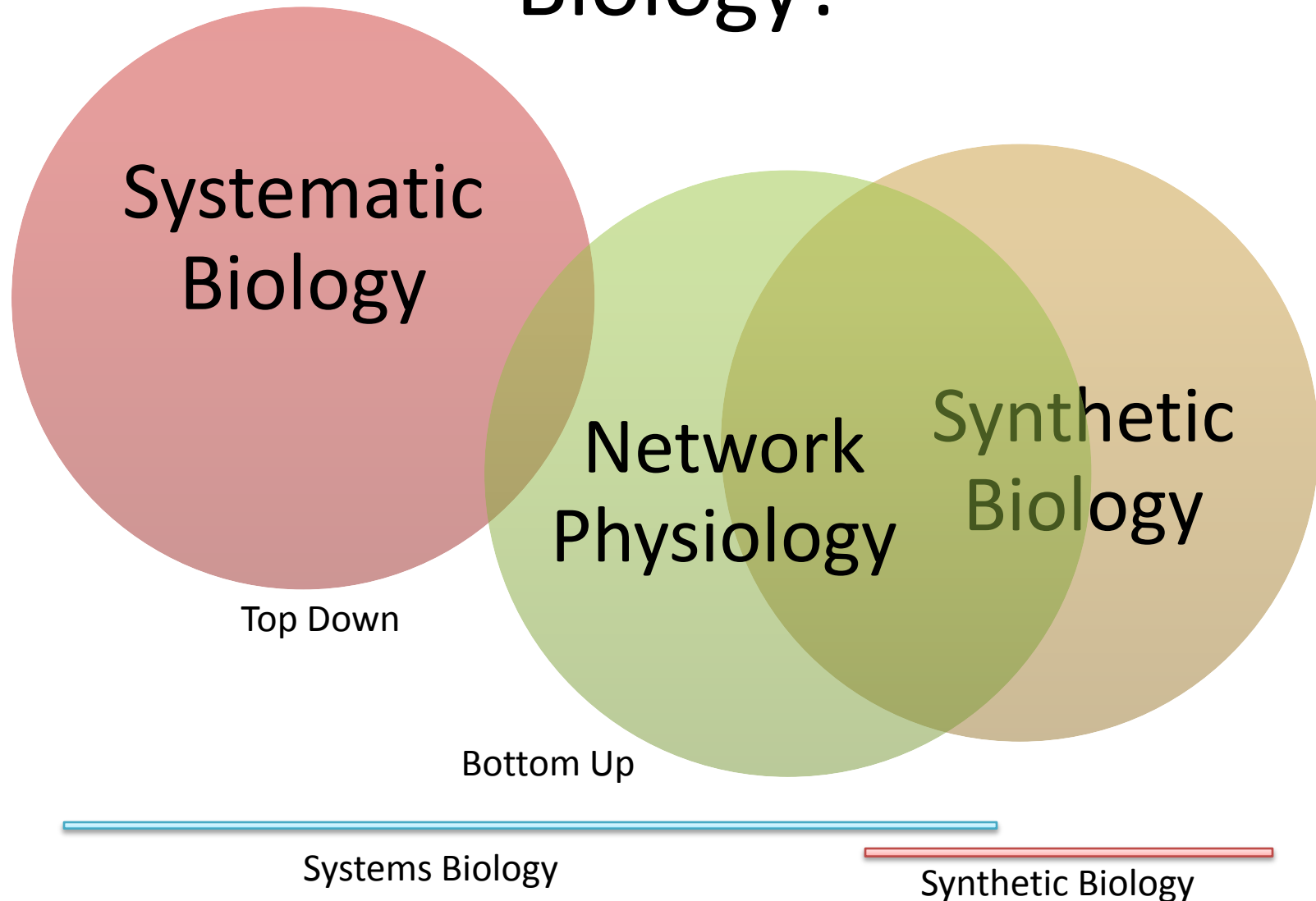
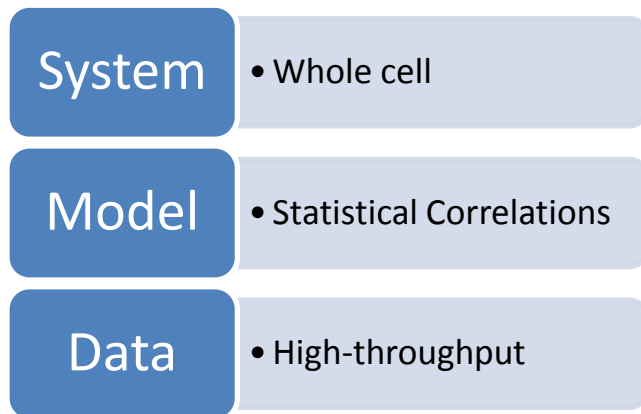


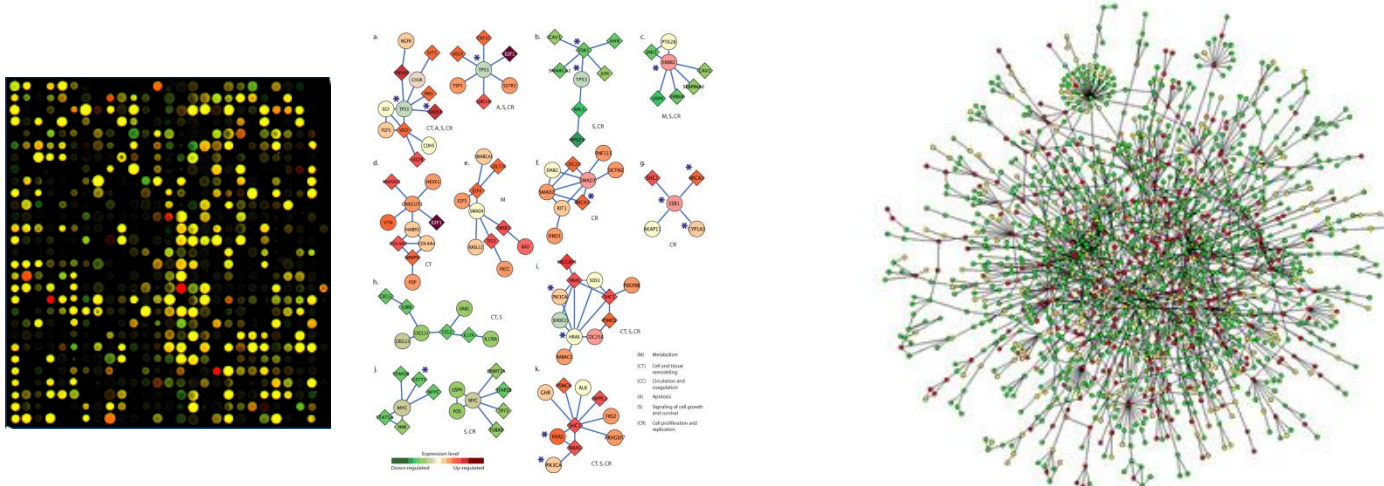
# What is Systems and Synthetic Biology?



# Top Down “-omics”



# Yeast Protein-Protein Interaction Map



# Top Down and Bottom Up

## Top Down “-omics”

System

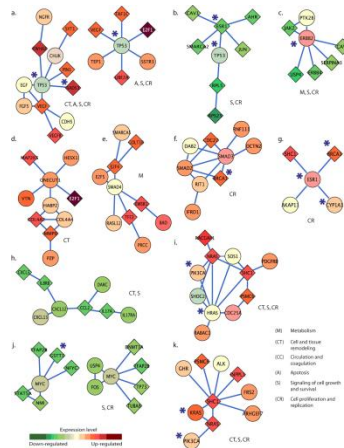
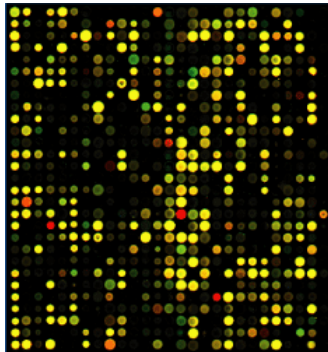
- Whole cell

