LECTURE 3: DETERMINISTIC MODELS OF CRN

Introduction to cellular system modelling

Daniel Georgiev

Summer 2015

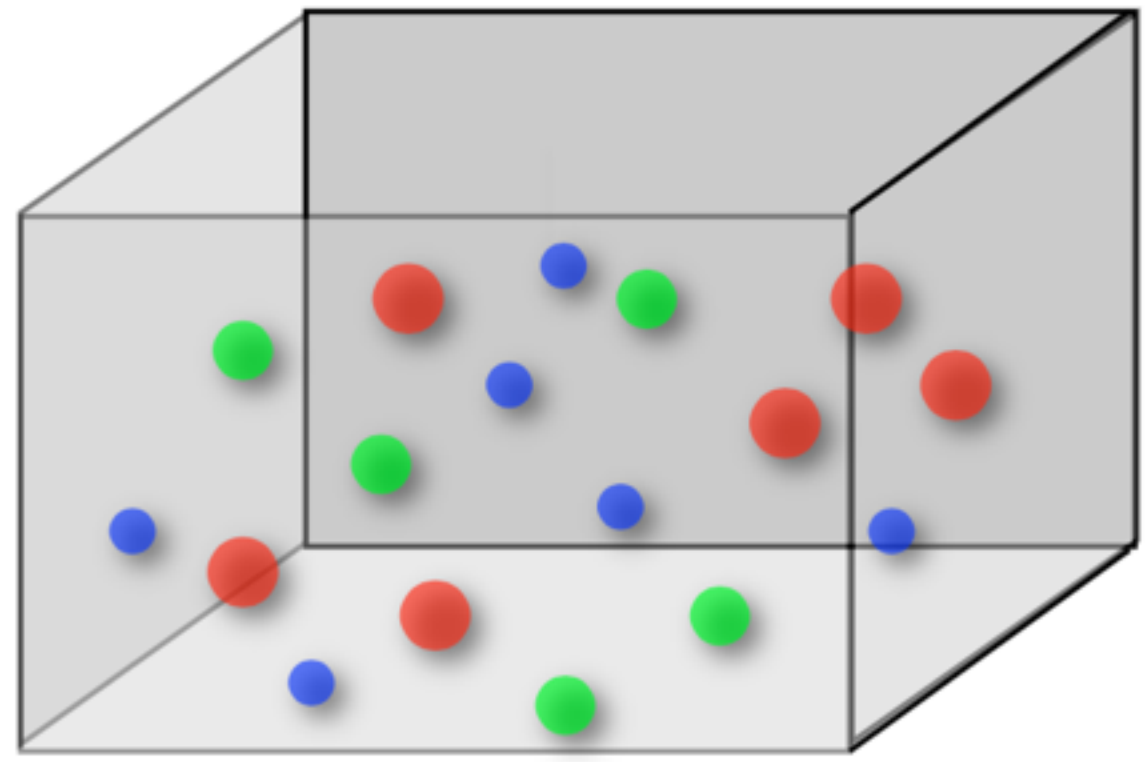
OUTLINE

- Review of chemical reaction networks
- Derivation of mass action kinetics (Brian Munsky, UC Boulder)
- Modelling gene expression
- Numbers behind gene expression
- Introduction of rule bender
- Modelling simple gene regulation
- Modelling cooperativity
- Cooperativity in rule bender
- Approximate gene regulation (Adam Arkin and Ron Weiss, MIT and UC Berkeley)
- Approximate gene regulation in rule bender

Formulation of Stochastic Chemical Kinetics

Gillespie, Physical A, 1992

Reaction volume=Ω



Key Assumptions

(**Well-Mixed**) The probability of finding any molecule in a region $d\Omega$ is given by $\frac{d\Omega}{\Omega}$.

