Modeling: ODEs and Hill Functions

Section 1: ODEs, Law of mass action and the central dogma

by Alejandro Vignoni (alvig2@upv.es)

An iGEM Measurement Committee Webinar
Week 2, June 23rd, 2020
Today Webinar’s Topics

- Section 1: ODEs, the law of mass action, and the central dogma (15 min)
- Section 2: Derivation of a Hill function from the law of mass action (15 min)
- Section 3: Hill function examples and intuitions: effects of parameters on activators, repressors, hybrid promoters, using a Matlab exploration package. (15 min)
- Q&A – (at the end of each 15 minutes block, total 15 min)
Types of models

Biochemical Reactions

Mathematical Model (ODEs)

Schematic

From Y. Boada (2018)
But what is an Ordinary Differential Equation (ODE)?

These are equations with **variables** and their **derivatives**

If we have any function (the typical one):

\[ y = f(t) \quad (y \text{ only depends on the variable } t, \text{ but we could have } y = f(t, x_1, x_2, \ldots x_n)) \]

Do you remember the definition of the derivative of a function?

\[ \dot{y} = \frac{df(t)}{dt} = \lim_{h \to 0} \frac{f(t+h)-f(t)}{h} \quad \text{(we can have higher order derivatives } y'', y''', y^{(n)} \text{)} \]
But they can be very challenging and difficult to solve!!
But if they're so complicated... how do we solve them?

We can solve differential equations in two ways:

- **Analytically**: solving for the unknown...

- **Numerically**: in an approximate way.

\[ \dot{y} \approx \frac{f(h+h) - f(x)}{h} \]

(with an \( h \) very small)
Why do we use them?

Differential equations describe biological behaviour, physical laws, human activities, and much more....

And the set of equations that describe a system, a phenomenon... is known as **ODE model**
Software for Ordinary Differential Equations (ODEs) solving

• **MATLAB**, a technical computing application (MATrix LABoratory)

FREE LICENSE WITH iGEM and the Measurement Committee has some software programed in MATLAB for flow cytometry and plate reader data analysis and calibration.

• **Maxima**, an open-source computer algebra system.
• **COPASI**, a free software package for the integration and analysis of ODEs.
• **GNU Octave**, a high-level language, basically a open-source versión of MATLAB.
• **Scilab**, an open source application for numerical computation.
• **Maple**, a proprietary application for symbolic calculations.
• **Mathematica**, a proprietary application primarily intended for symbolic calculations.
• **Julia (programming language)**, a high-level language primarily intended for numerical computations.
• **SageMath**, an open-source application that uses a Python-like syntax with a wide range of capabilities spanning several branches of mathematics.
• **SciPy**, a Python package that includes an ODE integration module.
• **GNU R**, an open source computational environment primarily intended for statistics, which includes packages for ODE solving.
Let us begin this journey **Part I** from:

Biochemical Reactions  \[\rightarrow\]  Mathematical Model (ODEs)
Reminder: Law of mass action and kinetic equations

Example: Reaction of Water

\[ 2 \text{H}_2 + \text{O}_2 \xrightarrow{k} 2 \text{H}_2\text{O} \]

Reactants

Products

Stoichiometric coefficients

Reaction rate
Law of mass action and kinetic equations

Reaction of Water – Kinetics of $H_2$

$$2 \text{H}_2 + \text{O}_2 \rightarrow 2 \text{H}_2\text{O}$$

Rate of change of $[\text{H}_2]$ decreases or it is consumed

$$[\dot{\text{H}}_2] = -2k[H_2]^2[O_2]$$

Stoichiometric coefficient of $[\text{H}_2]$ times the reaction rate $k$

Product of the concentrations of the reactants ($[\text{H}_2] \times [\text{H}_2] \times [\text{O}_2] = [\text{H}_2]^2[\text{O}_2]$)
Law of mass action and kinetic equations

Reaction of Water – Kinetics of $O_2$

$$2 \text{H}_2 + \text{O}_2 \xrightarrow{k} 2 \text{H}_2\text{O}$$

Rate of change of $[O_2]$ decreases or it is consumed

$$\dot{[O_2]} = -k[H_2]^2[O_2]$$

Stoichiometric coefficient of $[O_2]$ times the reaction rate $k$

Product of the concentrations of the reactants ($[H_2] \times [H_2] \times [O_2] = [H_2]^2[O_2]$)
Law of mass action and kinetic equations