Model

- Statistical Correlations

Data

- High-throughput



## Bottom Up “mechanistic”

System

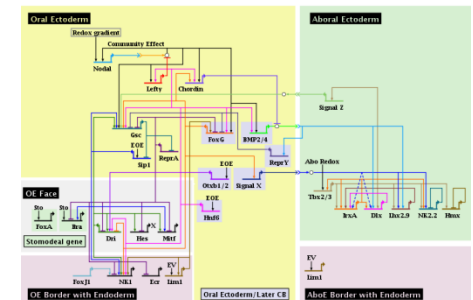
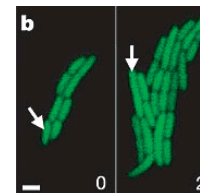
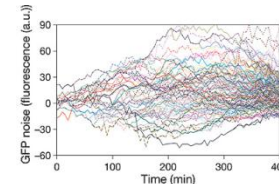
- Networks/Pathways

Model

- Mechanistic, biophysical

Data

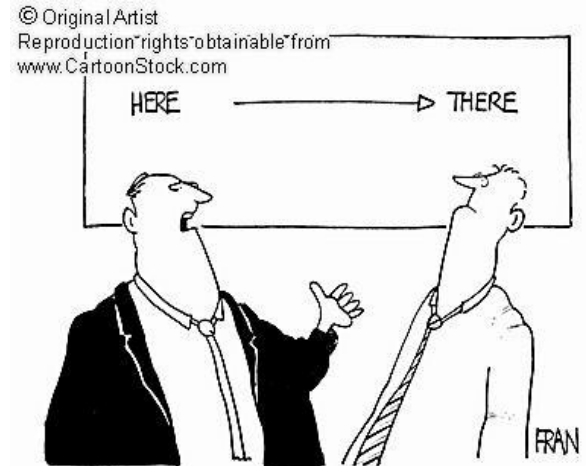
- Quantitative, single-cell



# What is a model?

From the Oxford English dictionary:

*“A simplified or idealized description or conception of a particular system, situation, or process, often in mathematical terms, that is put forward as a basis for theoretical or empirical understanding, or for calculations, predictions, etc.”*



"It's a simple model... but it works for me..."

# Biology is full of models

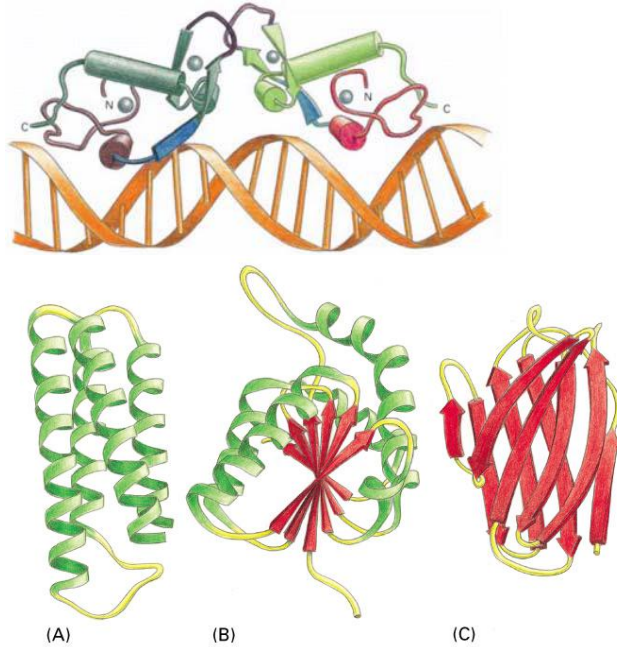
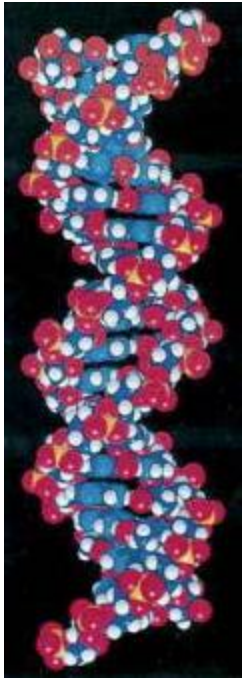


Figure 3-13. Molecular Biology of the Cell, 4th Edition.

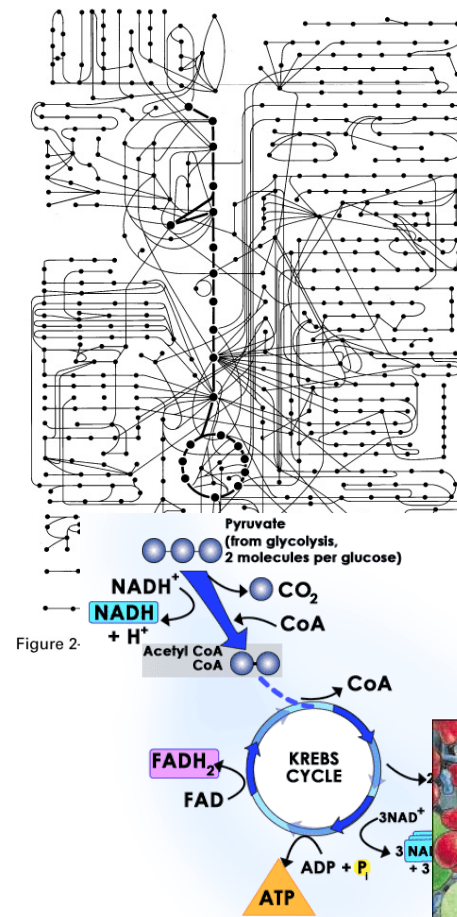


Figure 2-

100 nm

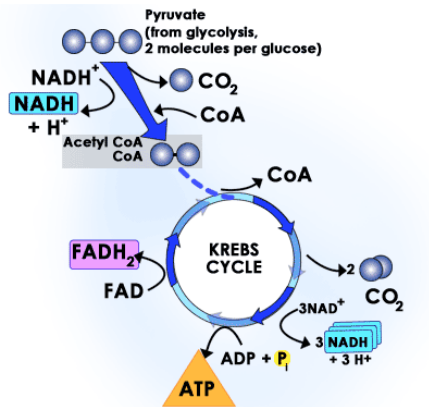
# Models are idealized descriptions of some part of a real world process.

Models are **not** replicas of reality, they are simplified descriptions.

Simplification allows us to comprehend the **essential features** of a complex process without being burdened and overwhelmed by **unnecessary details**.

Models come in various forms:

- Verbal
- Visual
- Mathematical



# All models are wrong and can never be proved correct \*.

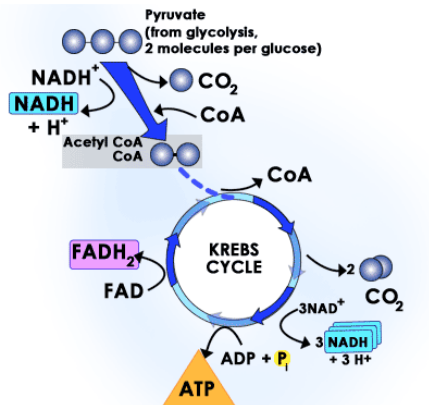
A model serves two purposes:

1. It should attempt to describe all **existing observations**
2. It should be able to make **non-trivial predictions**

The models we will be concerned with will be mechanistic in nature, that is dependent on some understanding of the physical makeup of the system.

Other types of model include empirical models which are based on fitting observations to simple mathematical functions, eg linear regression models. Empirical models are sometimes used to model reaction rates.

\*George Box: 'All models are wrong, some are useful'.



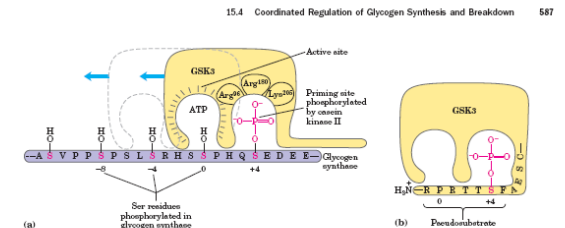


# Types of Models in Systems Biology

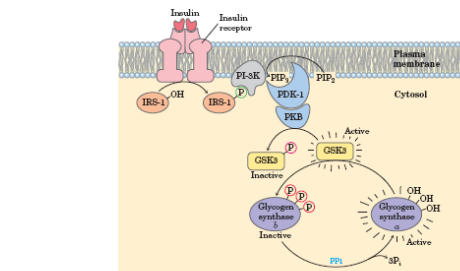
Visual models are very popular in biology - see any biochemistry or molecular biology textbook.