(**Thermal Equilibrium**) The molecules move due to the thermal energy. The reaction volume is at a constant temperature T. The velocity of a molecule is determined according to a Boltzman distribution:

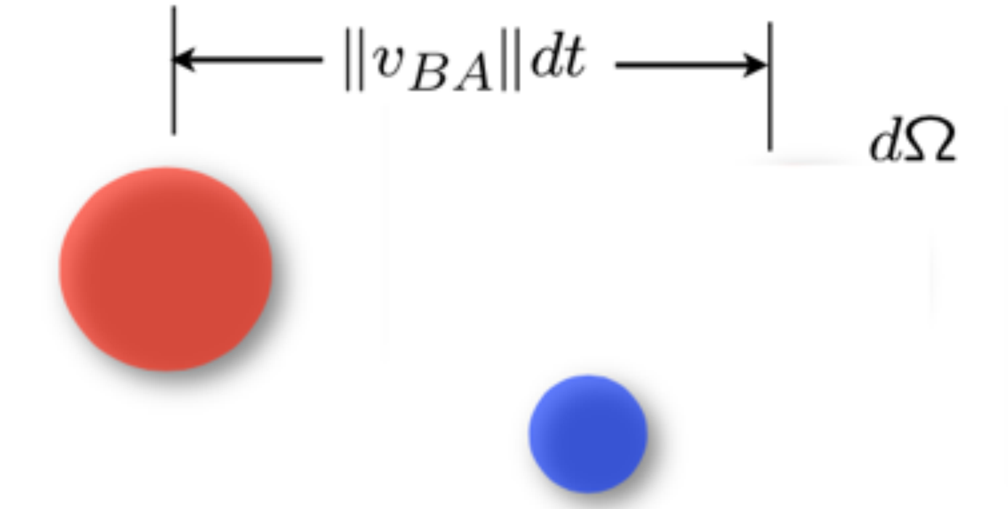
$$f_{v_x}(v) = f_{v_y}(v) = f_{v_z}(v) = \sqrt{\frac{m}{2\pi k_B T}}\; e^{-\frac{m}{2k_B T}v^2}$$

Probability of Collision: Two Specific Molecules

Given:

- Two spheres A and B with velocities v_A and v_B, and radii r_A and r_B.
- The probability that the center of either sphere lies in a volume $d\Omega$ is given by $\frac{d\Omega}{\Omega}$.

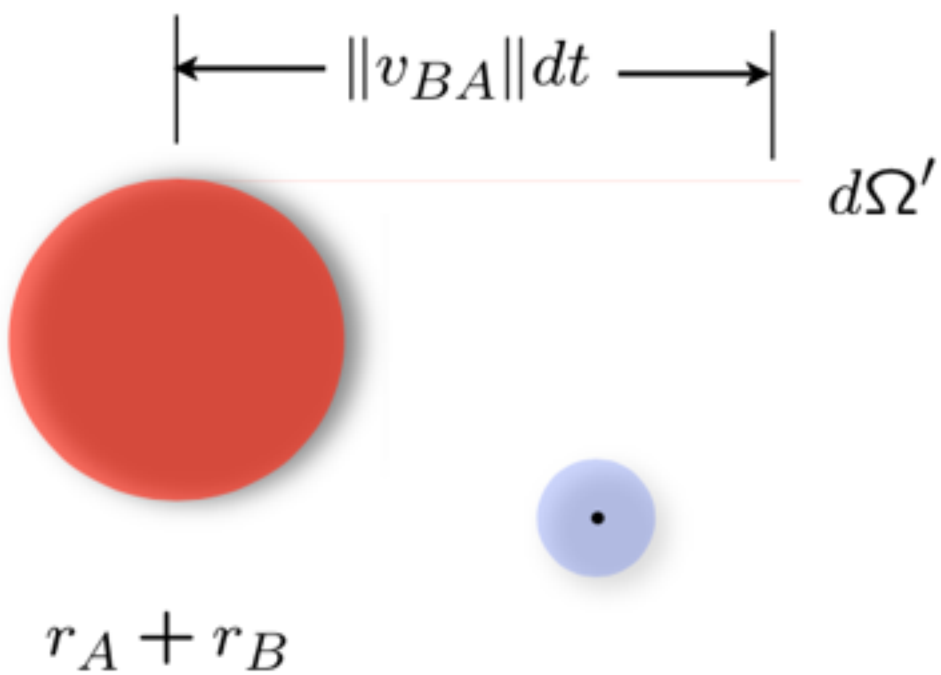
What is the probability that A and B will collide in the time $[t, t + dt]$?



