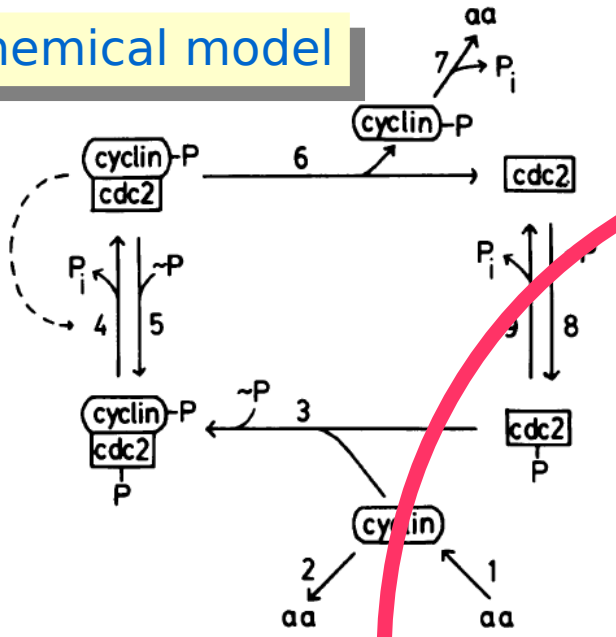
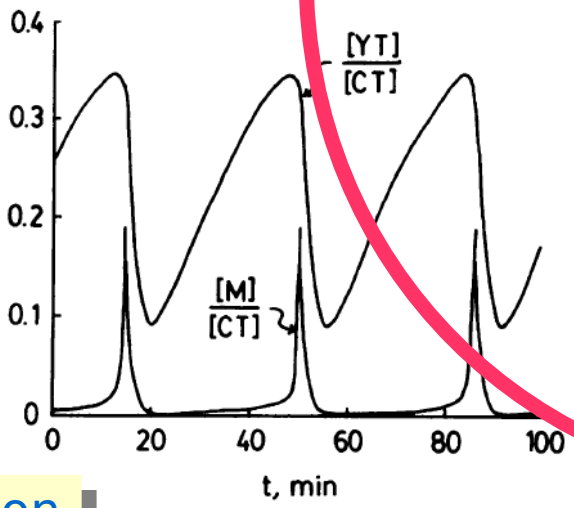
# Modeling chemical kinetics



# The Computational Systems Biology loop

biochemical model




simulation

mathematical model

$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
$$d[CP]/dt = -k_3[CP][Y] + k_8[\sim P][C2] - k_9[CP]$$
$$d[pM]/dt = k_3[CP][Y] - [pM]F([M]) + k_5[\sim P][M]$$
$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
$$d[YP]/dt = k_6[M] - k_7[YP]$$

| Parameter | Value | Notes |
|---|---|---|
| $k_1[aa]/[CT]$ | 0.015 $min^{-1}$ | * |
| $k_2$ | 0 | † |
| $k_3[CT]$ | 200 $min^{-1}$ | * |
| $k_4$ | 10–1000 $min^{-1}$ (adjustable) | |
| $k_4'$ | 0.018 $min^{-1}$ | |
| $k_5[\sim P]$ | 0 | ‡ |
| $k_6$ | 0.1–10 $min^{-1}$ (adjustable) | |
| $k_7$ | 0.6 $min^{-1}$ | † |
| $k_8[\sim P]$ | $>>k_9$ | § |
| $k_9$ | $>>k_6$ | § |

computational model

Tyson et al (1991) PNAS 88(1):7328-32

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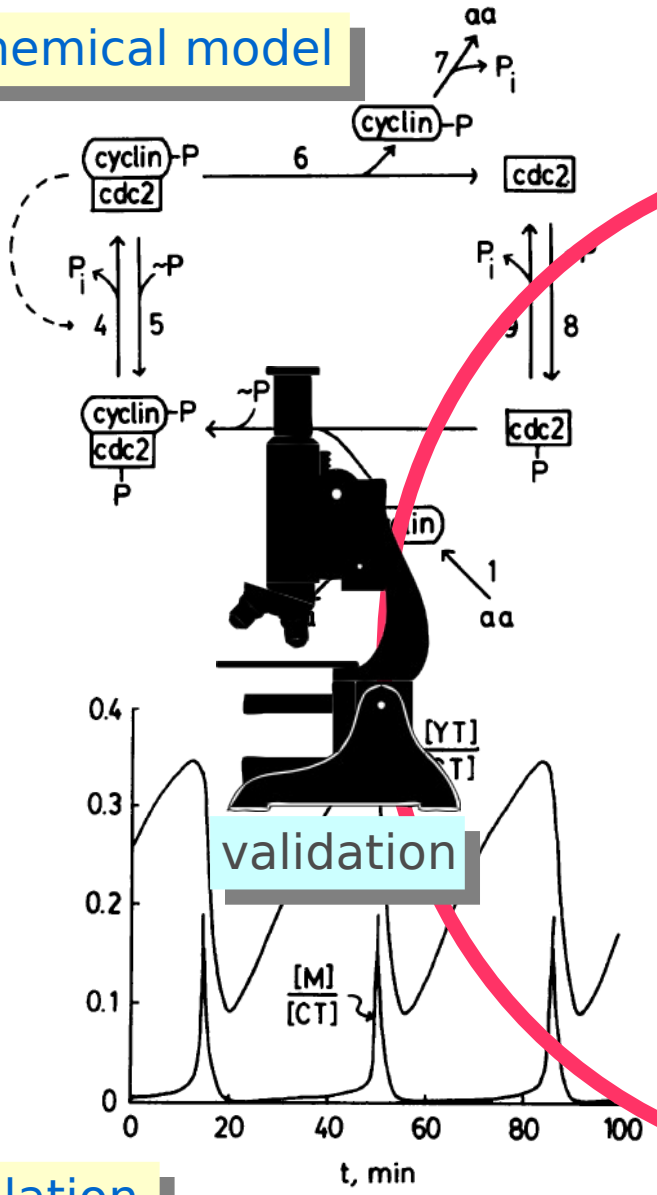
biochemical model