Although visual models can be used to make useful predictions the scope of such predictions is limited. In addition the reasoning power of visual models is very narrow.

In systems and synthetic biology, the most popular way to present models is to use mathematics.



**FIGURE 15-28** Priming of GSK3 phosphorylation of glycogen synthase. (a) Glycogen synthase kinase 3 first associates with its substrate glycogen synthase by interaction between three positively charged residues (Arg<sup>10</sup>, Arg<sup>11</sup>, Lys<sup>20</sup>) and a glycophosphoric residue at position +4 in the substrate. For orientation, the Ser or Thr residue to be phosphorylated in the substrate is assigned the index 0. Residues on the amino-terminal side of this residue are numbered -1, -2, and so forth; residues on the carboxyl-terminal side are numbered +1, +2, and so forth. This association aligns the active site of the enzyme with a Ser residue at position 0, which it phosphorylates. This creates a new



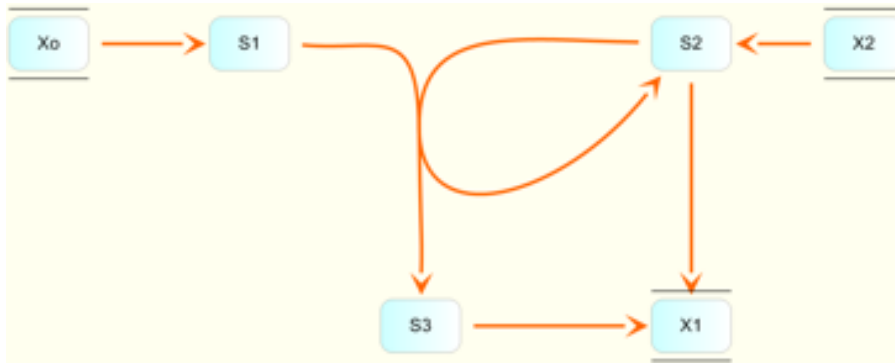
**FIGURE 15-29** The path from insulin to GSK3 and glycogen synthase. Insulin binding to its receptor activates a tyrosine protein kinase in the membrane which phosphorylates insulin receptor substrate-1 (IRS-1). The phosphorylation in this protein is then bound by phosphatidylinositol 3-kinase (PI-3K), which converts phosphatidylinositol 4,5-bisphosphate (PIP<sub>2</sub>) to the membrane to phosphatidylinositol 3,4,5-trisphosphate (PIP<sub>3</sub>). A protein kinase (PDK-1) that is activated when bound to PIP<sub>3</sub> activates a second protein kinase (PKB), which phosphorylates glycogen synthase kinase 3 (GSK3) in its pseudosubstrate region, inactivating it by the mechanism shown in Figure 15-28b. The inactivation of GSK3 allows phosphoprotein phosphatase 1 (PP1) to dephosphorylate glycogen synthase, converting it to its active form. In this way, insulin stimulates glycogen synthesis. (See Fig. 12-8 for more details on insulin action.)



# Conceptual and Concrete Models

There are two broad types of model in systems and synthetic biology:

## 1. Conceptual



```
p = defn cell
    $X0 -> S1; k1;
    S1 + S2 -> S3 + 2 S2; k2;
    S3 -> $X1; k3;
    $X2 -> S2; k4;
    S2 -> $X1; k5;

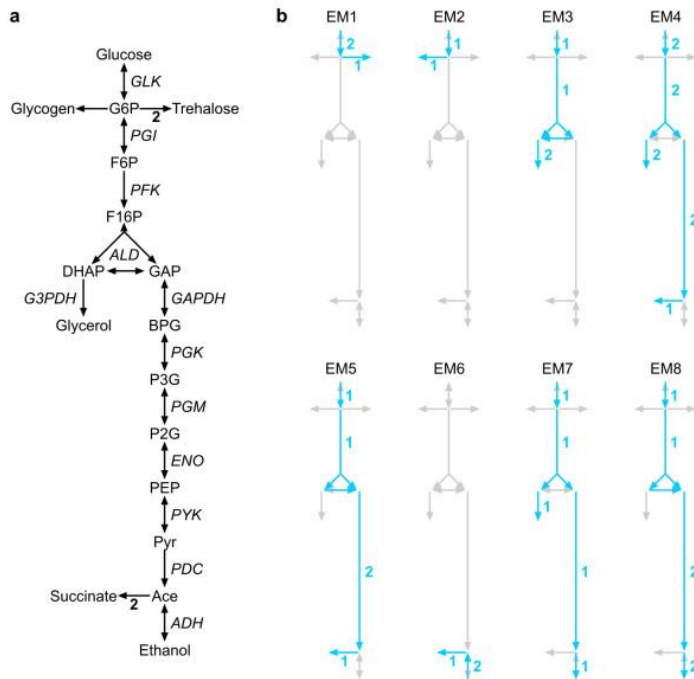
end;

p.k1 = 0.1;    p.k2 = 0.1;
p.k3 = 0.01;  p.k4 = 0.05;
p.k5 = 10.1;  p.X0 = 10;
p.X2 = 1;     p.S1 = 0;
p.S2 = 0;     p.S3 = 0;
```

# Conceptual and Concrete Models

There are two broad types of model in systems and synthetic biology:

## 2. Concrete



$$N = \begin{matrix} & \begin{matrix} \text{GLC1} & \text{HEX1} & \text{PGI} & \text{PFK} & \text{FBP} & \text{FBA} & \text{TPI} & \text{EX\_glc} \end{matrix} \\ \begin{matrix} \text{glc-D[e]} \\ \text{glc-D} \\ \text{atp} \\ \text{H} \\ \text{adp} \\ \text{g6p} \\ \text{f6p} \\ \text{fdp} \\ \text{pi} \\ \text{h2o} \\ \text{g3p} \\ \text{dhap} \end{matrix} & \begin{pmatrix} -1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \\ 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -1 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -1 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & -1 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \end{pmatrix} \end{matrix}$$

Stoichiometry matrix  
for part of glycolysis

# What makes a good concrete model?

## 1. ***Accuracy***

Does the model describe current experimental observations?

## 2. ***Predictability***

Does the model generate insight and/or new predictions that are beyond current knowledge?

## 3. ***Falsifiability***

The model must be falsifiable, that is, is there some experiment that can be carried out to show that the model is incorrect?

## 4. ***Parsimonious***

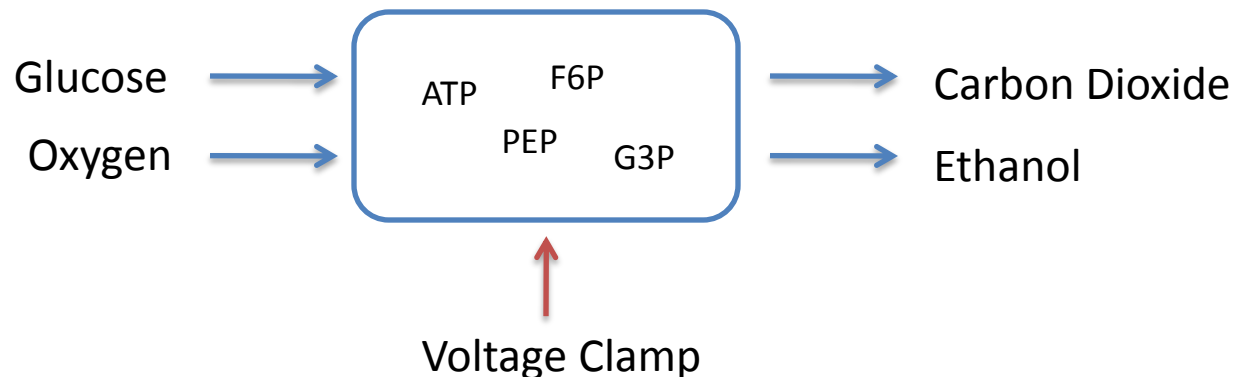
The model should be as simple as possible, “Occam’s infamous razor”.  
That is, given competing and equally good models, the simplest is preferred.

# Model Variables

When building a model, the first thing to do is to identify the **external** from the **internal** variables.

