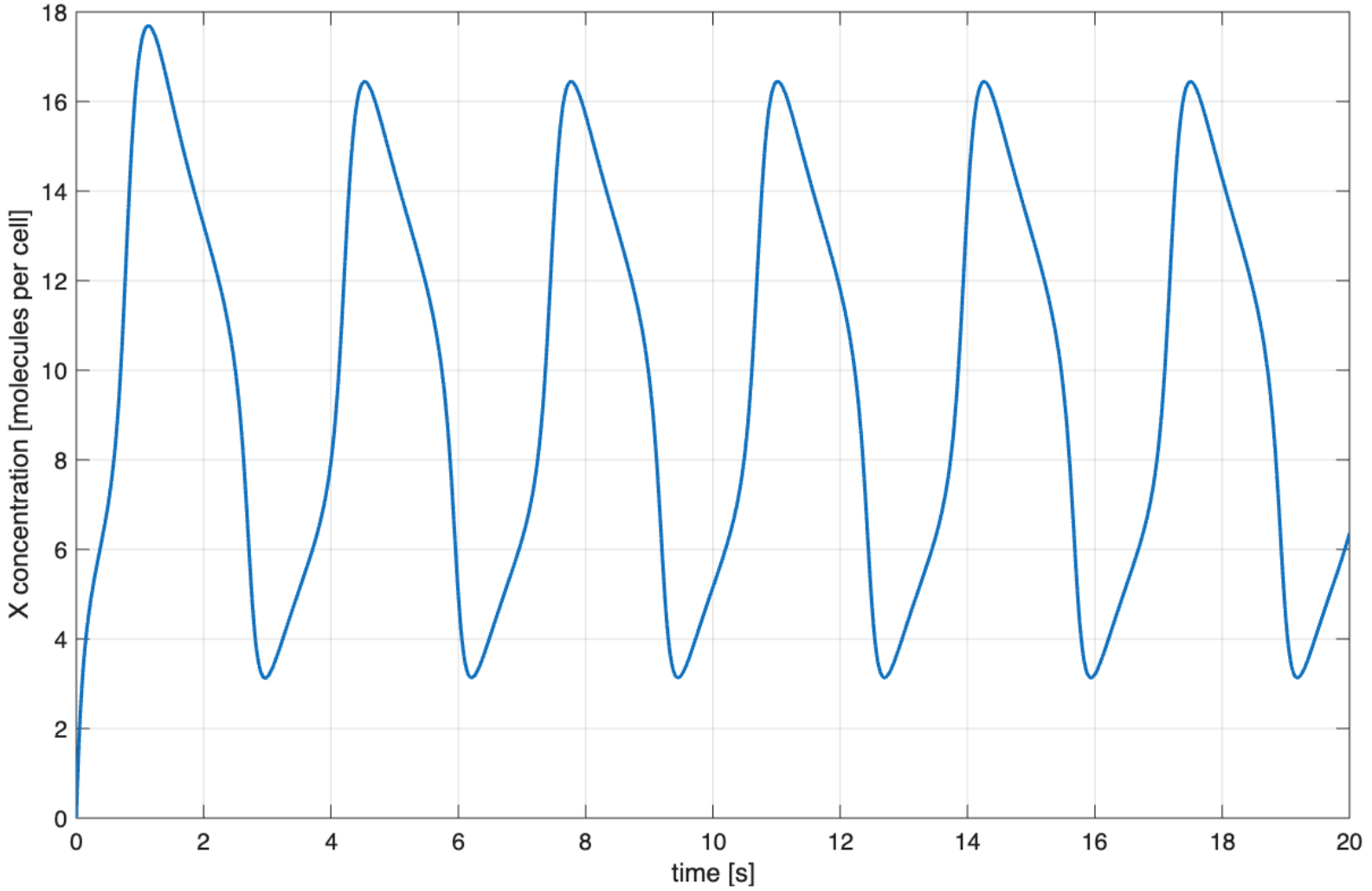
Here the goal is to get unstable linearized dynamics through PAR and exploit the saturation of the Hill function to obtain persistent oscillations over time



LINEARIZATION

$$J = \begin{bmatrix} P - \alpha_1 & k_1 \\ k_2 & -\alpha_2 \end{bmatrix}$$

P refers to the linearized PAR term, which is positive, unlike NAR, and can be tuned to generate the desired behaviours



CONCLUSIONS

Control engineering tools turn useful to analyze these types of biological system. Moreover, also other technics from control and system theory can be exploited, like system identification to obtain Hill functions' parameters without the necessity to run laboratory experiments.

PHARMACOLOGY

Production of intelligent probiotics and antibodies

BIOENERGY

Microorganisms able to degrade plastic materials and transform biological waste into biofuels

BIOSENSORS

Reprogram the DNA structure of certain types of bacteria in order to create biological sensors