In the time $[t, t + dt]$ molecule A sweeps a volume of $d\Omega = \pi r_B^2 \ \|v_{BA}\| \ dt$

Collision takes place if *any part of* A lies in the region $d\Omega$.

Equivalently . . .



During $[t, t + dt]$ a molecule with radius $r_A + r_B$ sweeps a volume of $d\Omega' = \pi(r_A + r_B)^2 \ \|v_{BA}\| \ dt$

Collision takes place if *the center of* A lies in the region $d\Omega'$.

The probability of A and B colliding during $[t, t + dt]$ is

$$\frac{1}{\Omega}\pi(r_A + r_B)^2\|v_{BA}\| \ dt$$

Note:

- The probability of A and B colliding was computed for a *given a relative velocity of v_{BA}* (conditional probability)
- The relative velocity is a *random variable*, and we must average over all velocities.

If we denote by $f_{BA}(\cdot)$ the probability density of the random variable V_{BA} we have

$$
\begin{aligned}
\text{Collision Probability in [t,t+dt]} \\
&= \int_{\mathbb{R}^3} P(\text{collision in } [t, t+dt] \mid V_{BA} = v)\ f_{BA}(v)dv \\
&= \int_{\mathbb{R}^3} \frac{1}{\Omega}\pi(r_A + r_B)^2 \|v\| dt\ f_{BA}(v)dv \\
&= \frac{1}{\Omega}\pi(r_A + r_B)^2 dt \int_{\mathbb{R}^3} \|v\| f_{BA}(v)dv
\end{aligned}
$$

mean relative speed

The probability density function of $f_{BA}(\cdot)$ can be easily computed from the Boltzman distribution of the velocity and the independence of V_x, V_y, and V_z.

$$f_{BA}(v) = \left(\frac{\hat{m}}{2\pi k_B T}\right)^{3/2} e^{-\frac{\hat{m}}{2k_B T}\|v\|^2}, \qquad \text{where } \hat{m} = \frac{m_A + m_B}{2}$$

Hence

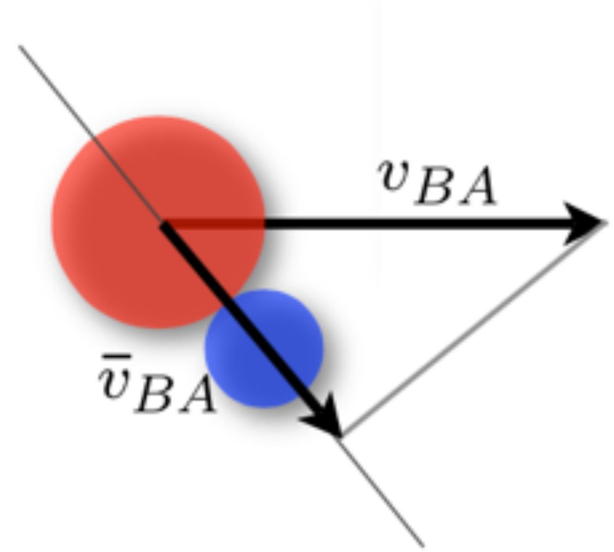
$$\begin{aligned} \text{Mean relative speed} &= \int_{\mathbb{R}^3} \|v\| f_{BA}(v) dv \\ &= \int_{\mathbb{R}^3} \|v\| \left(\frac{\hat{m}}{2\pi k_B T}\right)^{3/2} e^{-\frac{\hat{m}}{2k_B T}\|v\|^2} dv \\ &= \sqrt{\frac{8k_B T}{\pi \hat{m}}} \end{aligned}$$

Probability of A-B collision within [t,t+dt]:

$$\frac{1}{\Omega}\pi(r_A + r_B)^2 dt \sqrt{\frac{8k_B T}{\pi \hat{m}}}$$

Not all collisions lead to reactions. One can factor in the "reaction energy".