External variables are called the **boundary variables**.

The internal variables are called the **state variables**.



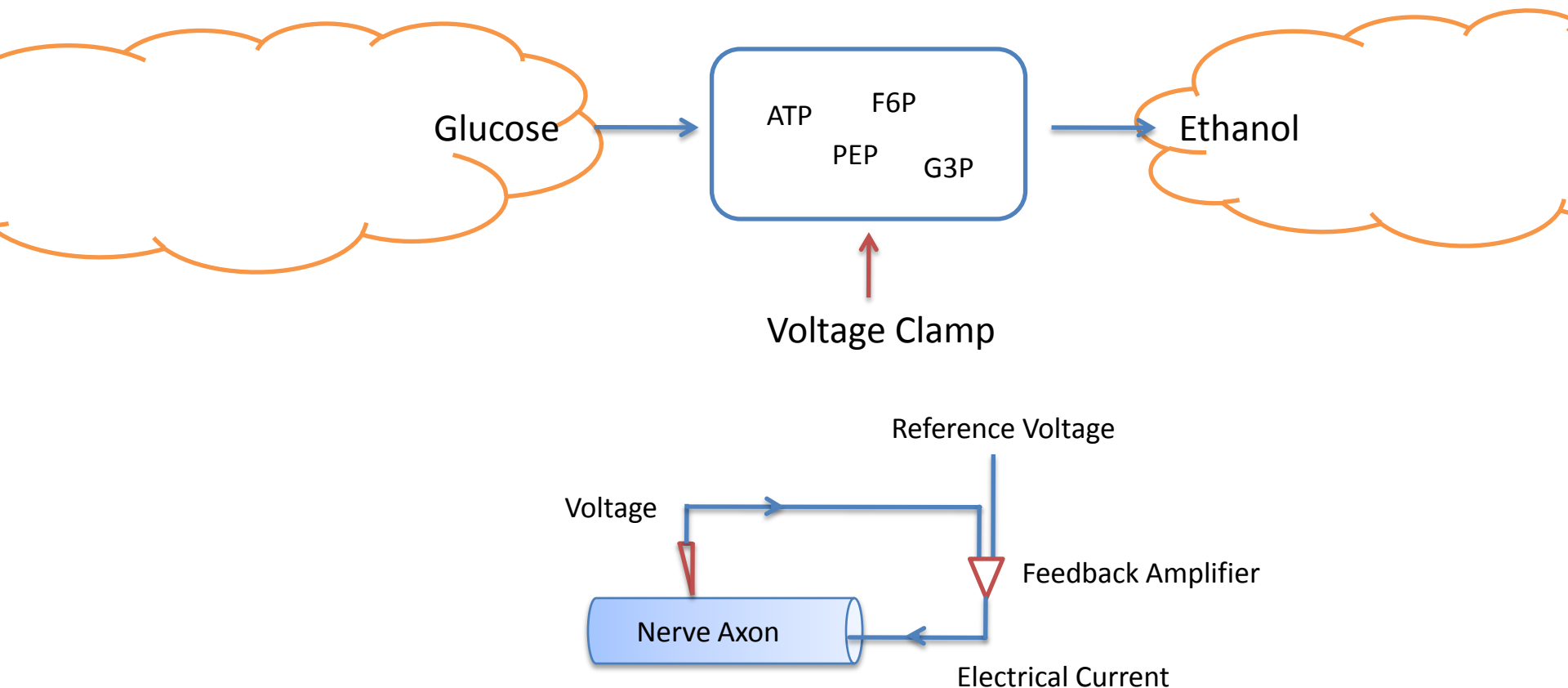
Boundary variables are, in principle, under the control of the experimenter and can include things such as the concentrations of molecular species or voltages.

State variables **cannot** be controlled directly by the experimenter but are a **function** of the system.

# Model Variables

External variables are called the **boundary variables**.

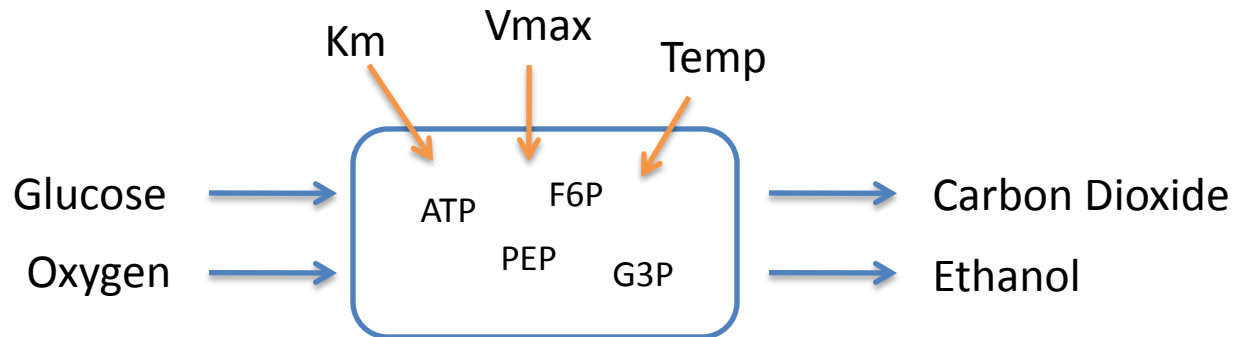
External concentrations can be clamped by supplying them from a large volume.



# Model Parameters

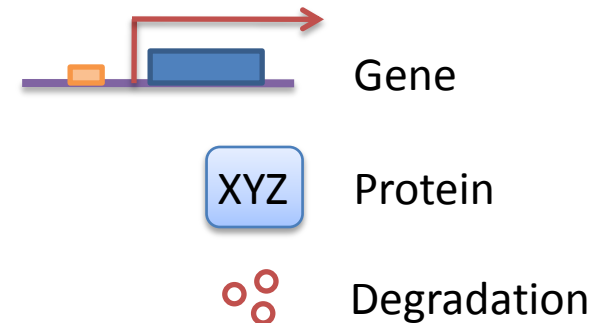
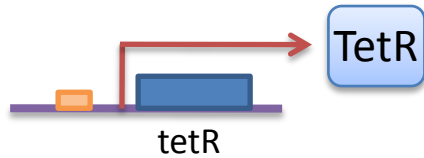
Parameters include everything that is potentially under the control of the experimenter and includes as a subset, the boundary variables.

Other parameters include things like, cell volume, kinetic constants, or enzyme activities.



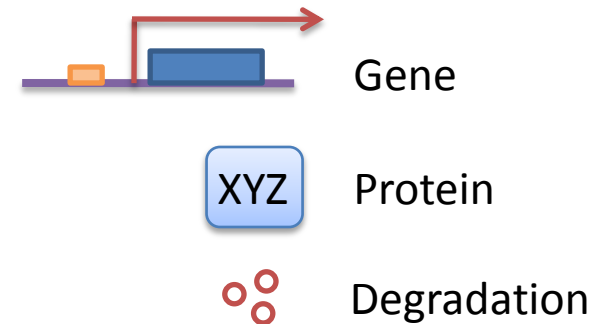
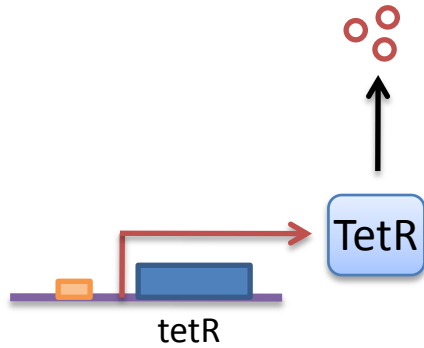
# Preview Model – Repressilator

A Synthetic Oscillatory Network of Transcriptional Regulators; Michael B. Elowitz and Stanislas Leibler; Nature. 2000 Jan 20;403(6767):335-8.