validation

simulation

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$$d[C2]/dt = k_6[M] - k_8[\sim P][C2] + k_9[CP]$$
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$$d[M]/dt = [pM]F([M]) - k_5[\sim P][M] - k_6[M]$$
$$d[Y]/dt = k_1[aa] - k_2[Y] - k_3[CP][Y]$$
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parameterisation

computational model

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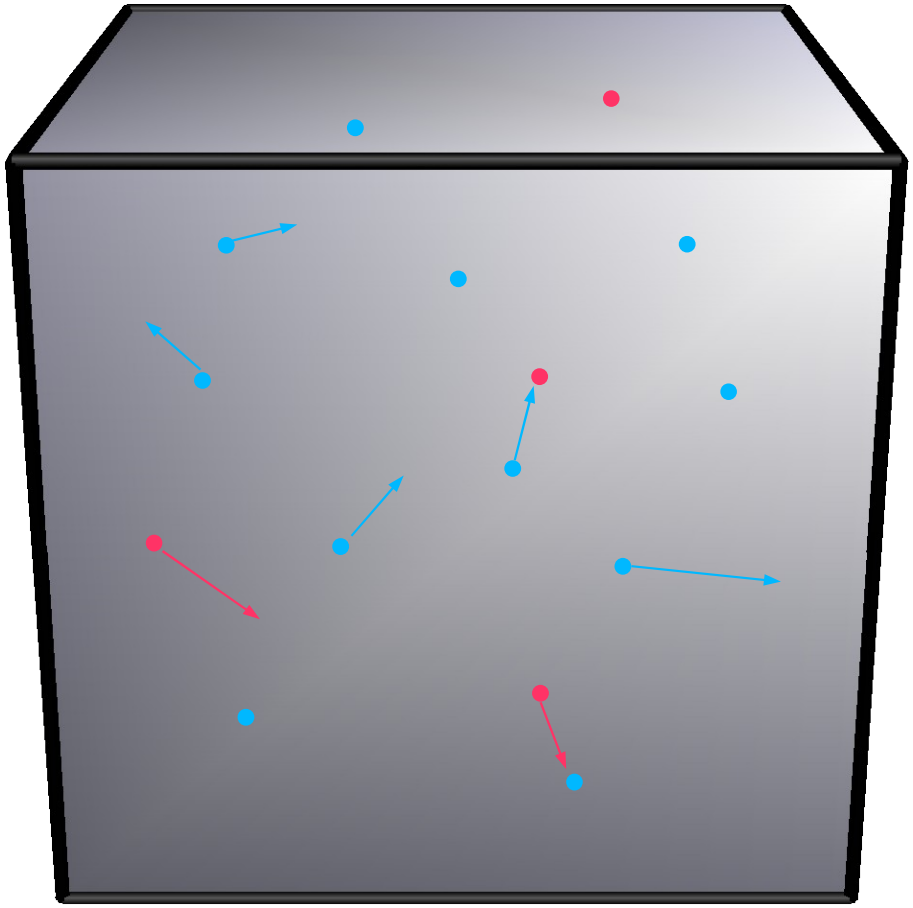
# Statistical physics and chemical reaction



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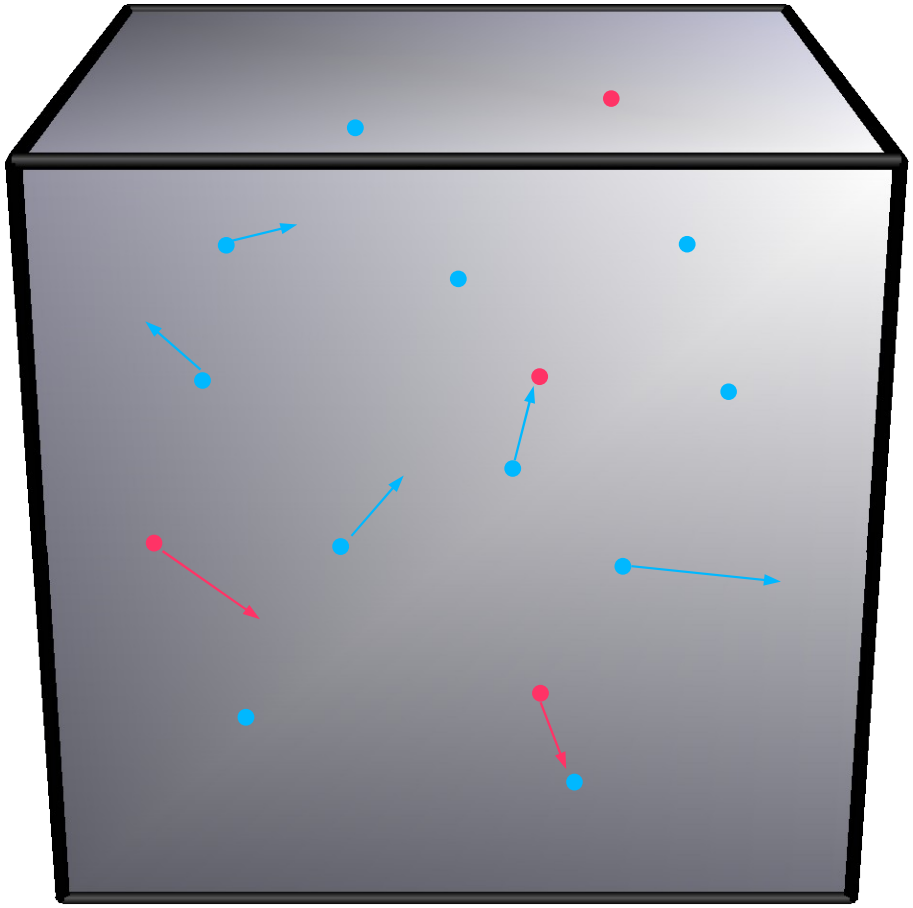