Reaction of Water – Kinetics of $H_2O$

$2 \text{H}_2 + \text{O}_2 \xrightarrow{k} 2 \text{H}_2\text{O}$

Rate of change of $[\text{H}_2\text{O}]$

$[\text{H}_2\text{O}] = +2k[\text{H}_2]^2[\text{O}_2]$  

Stoichiometric coefficient of $[\text{H}_2\text{O}]$ times the reaction rate $k$

Increases or it is produced

Product of the concentrations of the reactants ($[\text{H}_2] \times [\text{H}_2] \times [\text{O}_2] = [\text{H}_2]^2[\text{O}_2]$)
Law of mass action and kinetic equations

Reaction of Water – Kinetics

\[ 2 \text{H}_2 + \text{O}_2 \xrightarrow{k} 2 \text{H}_2\text{O} \]

\[
[\dot{\text{H}}_2] = -2k[\text{H}_2]^2[\text{O}_2]
\]

\[
[\dot{\text{O}}_2] = -k[\text{H}_2]^2[\text{O}_2]
\]

\[
[\dot{\text{H}}_2\text{O}] = 2k[\text{H}_2]^2[\text{O}_2]
\]
One equation for each one of the species

Rate of change of \([A]\) (concentration of species \(A\)) is proportional to:

- Stoichiometric coefficient of \(A\) time reaction rate \(k\)
- The product of the concentrations of the reactants
The central dogma of molecular biology

Transcription of DNA by RNA polymerase

Translation of mRNA by Ribosomes

From Y. Boada (2018)
Constitutive gene expression (Simplified version)

Transcription

Gene → mRNA

Transcription rate (Promoter) $k_1$

mRNA → Protein

Translation rate (RBS) $k_2$

mRNA degradation rate $d_1$

Protein degradation rate $d_2$

Degradation

Protein degradation rate (including growth related dilution)
Constitutive gene expression (Simplified version)

Transcription

Gene $\rightarrow$ mRNA

$\frac{1}{d_1}$ Degradation

Translation

mRNA $\rightarrow$ Protein

$\frac{1}{d_2}$ Degradation

$k_1$, $k_2$
Constitutive gene expression (Simplified version)

\[
[mRNA] = k_1 [\text{Gene}]
\]
Constitutive gene expression (Simplified version)

\[
\frac{\text{d}[mRNA]}{\text{d}t} = k_1 [\text{Gene}] - d_1 [mRNA]
\]
Constitutive gene expression (Simplified version)

\[
\dot{[\text{mRNA}]} = k_1[\text{Gene}] - d_1[\text{mRNA}]
\]

\[
[\text{Protein}] = k_2[\text{mRNA}]
\]
Constitutive gene expression (Simplified version)

\[
\begin{align*}
\dot{\text{mRNA}} &= k_1 [\text{Gene}] - d_1 [\text{mRNA}] \\
\dot{\text{Protein}} &= k_2 [\text{mRNA}] - d_2 [\text{Protein}]
\end{align*}
\]
Constitutive gene expression (Simplified version)

\[
\frac{d[mRNA]}{dt} = [mRNA] = k_1[\text{Gene}] - d_1[mRNA]
\]

\[
\frac{d[\text{Protein}]}{dt} = [\text{Protein}] = k_2[mRNA] - d_2[\text{Protein}]
\]
Constitutive gene expression - Simulation

ODE model

\[
\text{[mRNA]} = k_1 [\text{Gene}] - d_1 [\text{mRNA}]
\]
\[
\text{[Protein]} = k_2 [\text{mRNA}] - d_2 [\text{Protein}]
\]

Function defines the ODE model

```matlab
% Constitutive gene expression model.
% Updated 17/06/2020 Alejandro Vignoni
function [dxdt] = model_const(t,x,p)
    %x1 = mRNA
    dxdt(1,1) = p.CN*p.k1 - p.d1*x(1);
    %x2 = Protein
    dxdt(2,1) = p.k2*x(1) - p.d2*x(2);
end
```