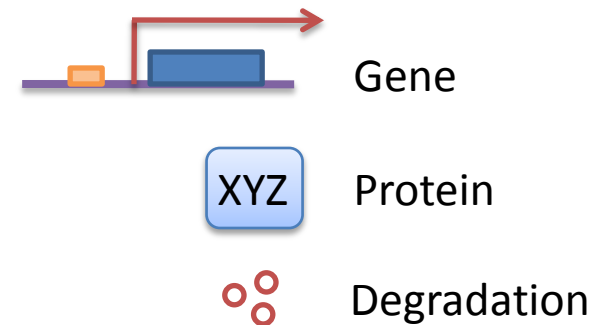
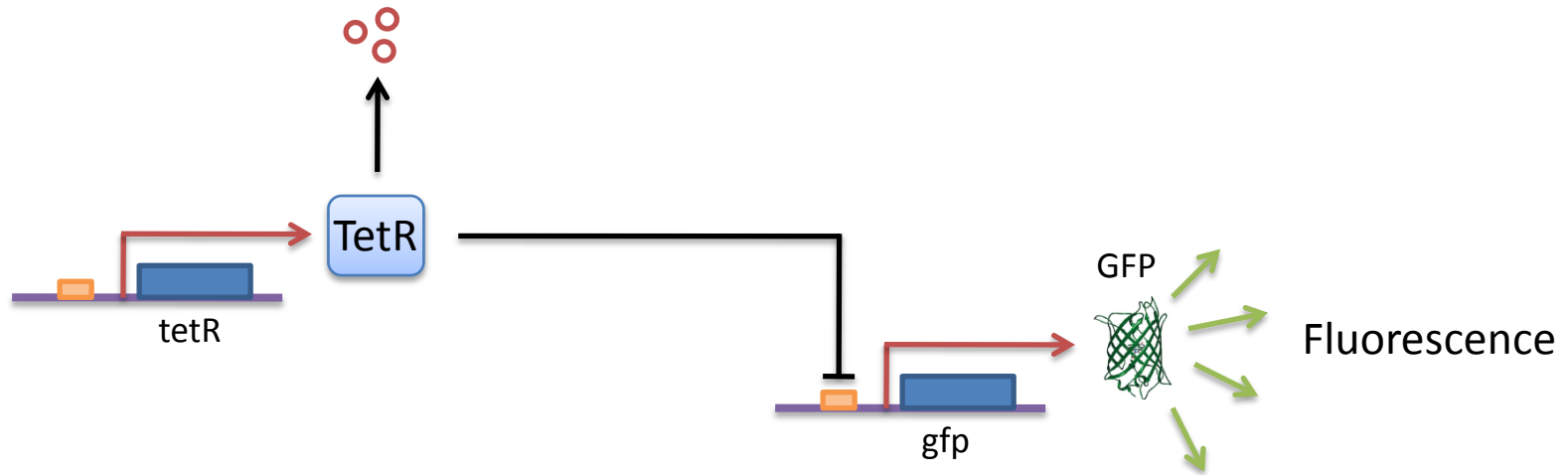