$$P(\bullet) \propto \frac{n(\bullet)}{V} = [\bullet]$$

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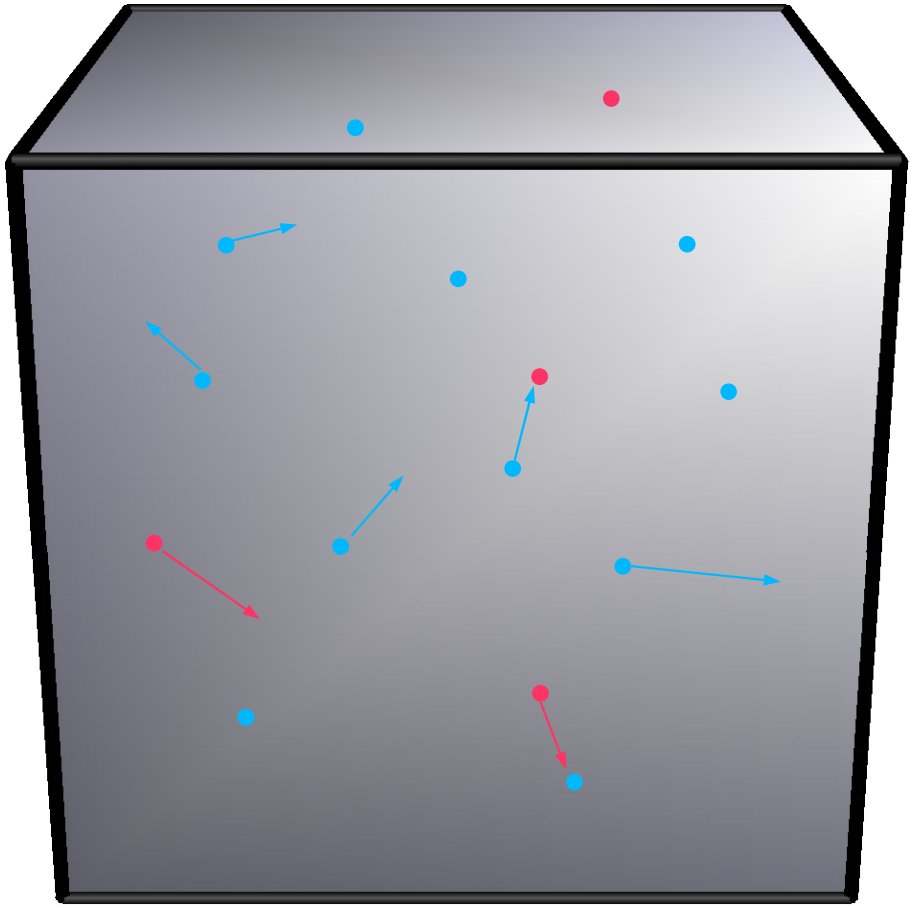

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$$P(\text{reaction } \bullet + \bullet) = P(\bullet) \times P(\bullet) \times P(\bullet \text{ reacts with } \bullet)$$

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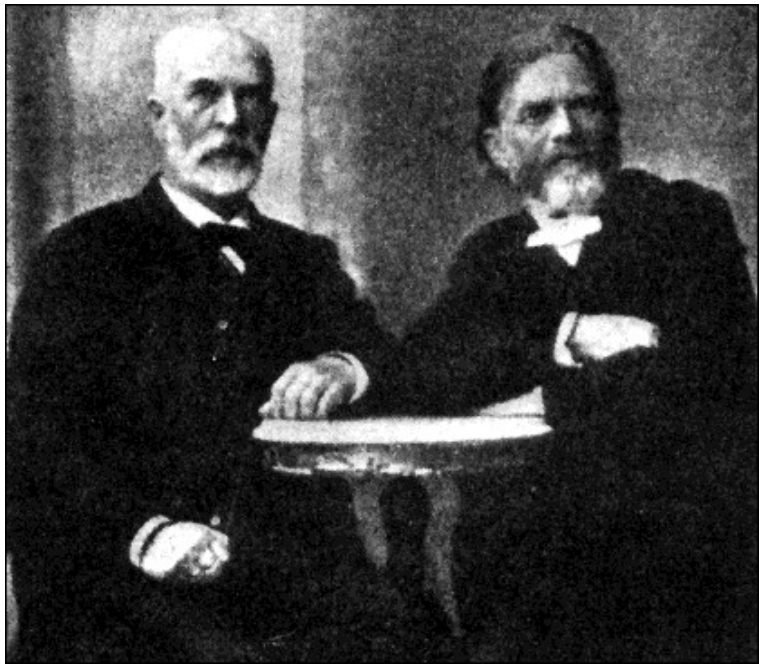
# Law of Mass Action