Main_const.m
Constitutive gene expression - Simulation

Parameters definition

```matlab
% Parameters
p.CN = 17; % plasmid number pACYC184 (17 copies/cell)
p.d1 = log(2)/3; % mRNA degradation rate [1/min]
p.d2 = 0.02; % degradation rate [1/min]
p.k2 = 8.23; % translation rate [1/min]
p.k1 = 1.19; % transcription rate [1/min]
```

Simulation configuration and execution

```matlab
tfin = 60*3; % simulation final time
step = 0.1; % simulation step
tspan = 0:step:tfin-step;
% options for ode function
opti = odeset('AbsTol',1e-8,'RelTol',1e-6);
Init = [0 0]; % initial conditions

[t0,x0] = ode23(@(t,x) model_const(t,x,p),tspan, Init, opti);
```

Constitutive gene expression - Simulation

Parameters definition

```matlab
%Parameters
p.CN = 17;          % plasmid number pACYC184 (17 copies/cell)
p.d1 = log(2)/3;   % mRNA degradation rate [1/min]
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p.k2 = 8.23;        % translation rate [1/min]
p.k1 = 1.19;        % transcription rate [1/min]
```

Simulation configuration and execution

```matlab
tfin = 60*3;        %simulation final time
step = 0.1;        %simulation step
```
[Gene] is considered a constant value and depends on: the Origin of Replication and the Plasmid Copy Number where the Gene is cloned.

We are considering:

- RNA polymerase and Ribosomes are sufficient enough so that they are not limiting the kinetics.
- Binding/Unbinding processes are much faster than transcription and translation.
- Protein degradation includes growth associated dilution.

\[ [\text{mRNA}] = k_1 [\text{Gene}] - d_1 [\text{mRNA}] \]
\[ [\text{Protein}] = k_2 [\text{mRNA}] - d_2 [\text{Protein}] \]
Questions?
Ask writing in the chat or contact me by email (alvig2 [at] upv [dot] es)

Stay tuned, next Section 2:
Derivation of a Hill function from the law of mass action (15 min)
Modeling: ODEs and Hill Functions

Section 2: Derivation of the Hill Function

by Alejandro Vignoni (alvig2@upv.es)

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菱 Q&A – (at the end of each 15 minutes block, total 15 min)
Remember: Constitutive gene expression

\[
\dot{[\text{mRNA}]} = k_1 [\text{Gene}] - d_1 [\text{mRNA}]
\]

\[
\dot{[\text{Protein}]} = k_2 [\text{mRNA}] - d_2 [\text{Protein}]
\]
Gene expression regulation by Transcription Factors (TF)

Promoter + Transcription Factor

Binding

$K_{on}$ $K_{off}$

Transcription

$K_1$

Translation

$K_2$

Degradation

$D_1$ $D_2$

Protein
Gene expression regulation by Transcription Factors (TF)

We will get: -5 Equations
- with 7 parameters

Problems:
- \( k_{on}, k_{off} \) are very difficult to measure.
- \( k_1, k_2, d_1 \) and \( d_2 \) become indistinguishable when we measure only the protein amount.
Gene expression regulation by Transcription Factors (TF)

We want to approximate and simplify the problem and obtain a model easier to relate with experimental data:

1. We will obtain all the equations.
2. Approximate and reduce them.

Problems: $k_{on}, k_{off}$, are very difficult to measure.
Gene expression regulation by Transcription Factors (TF)

Part I: Getting the model

Promoter + Transcription Factor

Binding \( k_{on} \) \( k_{off} \) Unbinding

Promoter . TF
Gene expression regulation by Transcription Factors (TF)

\[
[\text{Prom. TF}] = k_{on} [\text{Prom}][\text{TF}]
\]
Gene expression regulation by Transcription Factors (TF)

\[ \text{Prom. TF} = k_{on} \ [\text{Prom}][\text{TF}] \]

\[ \dot{[\text{Prom}]} = -k_{on} \ [\text{Prom}][\text{TF}] \]
Gene expression regulation by Transcription Factors (TF)

\[ [\text{Prom. TF}] = k_{on} [\text{Prom}][\text{TF}] \]

\[ [\dot{\text{Prom}}] = -k_{on} [\text{Prom}][\text{TF}] \]