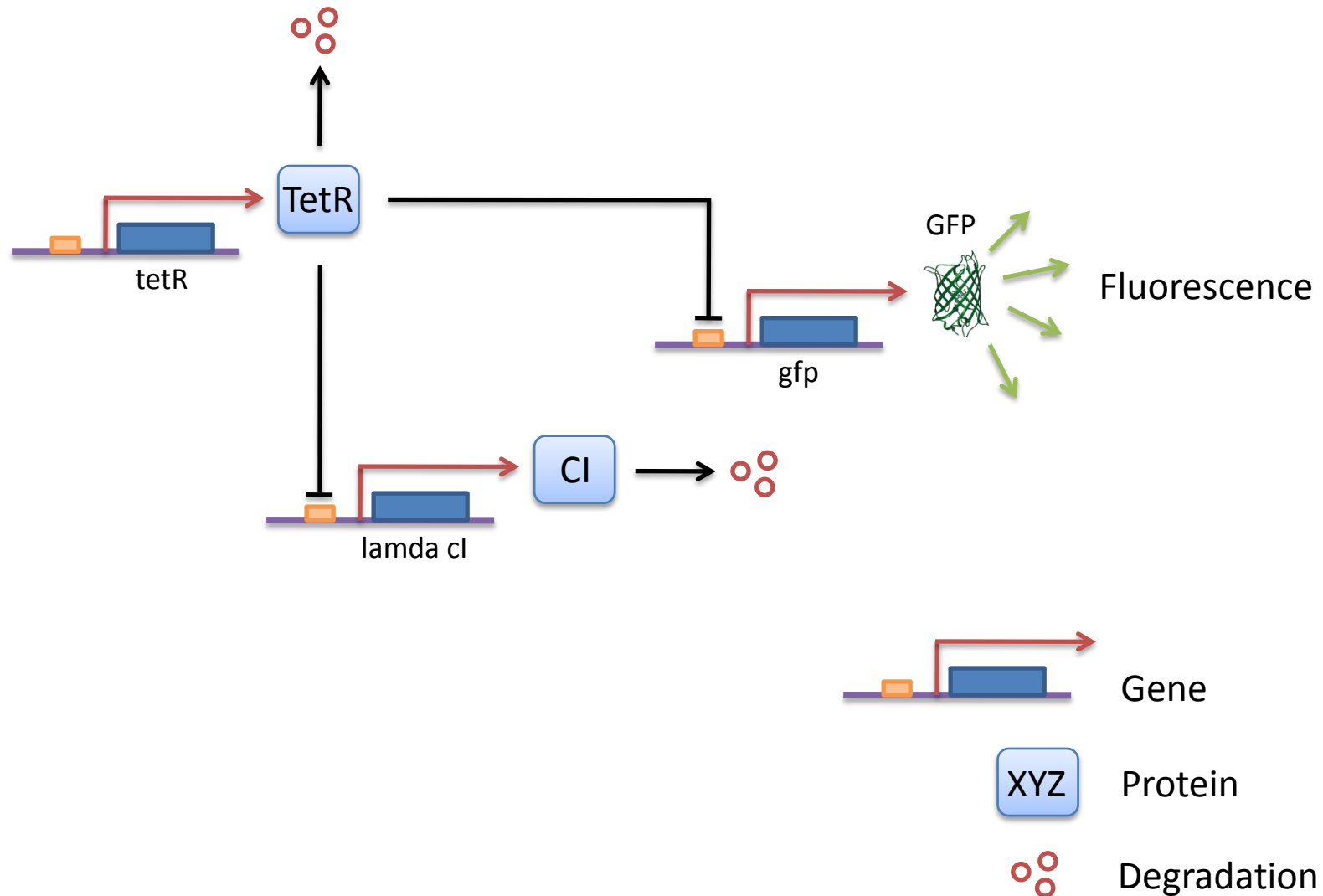
# Preview Model



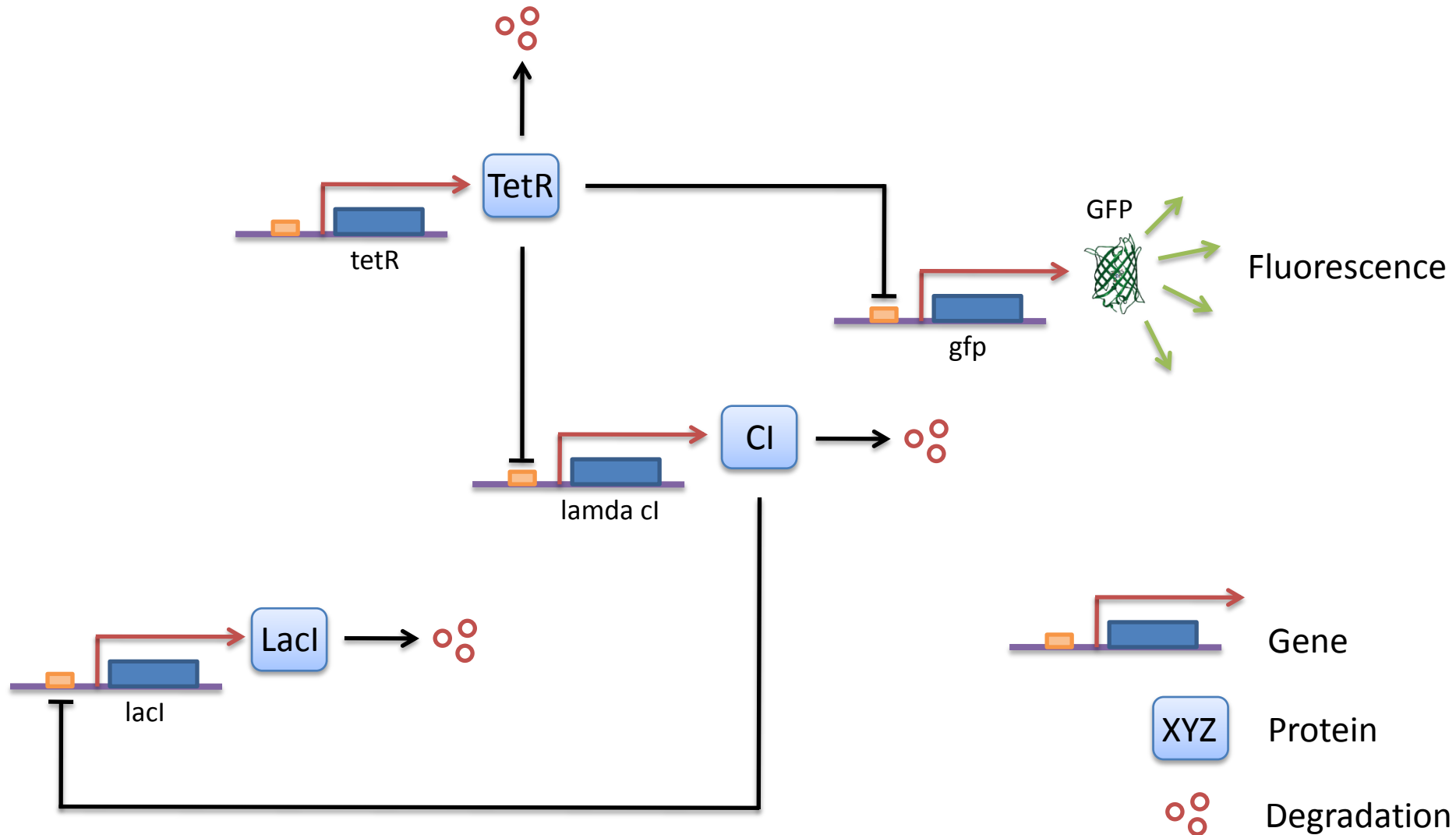
# Preview Model



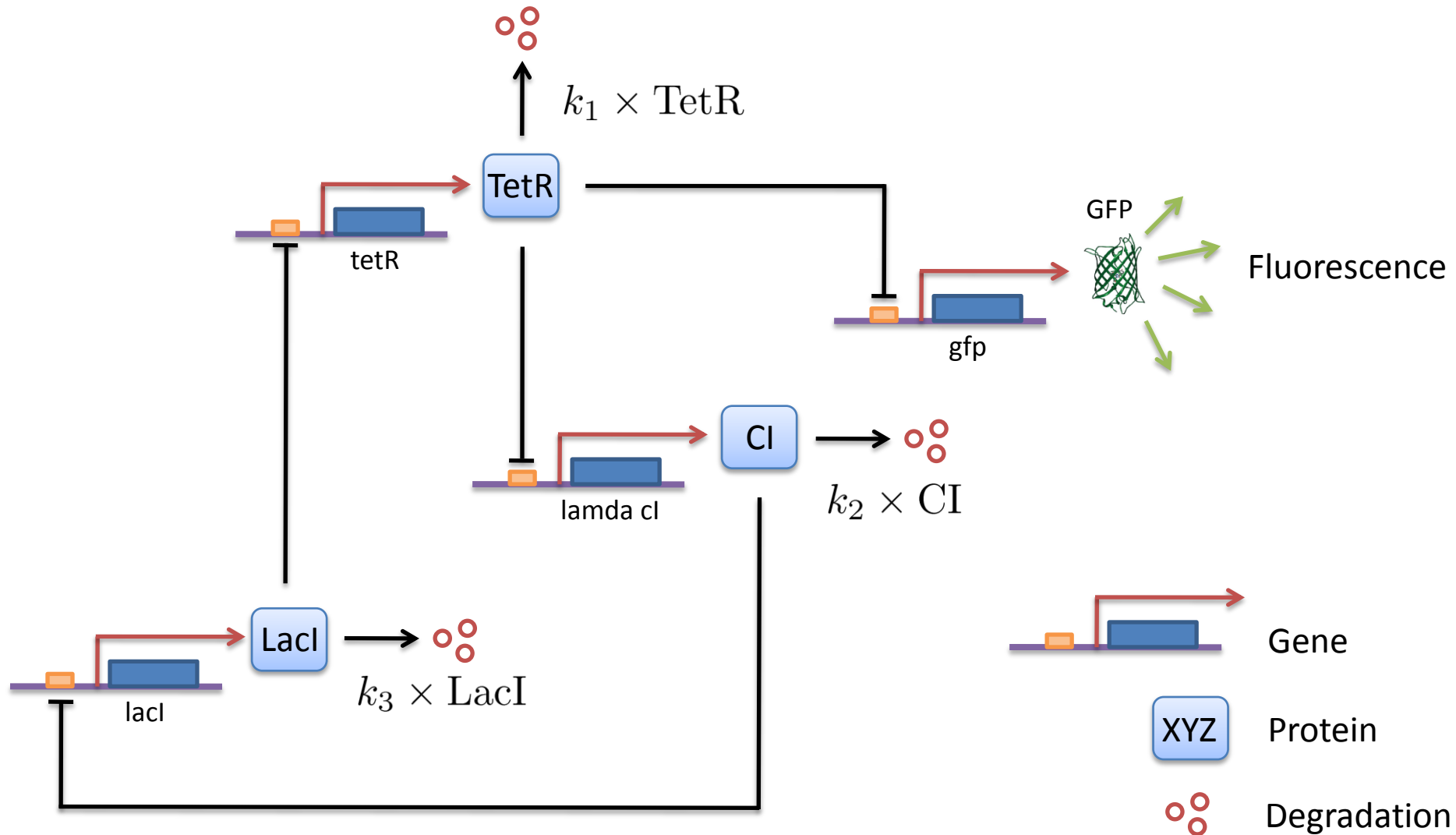
# Preview Model



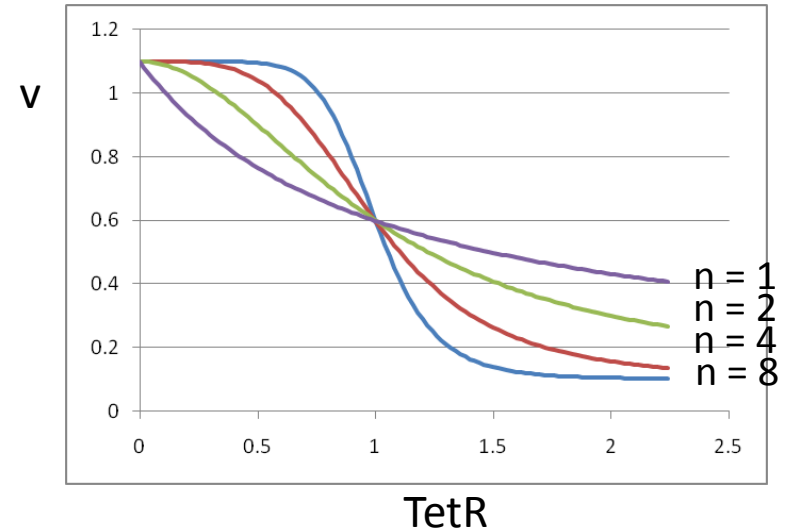
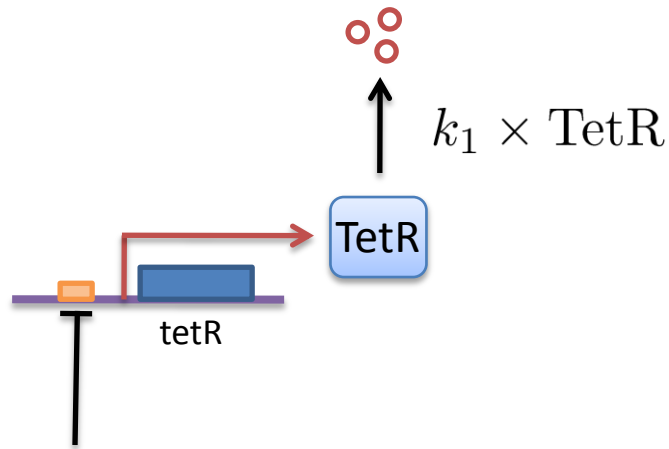
# Preview Model



# Preview Model



# Preview Model



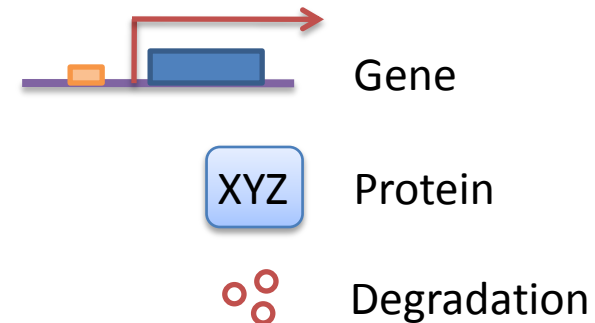
$$v = \alpha_0 + \alpha / (1 + \text{TetR}^n)$$

← This is an empirical model of gene expression.