Waage and Guldberg (1864)



activity

rate-constant

stoichiometry

$$v = k \cdot \prod_i a_i^{n_i}$$

velocity

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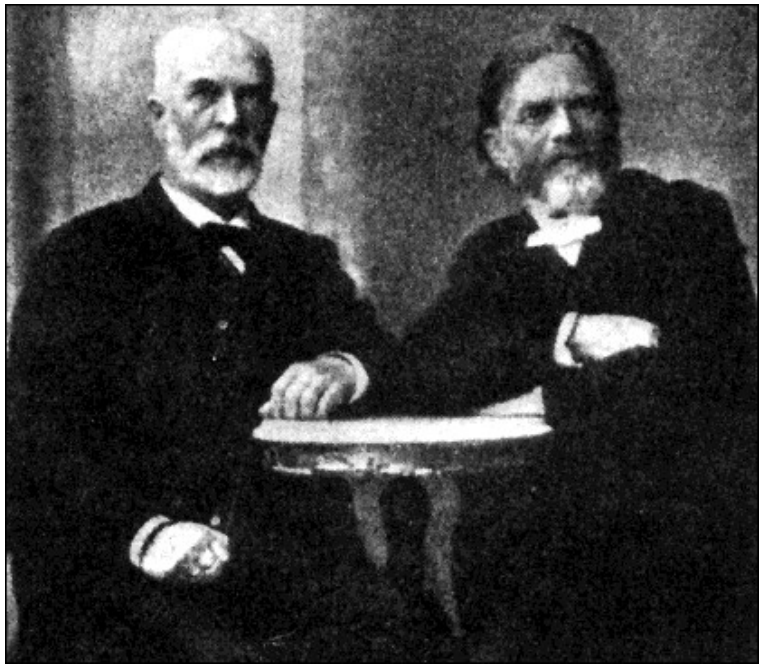

activity

rate-constant

stoichiometry

$$v = k \cdot \prod_i a_i^{n_i}$$

velocity

$$v = k \cdot \prod_i P_i^{n_i}$$ gas

velocity in reaction events per unit of time

$$v = k \cdot \prod_i [X_i]^{n_i}$$ solution

# Evolution of a reactant

- Velocity multiplied by stoichiometry
- negative if consumption, positive if production
- Example of a unimolecular reaction $x \xrightarrow{k} y$

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$$\frac{d[y]}{dt} = +1 \cdot v = +1 \cdot k \cdot [x]$$

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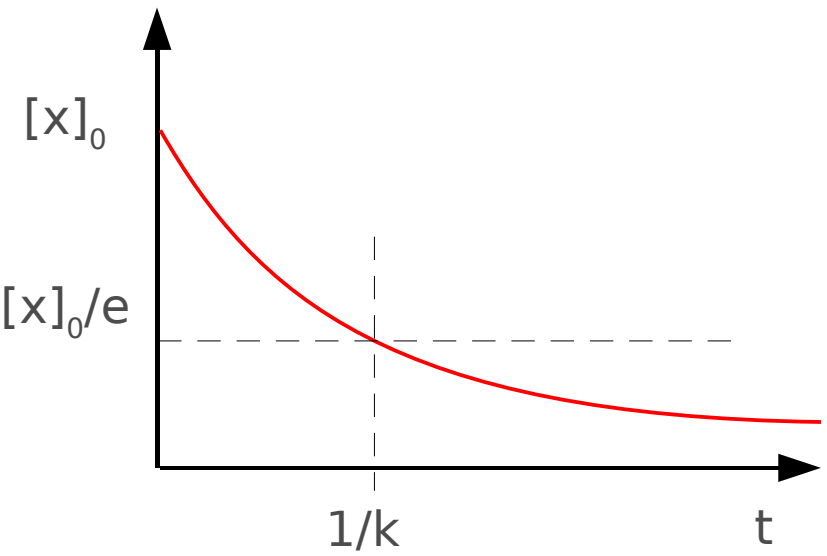
$$x(t) = [x]_0 \cdot e^{-kt}$$



# Reversible reaction

$2x \underset{k2}{\overset{k1}{\rightleftharpoons}} y$ is equivalent to

$$2x \rightarrow y; v1 = k1 \cdot [x]^2$$

$$y \rightarrow 2x; v2 = k2 \cdot [y]$$

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$$\frac{d[x]}{dt} = -2 \cdot v1 + 2 \cdot v2 = -2 \cdot k1 \cdot [x]^2 + 2 \cdot k2 \cdot [y]$$

$$\frac{d[y]}{dt} = +1 \cdot v1 - 1 \cdot v2 = +1 \cdot k1 \cdot [x]^2 - 1 \cdot k2 \cdot [y]$$

# Example of an enzymatic reaction

$$E + S \underset{k_2}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_3} E + P$$

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d[E]/dt &= -k_1[E][S] + k_2[ES] + k_3[ES] \\
d[ES]/dt &= +k_1[E][S] - k_2[ES] - k_3[ES]
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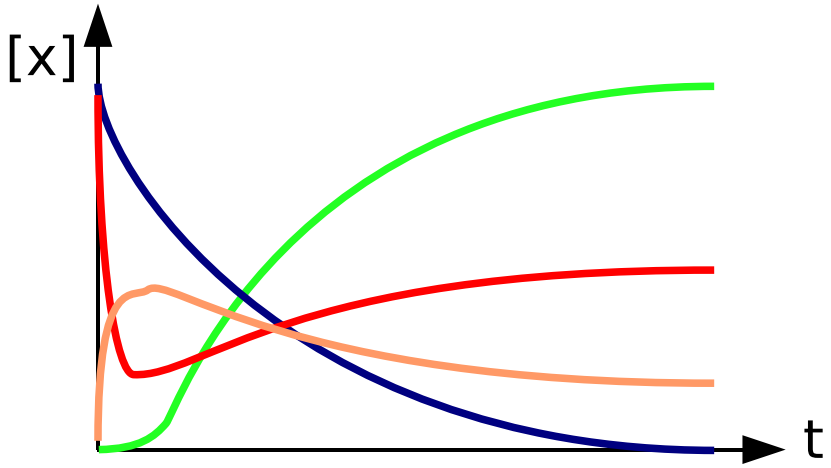