\[ [\dot{\text{TF}}] = -k_{on} [\text{Prom}][\text{TF}] \]
Gene expression regulation by Transcription Factors (TF)

\[
\begin{align*}
[\text{Prom. TF}] &= k_{on} [\text{Prom}][\text{TF}] \\
[\dot{\text{Prom}}] &= -k_{on} [\text{Prom}][\text{TF}] \\
[\dot{\text{TF}}] &= -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom. TF}]
\end{align*}
\]
Gene expression regulation by Transcription Factors (TF)

\[
[\text{Prom. TF}] = k_{on} \ [\text{Prom}][\text{TF}]
\]

\[
[\text{Prom}] = -k_{on} \ [\text{Prom}][\text{TF}] + k_{off} \ [\text{Prom. TF}]
\]

\[
[\text{TF}] = -k_{on} \ [\text{Prom}][\text{TF}] + k_{off} \ [\text{Prom. TF}]
\]
Gene expression regulation by Transcription Factors (TF)

\[
[\text{Prom. TF}] = k_{on} [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}]
\]

\[
[\text{Prom}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom. TF}]
\]

\[
[\text{TF}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom. TF}]
\]
Gene expression regulation by Transcription Factors (TF)

Simulation

Starting with:
- 17 Promoters (Plasmid copy number)
- 25 molecules of Transcription Factor (TF)

\[ [\text{Prom. TF}] = k_{on} [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}] \]

\[ [\text{Prom}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom. TF}] \]

\[ [\text{TF}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom. TF}] \]

\[ k_{on} = 0.5 \text{ molecules}^{-1} \text{ min}^{-1} \]
\[ k_{off} = 1 \text{ min}^{-1} \]

Main_TF.m
Gene expression regulation by Transcription Factors (TF)  

Part II: Model Reduction

\[
[\text{Prom}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom}.\text{TF}]
\]

\[
[\dot{\text{TF}}] = -k_{on} [\text{Prom}][\text{TF}] + k_{off} [\text{Prom}.\text{TF}]
\]

\[
[\dot{\text{Prom}.\text{TF}}] = k_{on} [\text{Prom}][\text{TF}] - k_{off} [\text{Prom}.\text{TF}]
\]

Remarks

△ First two equations are equal (Blue and red)!
△ The sum of the first one and the third one is identically zero (Blue and yellow)!
△ We can use this fact (promoter invariance) to simplify the equations and reduce the model.
Gene expression regulation by Transcription Factors (TF)

**Promoter invariance (constant Plasmid Copy Number)**

\[
\dot{\text{Prom}} = -k_{on} \text{Prom}[\text{TF}] + k_{off} \text{Prom. TF}
\]

\[
\dot{\text{Prom. TF}} = k_{on} \text{Prom}[\text{TF}] - k_{off} \text{Prom. TF}
\]

\[
\dot{\text{Prom. TF}} + \dot{\text{Prom}} = 0
\]

\[
\text{Prom. TF} + \text{Prom} = C_N
\]

\[
\text{Prom} = C_N - \text{Prom. TF}
\]

Save this one, we will use it later.
Gene expression regulation by Transcription Factors (TF)

Part I: Getting the model

Promoter + Transcription Factor

Binding $k_{on}$ $k_{off}$

Promoter . TF

Transcription

$k_1$

mRNA

Translation

$k_2$

Protein

Degradation

$d_1$

$\emptyset$

$d_2$

$\emptyset$
Gene expression regulation by Transcription Factors (TF)

\[ [\text{mRNA}] = k_1 [\text{Prom. TF}] \]

- **Promoter** + **Transcription Factor**
- Binding: \( k_{on} \)
- Degradation: \( d_1 \)
- Translation: \( k_2 \)
- Protein: \( d_2 \)

**Transcription**
- \( k_1 \)
Gene expression regulation by Transcription Factors (TF)

Note the difference in time scales: Binding in the seconds, transcription/translation from minutes to hours.
Gene expression regulation by Transcription Factors (TF)

**Fast Transcription Factor – Promoter binding**

\[
[	ext{Prom. TF}] \approx 0
\]

Because of the difference in time scales: Binding in the seconds, transcription/translation from minutes to hours; we can say that TF rapidly binds to the promoter and this reaction reaches equilibrium very fast. This is called Quasy Steady State Approximation (QSSA).