Assumption: An $A - B$ collision leads to a reaction only if the kinetic energy associated with the component of the velocity along the line of contact is greater than a critical energy ϵ.



Reaction if $\frac{1}{2}\hat{m}\bar{v}_{BA}^2 > \epsilon$

It can be shown that:

$$\text{Probability (A-B reaction | A-B collision)} = e^{-\frac{\epsilon}{k_B T}}$$

Probability of A-B reaction within [t,t+dt]:

$$\frac{1}{\Omega}\pi(r_A + r_B)^2 \sqrt{\frac{8k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} dt$$

Given N species: $\mathcal{S}_1, \ldots, \mathcal{S}_N$ with populations $x_1, \ldots, x_N$ at time t.

Consider the bimolecular reaction channel (with distinct species):

$$R: \ \mathcal{S}_i + \mathcal{S}_j \rightarrow \text{products}$$

The number of distinct $\mathcal{S}_i - \mathcal{S}_j$ pairs that can react is: $x_i \cdot x_j$. Therefore,

Probability of an R reaction within [t,t+dt]:

$$x_i x_j \frac{1}{\Omega} \pi (r_i + r_j)^2 \sqrt{\frac{8 k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} dt = w(x)$$

$w(\cdot)$ is called the **propensity function**.

Consider the bimolecular reaction channel (with same species):

$$R': \ \mathcal{S}_i + \mathcal{S}_i \rightarrow \text{products}$$

The number of distinct $\mathcal{S}_i - \mathcal{S}_i$ pairs that can react is: $\frac{x_i(x_i-1)}{2}$. Therefore,

Probability of an R' reaction within [t,t+dt]:

$$\frac{x_i(x_i-1)}{2} \frac{1}{\Omega} \pi r_i^2 \sqrt{\frac{8 k_B T}{\pi \hat{m}}} e^{-\frac{\epsilon}{k_B T}} \ dt = w(x) \ dt$$

Reactions and Propensity Functions

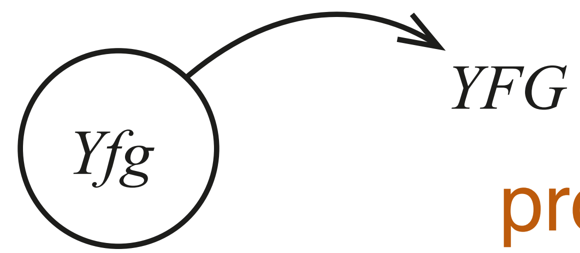
Reaction	Propensity $w(x)$	Rate c
$\phi \xrightarrow{c}$ Products	c	$k\Omega$
$\mathcal{S}_i \xrightarrow{c}$ Products	$c \cdot x_i$	k
$\mathcal{S}_i + \mathcal{S}_j \xrightarrow{c}$ Products	$c \cdot x_i x_j$	$\frac{1}{\Omega}\pi(r_i + r_j)^2 \sqrt{\frac{8k_BT}{\pi\hat{m}}}e^{-\frac{\epsilon}{k_BT}}$
$\mathcal{S}_i + \mathcal{S}_i \xrightarrow{c}$ Products	$c \cdot \frac{x_i(x_i - 1)}{2}$	$\frac{4}{\Omega}\pi r_i^2 \sqrt{\frac{8k_BT}{\pi\hat{m}}}e^{-\frac{\epsilon}{k_BT}}$

For a monomolecular reaction: c is numerically equal to the reaction rate constant k of conventional deterministic chemical kinetics

For a bimolecular reaction: c is numerically equal to k/Ω, where k is the reaction rate constant of conventional deterministic chemical kinetics