Not feasible in general

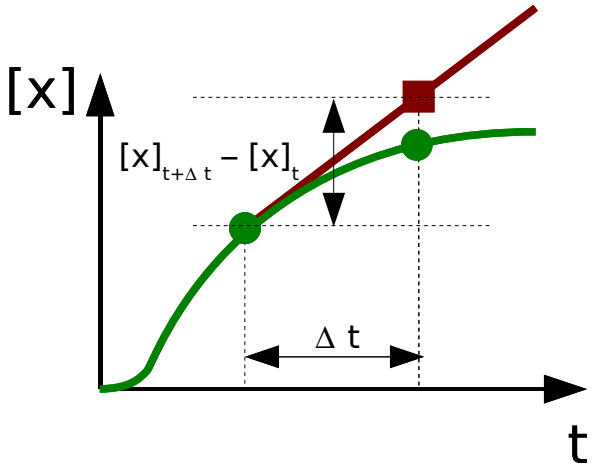
→ Numerical integration

# Numerical integration

Euler method:

$$d[x]/dt \approx ([x]_{t+\Delta t} - [x]_t) / \Delta t$$

$$[x]_{t+\Delta t} \approx [x]_t + d[x]/dt \cdot \Delta t$$



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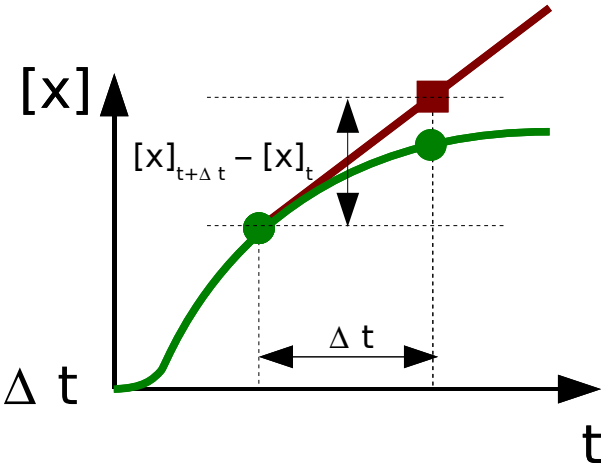


$$[P]_{t+\Delta t} = [P]_t + k_3[ES]_t \cdot \Delta t$$

$$[E]_{t+\Delta t} = [E]_t + ((k_2 + k_3)[ES]_t - k_1[E]_t[S]_t) \cdot \Delta t$$

$$[S]_{t+\Delta t} = [S]_t + (k_2[ES]_t - k_1[E]_t[S]_t) \cdot \Delta t$$

$$[ES]_{t+\Delta t} = [S]_t + (k_1[E]_t[S]_t - (k_2+k_3)[ES]_t) \cdot \Delta t$$

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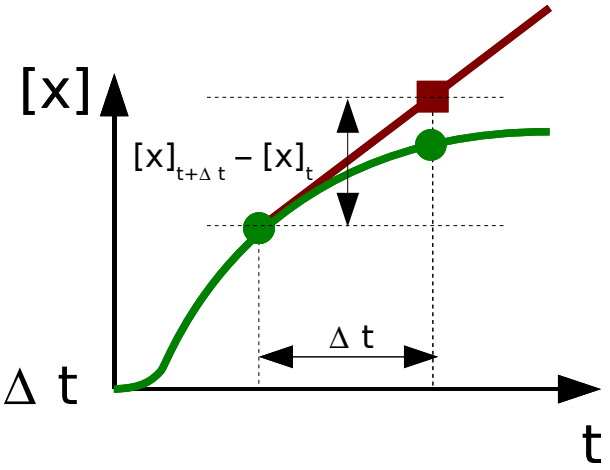


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$$[ES]_{t+\Delta t} = [S]_t + (k_1[E]_t[S]_t - (k_2+k_3)[ES]_t) \cdot \Delta t$$

$4^{th}$ order Runge-Kutta:

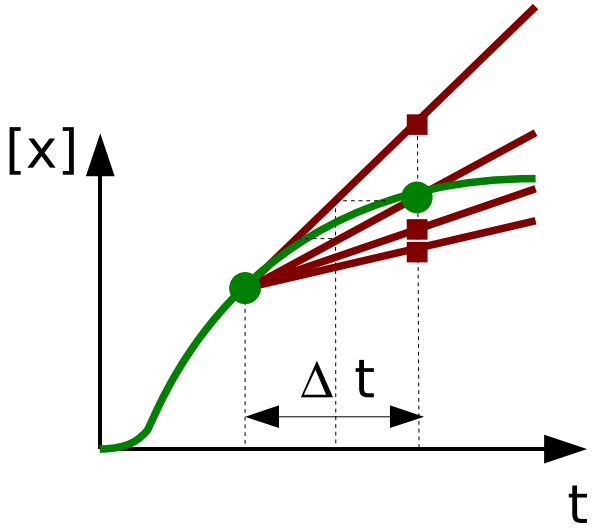
$$[x]_{t+\Delta t} = [x]_t + (F_1+2F_2+2F_3+F_4)/6 \cdot \Delta t$$

with $F_1 = d[x]/dt = f([x], t)$

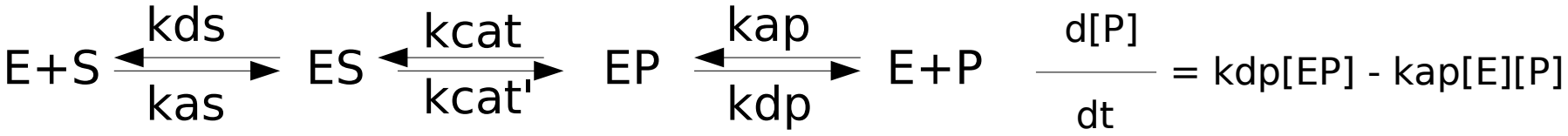
$F_2 = f([x]_t + \Delta t/2 \cdot F_1, t + \Delta t/2)$