\[
\dot{[\text{Prom. TF}]} = k_{on} \ [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}]
\]

\[
0 = k_{on} \ [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}]
\]

From invariance (previous slide)

\[
[\text{Prom}] = C_N - [\text{Prom. TF}]
\]
Gene expression regulation by Transcription Factors (TF)

Fast Transcription Factor – Promoter binding

\[ [\text{Prom. TF}] \approx 0 \]

Because of the difference in time scales: Binding in the seconds, transcription/translation from minutes to hours; we can say that TF rapidly binds to the promoter and this reaction reaches equilibrium very fast. This is called Quasy Steady State Approximation (QSSA).

\[ [\text{Prom. TF}] = k_{on} \ [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}] \]

\[ 0 = k_{on} \ [\text{Prom}][\text{TF}] - k_{off} [\text{Prom. TF}] \]

From invariance (previous slide)

\[ [\text{Prom}] = C_N - [\text{Prom. TF}] \]

Using these two, we will derive the Hill function
Gene expression regulation by Transcription Factors (TF)

Replacing the free promoter equation into the TF bound Promoter one:

\[ \text{[Prom]} = C_N - \text{[Prom. TF]} \]

\[ 0 = k_{on} \text{[Prom][TF]} - k_{off} \text{[Prom. TF]} \]

\[ 0 = k_{on} (C_N - \text{[Prom. TF]})[TF] - k_{off} \text{[Prom. TF]} \]
Gene expression regulation by Transcription Factors (TF)

Solving for the TF bound Promoter:

\[ k_{on} \left(C_N - [\text{Prom. TF}]\right)[\text{TF}] = k_{off} [\text{Prom. TF}] \]

\[ k_{on} [\text{TF}]C_N - k_{on} [\text{TF}][\text{Prom. TF}] = k_{off} [\text{Prom. TF}] \]

\[ k_{on} [\text{TF}]C_N = k_{on} [\text{TF}][\text{Prom. TF}] + k_{off} [\text{Prom. TF}] \]

\[ k_{on} [\text{TF}]C_N = \left( k_{on} [\text{TF}] + k_{off} \right) [\text{Prom. TF}] \]

\[ [\text{Prom. TF}] = C_N \frac{k_{on}[\text{TF}]}{k_{on} [\text{TF}] + k_{off}} = C_N \frac{[\text{TF}]}{k_{off} + [\text{TF}]} = C_N \frac{[\text{TF}]}{K_d + [\text{TF}]} \]
Gene expression regulation by Transcription Factors (TF)

We get the Hill function (with Hill coefficient \( n = 1 \))

\[
[\text{Prom. TF}] = C_N \frac{[\text{TF}]}{K_d + [\text{TF}]}
\]

![Diagram of promoter and transcription factor activation]
Gene expression regulation by Transcription Factors (TF)

The complete equation for the mRNA

\[
[mRNA] = k_1 \frac{[TF]}{K_d + [TF]} - d_1[mRNA]
\]

\[
[\text{Prom. TF}] = C_N \frac{[TF]}{K_d + [TF]}
\]
Gene expression regulation by Transcription Factors (TF)

\[
\frac{d[\text{mRNA}]}{dt} = [\text{mRNA}] = k_1 C_N \frac{[\text{TF}]}{K_d + [\text{TF}]} - d_1[\text{mRNA}]
\]

\[
\frac{d[\text{Protein}]}{dt} = [\text{Protein}] = k_2 [\text{mRNA}] - d_2[\text{Protein}]
\]
Gene expression regulation by Transcription Factors (TF)

Simulation

\[
\begin{align*}
\text{[mRNA]} &= k_1 \frac{C_N \text{[TF]}}{K_d + \text{[TF]}} - d_1 \text{[mRNA]} \\
\text{[Protein]} &= k_2 \text{[mRNA]} - d_2 \text{[Protein]}
\end{align*}
\]

Parameters:
- \(CN = 17\) molecules (Plasmid copy number)
- \(K_d = 2\) molecules
- \(TF = 25\) molecules (Transcription Factor)
- The other parameters same than constitutive
Gene expression regulation by Transcription Factors (TF)