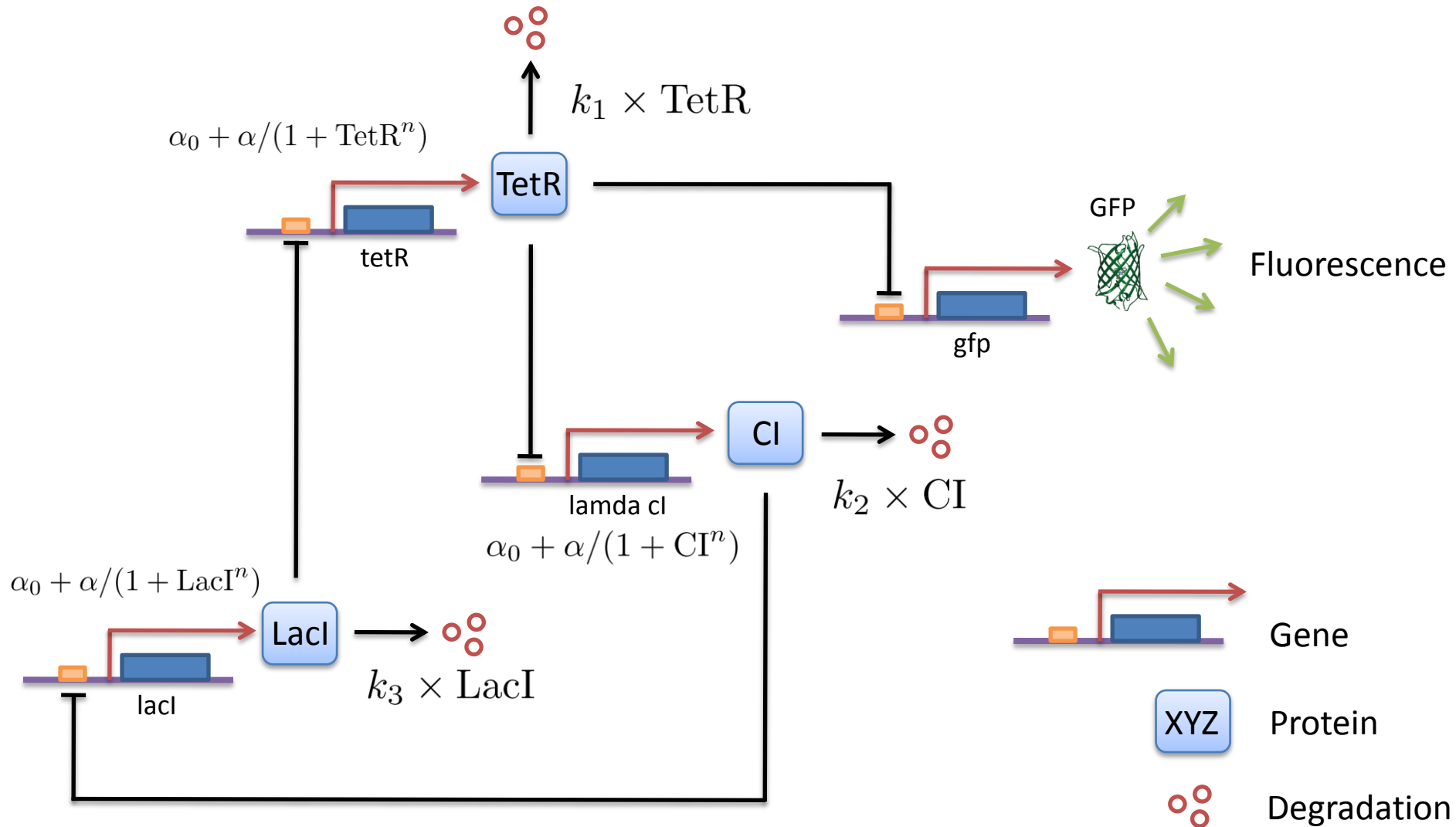
Basal Rate (leakage)  $\uparrow$   $\alpha_0$