$F_3 = f([x]_t + \Delta t/2 \cdot F_2, t + \Delta t/2)$

$F_4 = f([x]_t + \Delta t \cdot F_3, t + \Delta t)$



# Choose the right formalism



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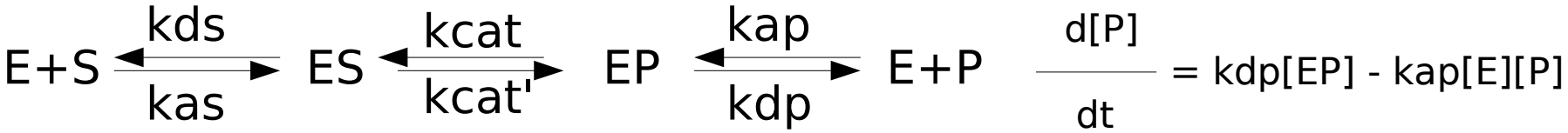


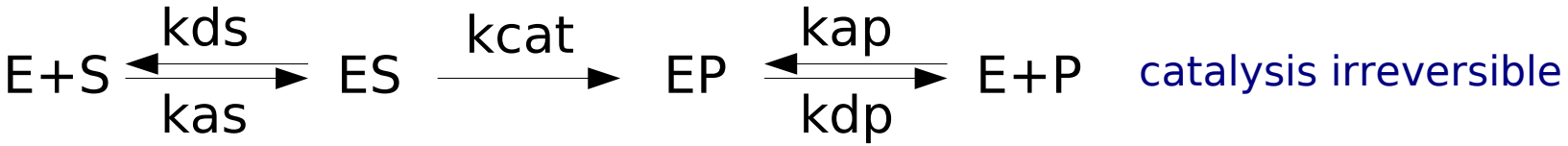

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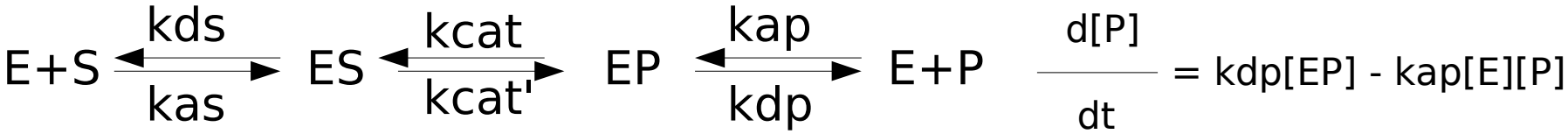


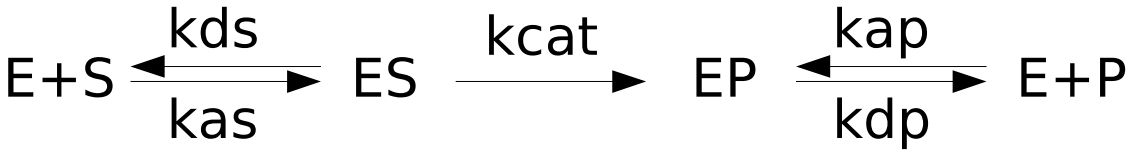


catalysis irreversible


product is consumed
before rebinding

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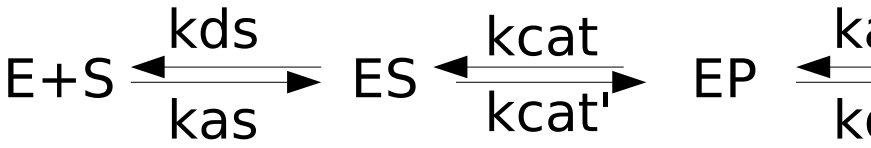
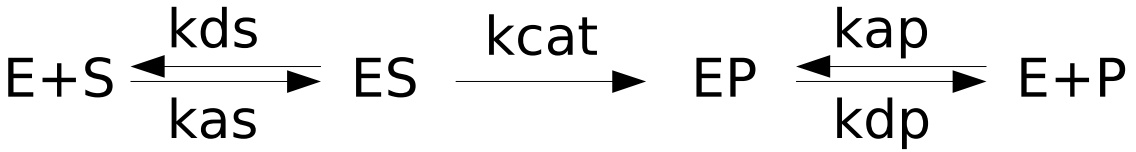



$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$

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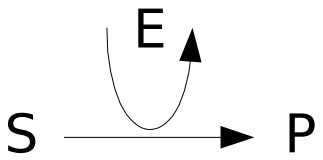



steady-state

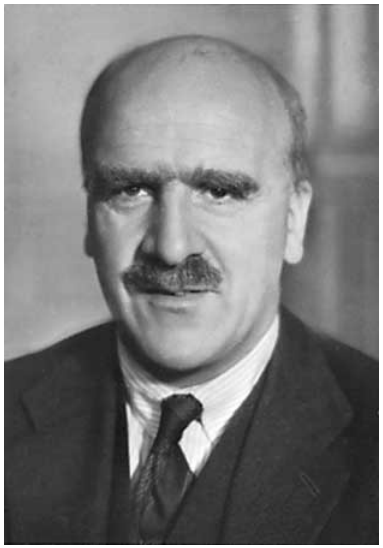
$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

# Enzyme kinetics

Victor Henri (1903) Lois Générales de l'Action des Diastases. Paris, Hermann.