GENE EXPRESSION - MODELLING

constitutive GENE



product

SOURCE

reaction rate

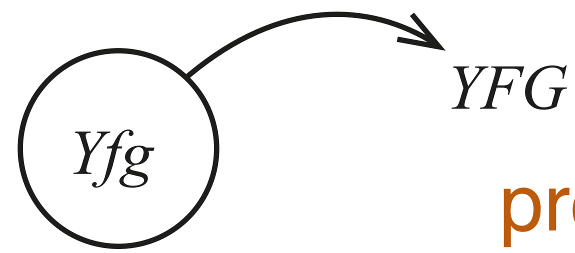
$$\emptyset \xrightarrow{k} YFG$$

infinite source/sink

molecular species

GENE EXPRESSION - MODELLING

constitutive GENE



product

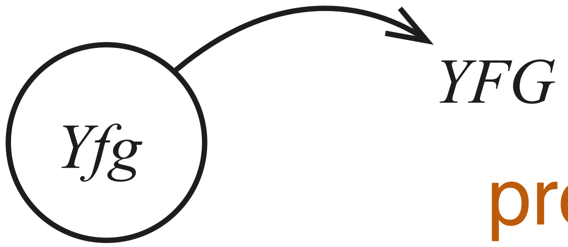
SOURCE

$$\emptyset \xrightarrow{k} YFG$$

$$\frac{d\,\mathrm{YFG}}{dt} = k$$

GENE EXPRESSION - MODELLING

