Advanced Special Topics I
Genetic Circuit Design

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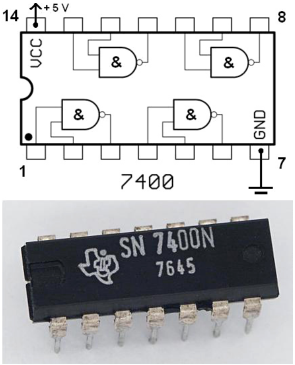
Overview

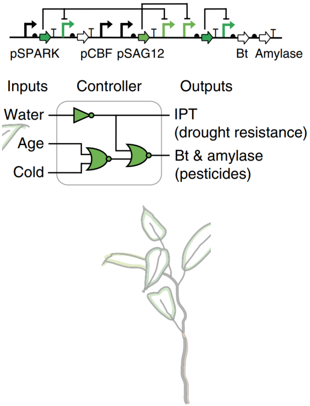
Literature Review: Overview

1. Hardware vs Wetware Analogy
2. Logic Gates
3. Gate Implementation
4. Composability
5. Continuous Response Variables
6. Applications
7. Challenges

Hardware vs Wetware Analogy



(CC BY-SA 3.0: Audrius Meskauskas)



(Brophy and Voigt, 2014)

Logic Gates

YES

INPUT	OUTPUT
A	
0	0
1	1

NOT

INPUT	OUTPUT
A	
0	1
1	0

AND

INPUT		OUTPUT
A	B	
0	0	0
1	0	0
0	1	0
1	1	1

OR

INPUT		OUTPUT
A	B	
0	0	0
1	0	1
0	1	1
1	1	1

XOR

INPUT		OUTPUT
A	B	
0	0	0
1	0	1
0	1	1
1	1	0

NAND

INPUT		OUTPUT
A	B	
0	0	1
1	0	1
0	1	1
1	1	0

NOR

INPUT		OUTPUT
A	B	
0	0	1
1	0	0
0	1	0
1	1	0

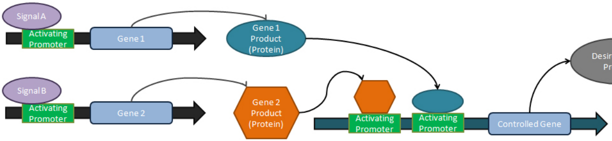
XNOR

INPUT		OUTPUT
A	B	
0	0	1
1	0	0
0	1	0
1	1	1

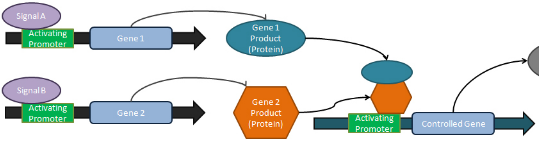
(Abels *et al.* 2015)

Gate Implementation

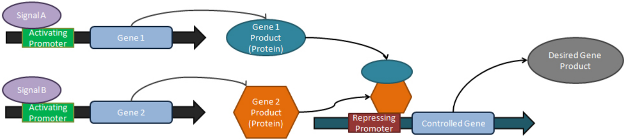
OR Gate (🄮 Public Domain)



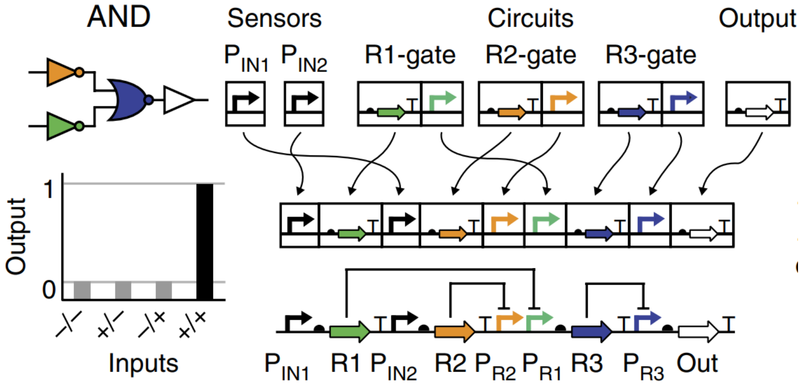
AND Gate (🄮 Public Domain)



NAND Gate (🄮 Public Domain)