Leonor Michaelis, Maud Menten (1913). Die Kinetik der Invertinwirkung, Biochem. Z. 49:333-369

George Edward Briggs and John Burdon Sanderson Haldane (1925) A note on the kinetics of enzyme action, Biochem. J., 19: 338-339



# Briggs-Haldane on Henri-Michaelis-Menten

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \overset{k_2}{\rightarrow} E + P$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$K_m = \frac{k_{-1} + k_2}{k_1}$$

$$[ES] = \frac{[E][S]}{K_m}$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$[E] = [E_0] - [ES]$$

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

$$[ES] = [E_0]\frac{1}{1 + \frac{K_m}{[S]}}$$

$$\frac{d[P]}{dt} = k_2[E_0]\frac{[S]}{K_m + [S]} = V_{max}\frac{[S]}{K_m + [S]}$$

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$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

$$\frac{d[P]}{dt} = k_2[ES]$$

$$\frac{d[ES]}{dt} = k_1[E][S] - k_{-1}[ES] - k_2[ES] = 0$$

$$[E]=[E_0]-[ES]$$

steady-state!!!

$$[ES]\frac{K_m}{[S]} = [E_0] - [ES]$$

$$[ES] = \frac{k_1[E][S]}{k_{-1} + k_2}$$

$$[ES](1 + \frac{K_m}{[S]}) = [E_0]$$

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$$[ES] = \frac{[E][S]}{K_m}$$

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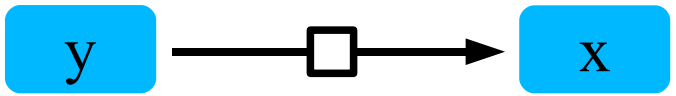
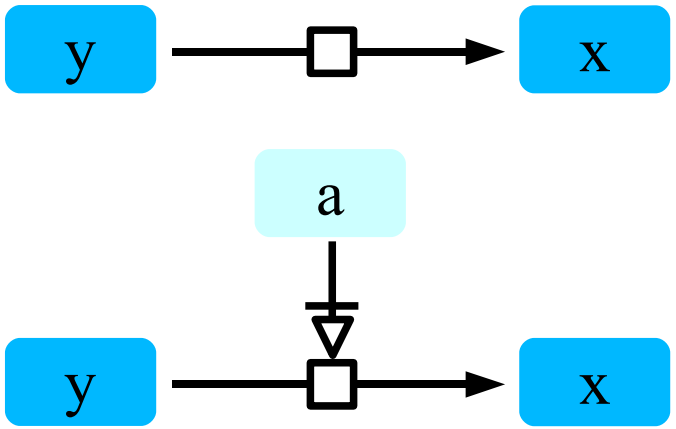
# Generalisation of modulation



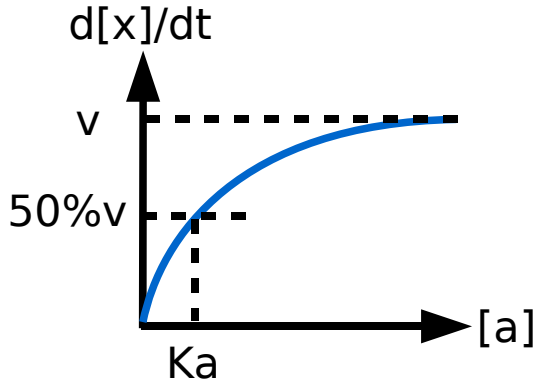

$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

# Generalisation: activators




$$\frac{d[x]}{dt} = v(= k \cdot [y])$$

$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



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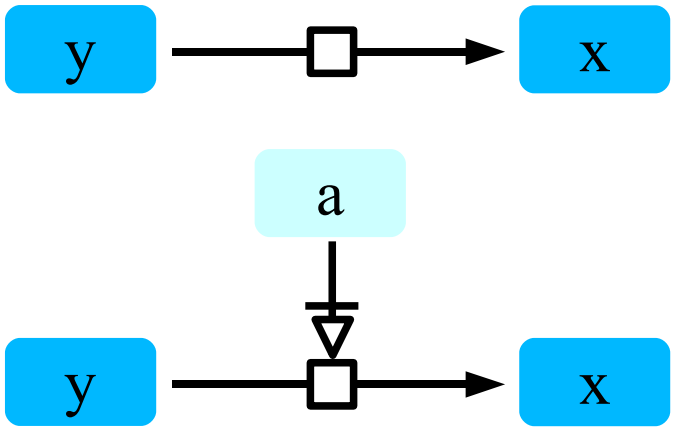


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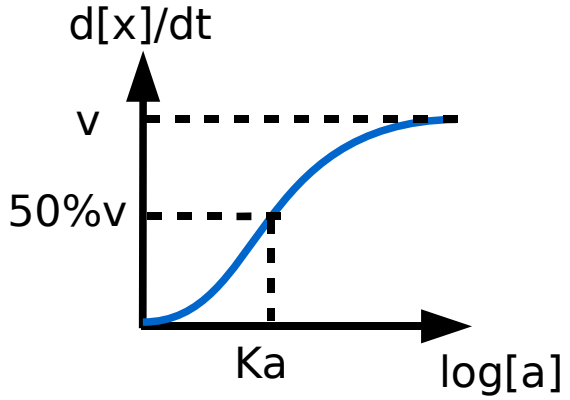
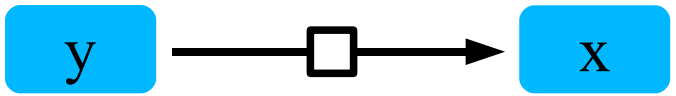
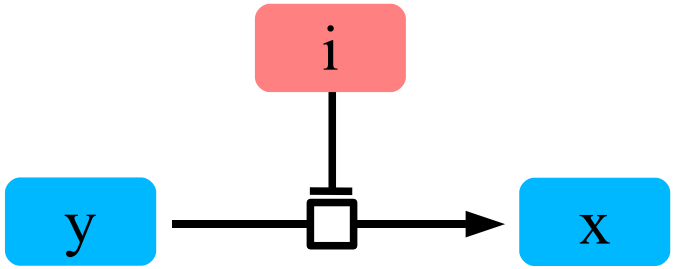