Simulation

\[
\begin{align*}
\text{[mRNA]} &= k_1 \frac{CN}{K_d + [\text{TF}]} - d_1 \text{[mRNA]} \\
\text{[Protein]} &= k_2 \text{[mRNA]} - d_2 \text{[Protein]}
\end{align*}
\]

Parameters:
- \(CN = 17\) molecules (Plasmid copy number)
- \(K_d = 2\) molecules
- \(TF = 25\) molecules (Transcription Factor)
- The other parameters same than constitutive

Note the difference in time scales: transcription (mRNA) in minutes, translation (Protein) hours.
Gene expression regulation by Transcription Factors (TF)

Now, as mRNA is much faster than Protein production... we use the same trick than before (QSSA):

\[ [\text{mRNA}] \approx 0 \]

\[ 0 = k_1 C_N \frac{[\text{TF}]}{K_d + [\text{TF}]} - d_1 [\text{mRNA}] \Rightarrow [\text{mRNA}] = \frac{k_1}{d_1} C_N \frac{[\text{TF}]}{K_d + [\text{TF}]} \]

\[ \frac{d[\text{Protein}]}{dt} = [\text{Protein}] = \alpha \frac{[\text{TF}]}{K_d + [\text{TF}]} - d_2 [\text{Protein}] \]

\[ \alpha = k_2 \frac{k_1}{d_1} C_N \]
Gene expression regulation by Transcription Factors (TF)

Simulation

\[
[\text{Protein}] = \alpha \frac{[\text{TF}]}{K_d + [\text{TF}]} - d_2[\text{Protein}]
\]

With:
- \( \alpha = 720 \) molecules min\(^{-1}\)
- \( K_d = 2 \) molecules
- \( d_2 = 0.02 \) min\(^{-1}\)
  
  (this means 34 min of doubling time)

\[\alpha = k_2 \frac{k_1}{d_1} C_N\]

[TF]: from 0.1 molecule to 25 molecules of Transcription Factor
Gene expression regulation by Transcription Factors (TF)

Now, if we want the steady state we can use the same trick (QSSA) that we used before (equilibrium expression of protein, data at the end of the experiment)

\[
[\text{Protein}] \approx 0
\]

\[
[\text{Protein}] = \frac{\alpha [\text{TF}]}{d_2 K_d + [\text{TF}]}
\]

\[
\alpha = k_2 \frac{k_1}{d_1} C_N
\]
Questions?
Ask writing in the chat or contact me by email (alvig2 [at] upv [dot] es)

Stay tuned, next Section 3:
Hill function examples and intuitions: effects of parameters on activators, repressors, hybrid promoters, using a Matlab exploration package.
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Section 3: Hill function examples and intuitions

by Alejandro Vignoni (alvig2@upv.es)

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Gene expression regulation by Transcription Factors (TF)

Activator

\[
[\text{Protein}] = \alpha_{\text{max}} \left( \beta_0 + (1 - \beta_0) \frac{[\text{TF}]^n}{K_d + [\text{TF}]^n} \right)
\]

\[
\alpha_{\text{max}} = k_2 \frac{k_1}{d_1 d_2} C_N
\]
Gene expression regulation by Transcription Factors (TF)

Repressor

\[
[\text{Protein}] = \alpha_{\text{max}} \left( \beta_0 + (1 - \beta_0) \frac{K_d}{K_d + [\text{TF}]_n} \right) \quad \alpha_{\text{max}} = k_2 \frac{k_1}{d_1 d_2} C_N
\]
Gene expression regulation by Transcription Factors (TF) Hybrid Promoter

\[
[\text{Protein}] = \alpha_{max} \left(\beta_0 + (1 - \beta_0) \frac{\frac{1}{k_{dlux}} \left(\frac{[R][A]}{k_{d2}C_N}\right)^2}{1 + \frac{1}{k_{dlux}} \left(\frac{[R][A]}{k_{d2}C_N}\right)^2} \frac{1}{1 + \frac{[cI]^2}{k_{dc1}C_N}}\right)
\]
Questions?
Contact me by email (alvig2 [at] upv [dot] es)

Thank You & Have an Exceptional Year of iGEM!

Next Modeling seminar
Week 3a Modeling circuits with ODEs and experimental data,
stay tuned!

Go check out the Measurement Hub!
https://2020.igem.org/Measurement