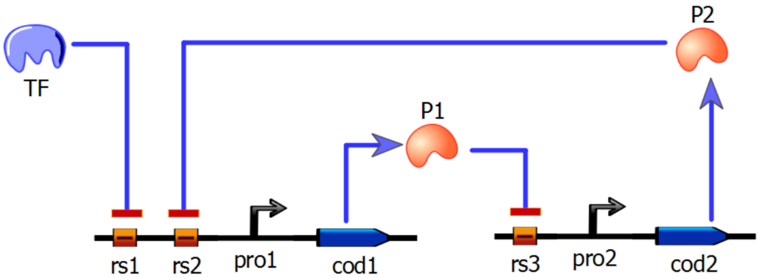


Composability



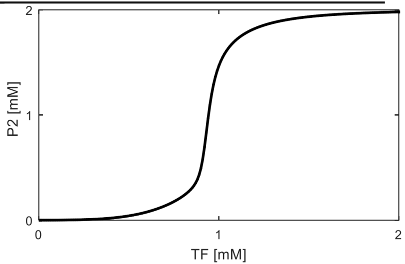
(Brophy and Voigt, 2014)

Continuous Response Variables



$$\frac{dP_1}{dt} = s_1 \times \frac{k_{11}^{h_{11}}}{TF^{h_{11}} + k_{11}^{h_{11}}} \times \frac{k_{12}^{h_{12}}}{P_2^{h_{12}} + k_{12}^{h_{12}}} - d_1 P_1$$

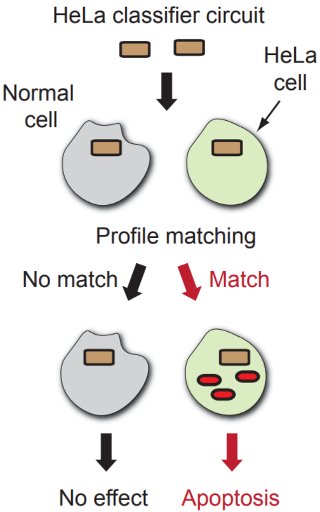
$$\frac{dP_2}{dt} = s_2 \times \frac{k_2^{h_2}}{P_1^{h_2} + k_2^{h_2}} - d_2 P_2$$



(Kazemi *et al.* 2016)

Applications

- Disease diagnosis
- Environmental sensing
- Research and development
- Material and chemical production



(Xie et al 2011)

Challenges

1. Non-orthogonality of components.
   - Undesired behaviour.
2. Metabolic load.
   - Mortality.
   - Evolutionary pressure.

Possible Solution: Distributed circuits.

Project: Overview

1. Hill Equation
2. YES Gate
3. NOT Gate
4. Time-Dependent NAND Gate
5. Limitations
6. Learning Outcomes

Hill Equation

$$\theta = \frac{1}{1 + \left(\frac{K_A}{[L]}\right)^n}$$

- θ is the fraction of protein bound by ligand.
- $[L]$ is the total ligand concentration.
- K_A is the half-occupation concentration of ligand.
- n is the Hill coefficient.
  - $n < 1 \implies$ negatively-cooperative binding.
  - $n > 1 \implies$ positively-cooperative binding.
  - $n = 1 \implies$ non-cooperative binding.

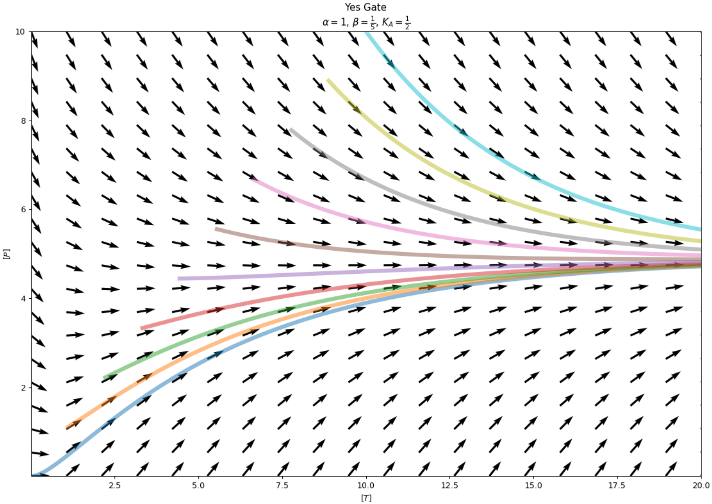
Example: YES Gate

$$\frac{d[P]}{d[T]} = \frac{\alpha}{1 + \left(\frac{K_A}{[T]}\right)} - \beta[P]$$