constitutive GENE

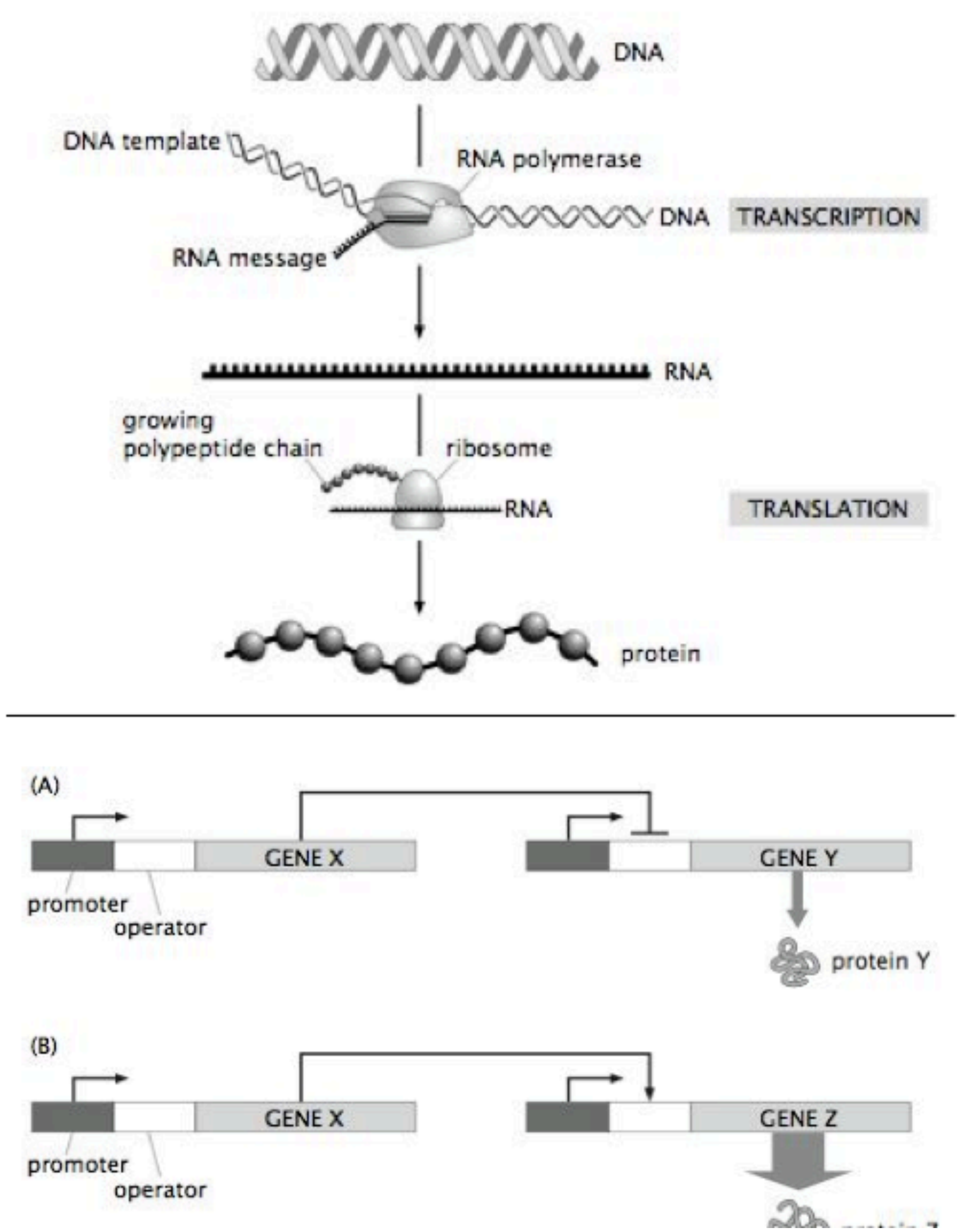


product

SOURCE

$$\emptyset \underset{k^-}{\overset{k^+}{\rightleftharpoons}} \mathrm{YFG} \qquad \frac{d\,\mathrm{YFG}}{dt} = k^+ - k^- \,\mathrm{YFG}$$

GENE EXPRESSION - NUMBERS



Primary timescales:

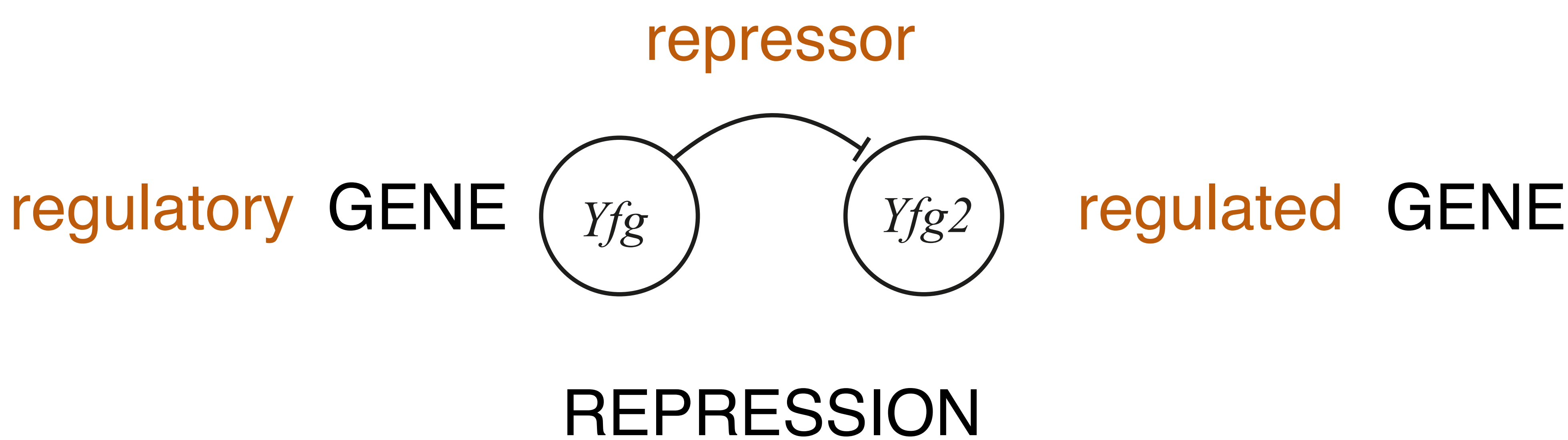
- DNA production: 250-1000 bp/sec
- mRNA production: 10-30 bp/sec
- Protein production: 10-30 aa/sec