Maximal Rate (Vmax)  $\uparrow$   $\alpha$

Hill coefficient  $\uparrow$   $n$



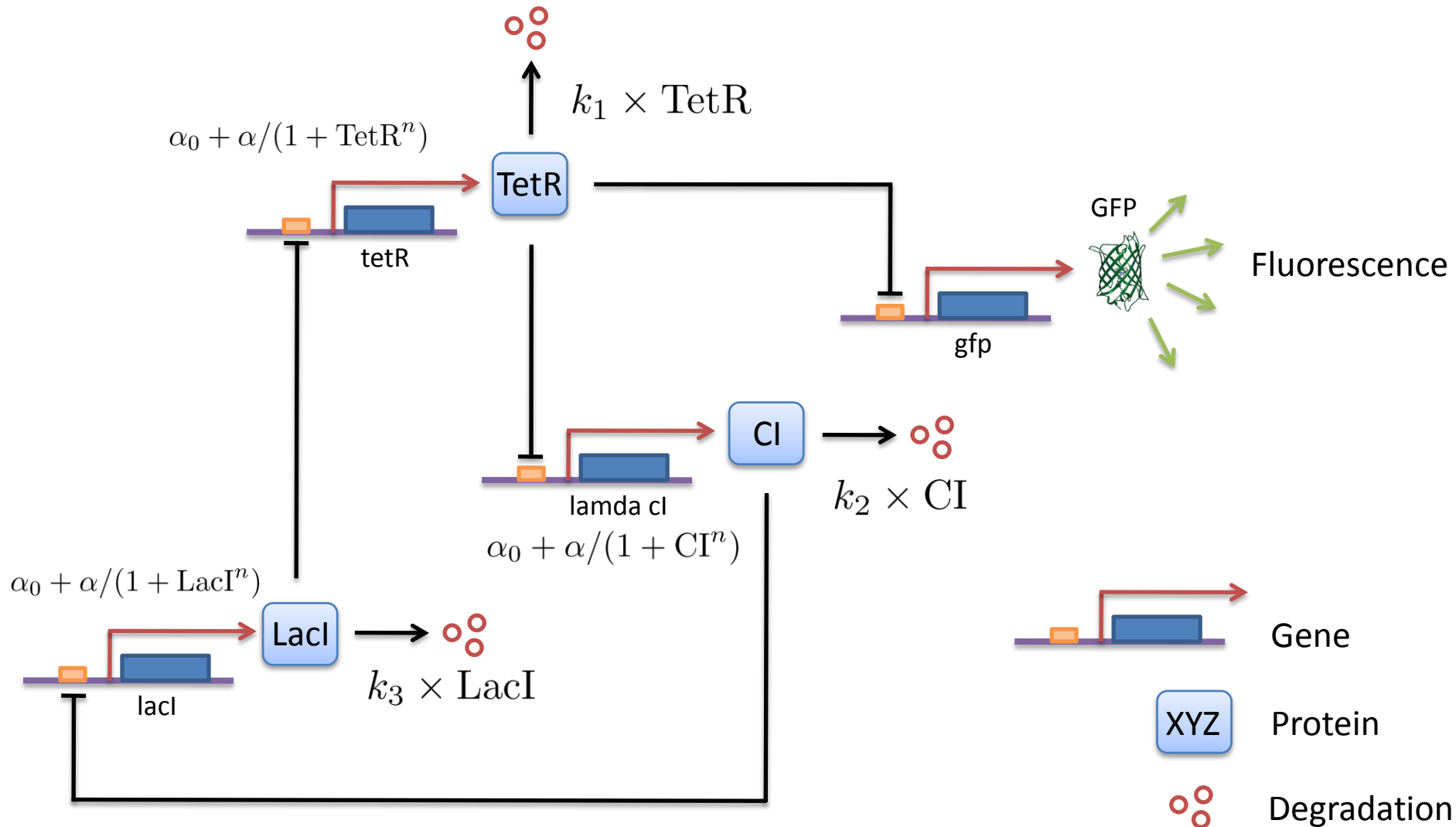
# Preview Model





# Preview Model

$$dX/dt = \text{input} - \text{output}$$

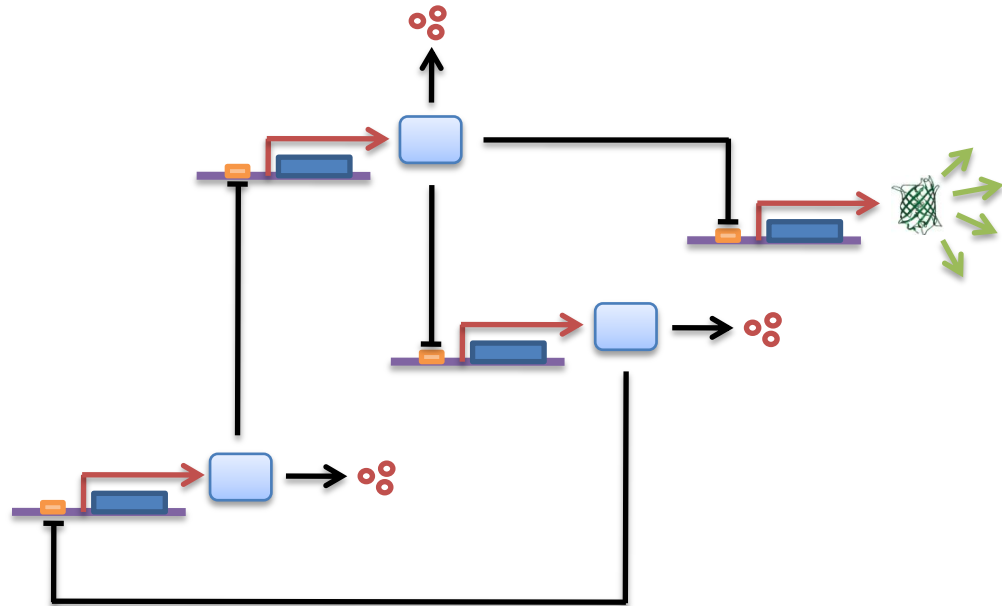


# Preview Model

$$dTetR/dt = \alpha_0 + \alpha/(1 + TetR^n) - k_1 TetR$$

$$dLacI/dt = \alpha_0 + \alpha/(1 + CI^n) - k_3 LacI$$

$$dCI/dt = \alpha_0 + \alpha/(1 + LacI^n) - k_2 CI$$



# Preview Model

$$dTetR/dt = \alpha_0 + \alpha/(1 + TetR^n) - k_1 TetR$$

$$dLacI/dt = \alpha_0 + \alpha/(1 + CI^n) - k_3 LacI$$

$$dCI/dt = \alpha_0 + \alpha/(1 + LacI^n) - k_2 CI$$

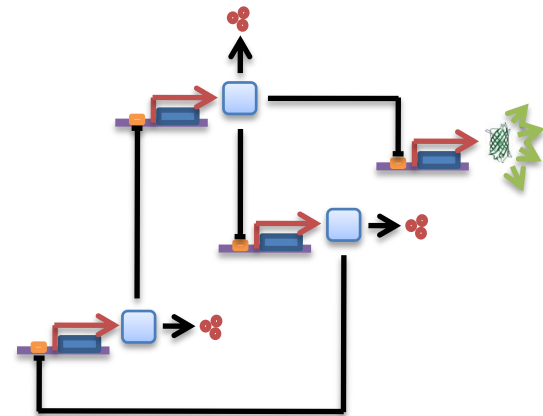
```
p = defn cell
  TetR -> $w; k1*TetR;
  LacI -> $w; k2*LacI;
  CI -> $w; k3*CI;

  $s -> TetR; a0 + a/(1+LacI^n);
  $s -> CI; a0 + a/(1+TetR^n);
  $s -> LacI; a0 + a/(1+CI^n);
end;

p.a0 = 0.1;
p.k1 = 0.127;
p.k2 = 0.116;
p.k3 = 0.08;

p.a = 1;
p.n = 8;

m = p.sim.eval (0, 450, 1000, [<p.Time>, <p.TetR>, <p.LacI>, <p.CI>]);
graph (m);
```



# Preview Model

$$dTetR/dt = \alpha_0 + \alpha/(1 + TetR^n) - k_1 TetR$$

$$dLacI/dt = \alpha_0 + \alpha/(1 + CI^n) - k_3 LacI$$

$$dCI/dt = \alpha_0 + \alpha/(1 + LacI^n) - k_2 CI$$

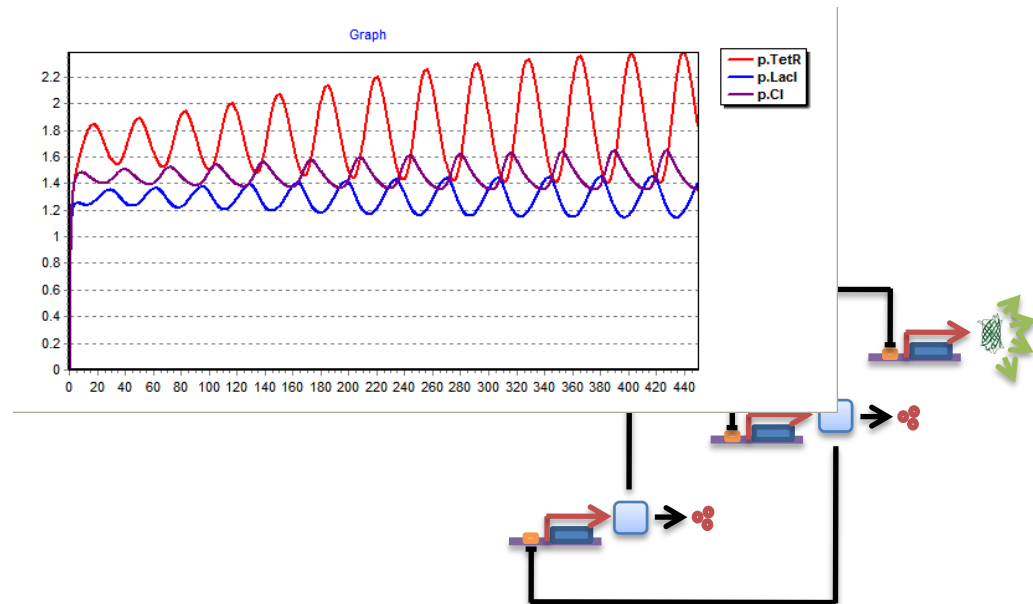
```
p = defn cell
  TetR -> $w; k1*TetR;
  LacI -> $w; k2*LacI;
  CI -> $w; k3*CI;

  $s -> TetR; a0 + a/(1+LacI^n);
  $s -> CI; a0 + a/(1+TetR^n);
  $s -> LacI; a0 + a/(1+CI^n);
end;
```

```
p.a0 = 0.1;
p.k1 = 0.127;
p.k2 = 0.116;
p.k3 = 0.08;
```

```
p.a = 1;
p.n = 8;
```

```
m = p.sim.eval (0, 450, 1000, [<p.Time>, <p.TetR>, <p.LacI>, <p.CI>]);
graph (m);
```



# Linear and non-linear Models

Linear Model:  $v = k_1 \times \text{TetR}$

Non-linear Model:  $v = \alpha_0 + \alpha / (1 + \text{TetR}^n)$

Additivity :  $f(\alpha x) = \alpha f(x)$

Homogeneity:  $f(x + y) = f(x) + f(y)$

Why is this important?

Because nonlinear models are mathematically intractable and must be numerically solved (simulated) in order to obtain a solution.