- $[P]$: Concentration of protein product.
- $[T]$: Concentration of transcription factor.
- α: Maximum rate of synthesis of P.
- β: Protein degradation rate.
- K_A: Half-occupation concentration transcription factor.

$$[P] = \frac{\alpha}{\beta} \frac{[T]}{K_A + [T]}$$

Example: YES Gate



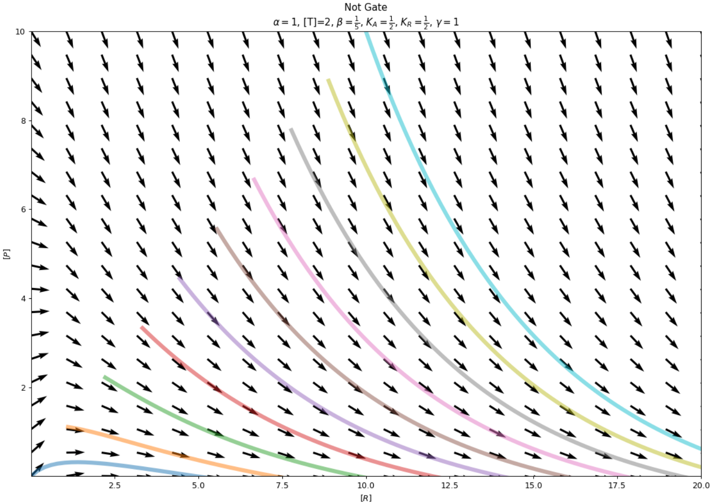
Example: NOT Gate

$$\frac{d[P]}{d[R]} = \frac{\alpha}{1 + \left(\frac{K_A}{[T]}\right)} - \frac{\gamma}{1 + \left(\frac{K_R}{[R]}\right)} - \beta[P]$$

- $[P]$: Concentration of protein product.
- $[R]$: Concentration of repressor.
- $[T]$: Concentration of transcription factor.
- α: Maximum rate of synthesis of P.
- γ: Maximum rate of inhibition of synthesis of P.
- β: Protein degradation rate.
- K_A: Half-occupation concentration transcription factor.
- K_R: Half-occupation concentration inhibition factor.

$$[P] = \left(C_1 - \frac{\int \frac{K_A[R]\gamma e^{[R]\beta}}{K_R+[R]}\, d[R] + \int \left(-\frac{K_R[T]\alpha e^{[R]\beta}}{K_R+[R]}\right) d[R] + \int \left(-\frac{[R][T]\alpha e^{[R]\beta}}{K_R+[R]}\right) d[R] + \int \frac{[R][T]\gamma e^{[R]\beta}}{K_R+[R]}\, d[R]}{K_A+[T]} \right) e^{-[R]\beta}$$

Example: NOT Gate

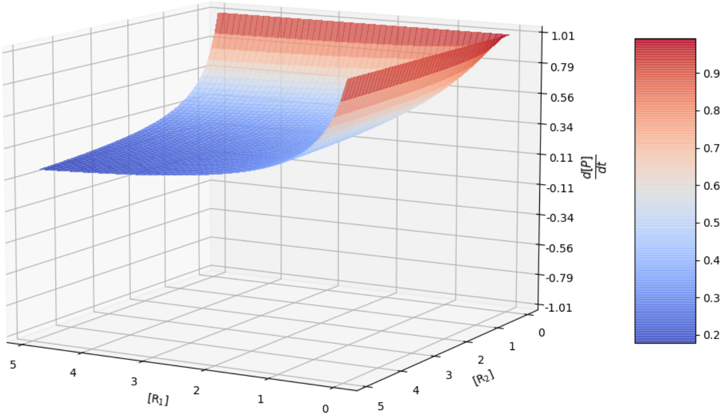


Time-Dependent NAND

$$\frac{d[P](t,[R_1],[R_2])}{dt} = \left(1 - \left[\frac{\alpha}{1+\frac{K_{A_1}}{[R_1](t)}}\right]\left[\frac{\gamma}{1+\frac{K_{A_2}}{[R_2](t)}}\right]\right) - \beta[P](t,[R_1],[R_2])$$