DNA, protein from KPT07, mRNA production from Vogel & Jensen

Other important rates

- mRNA half life: ~100 sec
- Protein half life: ~5 x 10^4 sec
- Protein diffusion (along DNA): up to 10^4 bp/sec

GENE REPRESSION - MODELLING



$$\emptyset \xrightarrow{k_1} YFG,\ Yfg2 \xrightarrow{k_2} Yfg2 + YFG2,$$

$$n_1 YFG^* + Yfg2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} Yfg2^*$$

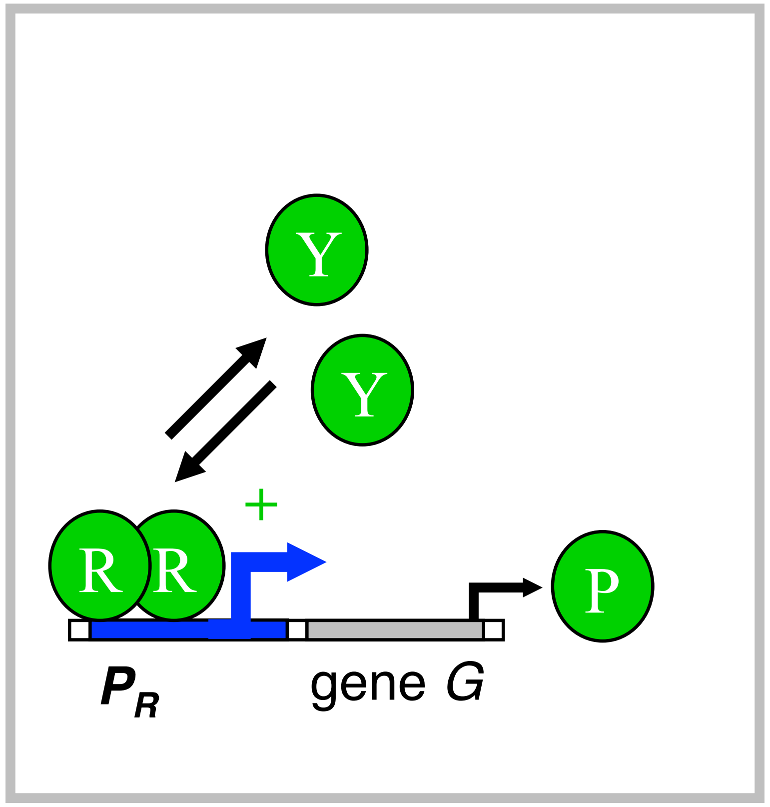
GENE REPRESSION - MODELLING

WRITE DOWN THE MASS ACTION ODE MODEL

$$\emptyset \xrightarrow{k_1} YFG, \; Yfg2 \xrightarrow{k_2} Yfg2 + YFG2,$$

$$n_1 YFG^* + Yfg2 \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} Yfg2^*$$

GENE REPRESSION WITH COOPERATIVITY - MODELLING



$$G^* \xrightarrow{k_1} G^* + P, \; G^{**} \xrightarrow{k_2} G^{**} + P,$$

$$R + G \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} G^*,$$

$$R + G^* \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} G^{**}.$$

GENE REPRESSION WITH COOPERATIVITY - SIMPLIFICATION

$$G^{**} \approx \frac{\alpha}{1 + \left(\frac{R}{K_d}\right)^2}$$

$$G^* \xrightarrow{k_1} G^* + P, \; G^{**} \xrightarrow{k_2} G^{**} + P,$$

$$R + G \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} G^*,$$

$$R + G^* \underset{k_3^-}{\overset{k_3^+}{\rightleftharpoons}} G^{**}.$$

OUTLINE