- $[P]$: Concentration of protein product.
- $[R_1]$: Concentration of repressor.
- $[R_2]$: Concentration of repressor.
- α: Maximum rate of synthesis of P.
- γ: Maximum rate of inhibition of synthesis of P.
- β: Protein degradation rate.
- K_{A_1}: Half-occupation concentration inhibition factor 1.
- K_{A_2}: Half-occupation concentration inhibition factor 2.

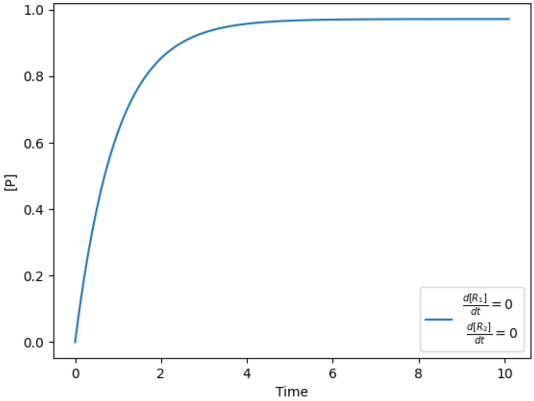
Time-Dependent NAND



Letting $\alpha = \beta = \gamma = 1$, $[P] = 0$, and $K_{A_1} = K_{A_2} = \frac{1}{2}$.

Time-Dependent NAND: Constant

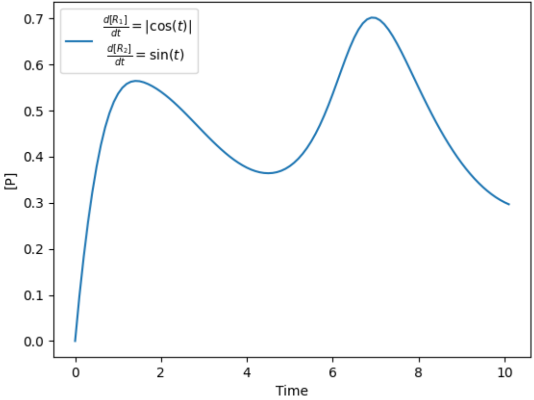
What happens over time?



Letting $\alpha = \beta = \gamma = 1$, $[P]_0 = 0$, and $K_{A_1} = K_{A_2} = \frac{1}{2}$.

Time-Dependent NAND: Non-Monotonicity

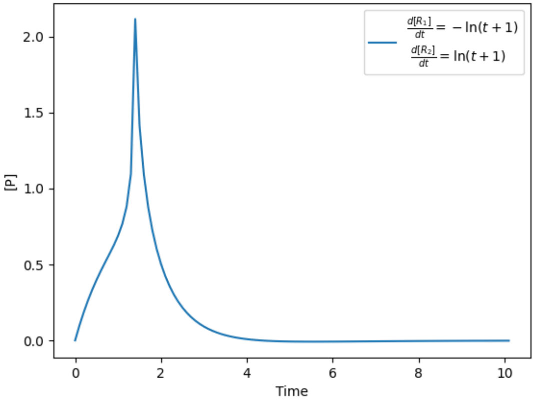
What happens over time?



Letting $\alpha = \beta = \gamma = 1$, $[P]_0 = 0$, and $K_{A_1} = K_{A_2} = \frac{1}{2}$.

Time-Dependent NAND: Discontinuity

What happens over time?



Letting $\alpha = \beta = \gamma = 1$, $[P]_0 = 0$, and $K_{A_1} = K_{A_2} = \frac{1}{2}$.

Limitations

- Our models are possibly too simple for a real cell.
- Parameters in real life cannot be arbitrary tweaked; depend on choice of molecules.
- Untested predictive power.

Learning Outcomes

- Learned about genetic circuit design.
- Learned about solving elementary ODE's.
    - Symbolically: Separation of variables
    - Numerically: Euler's method
- Learned about software packages.
    - SymPy
    - py-PDE