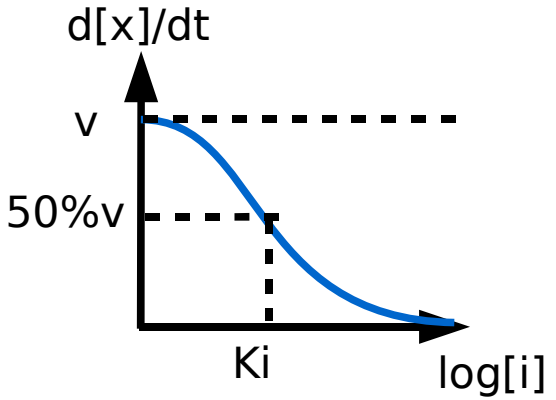
# Generalisation: inhibitors



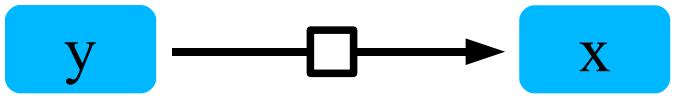

$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



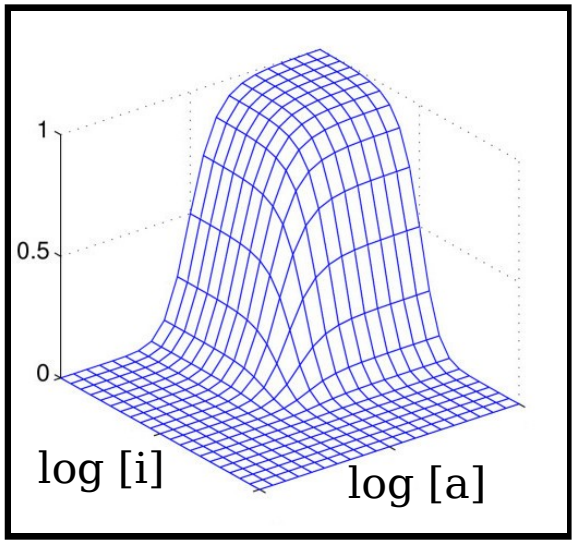

$$\frac{d[x]}{dt} = v \cdot \frac{Ki}{Ki + [i]}$$

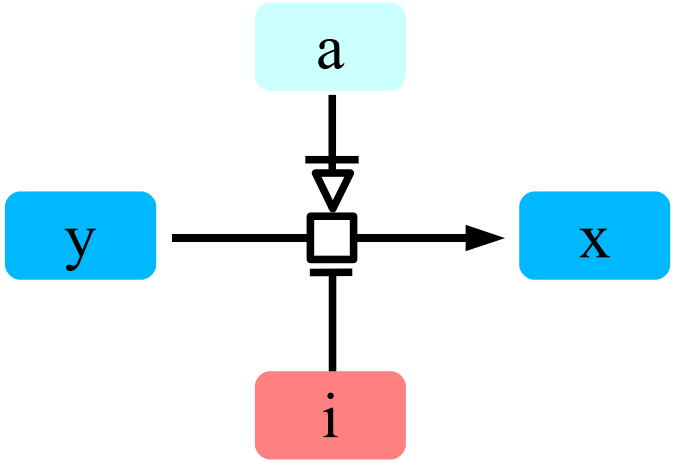


# Generalisation: activators and inhibitors



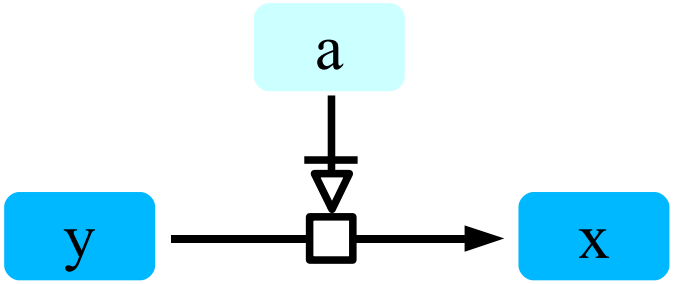

$$\frac{d[x]}{dt} = v(= k \cdot [y])$$



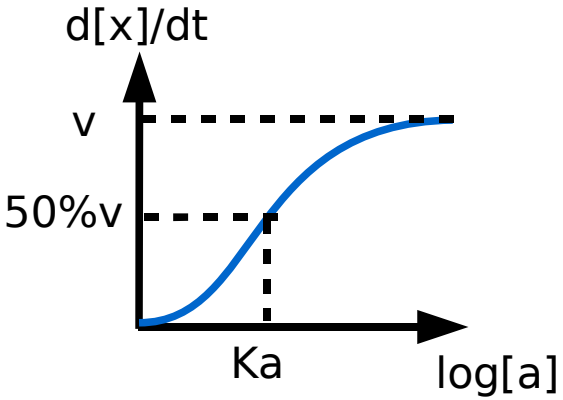




$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]} \cdot \frac{Ki}{Ki + [i]}$$

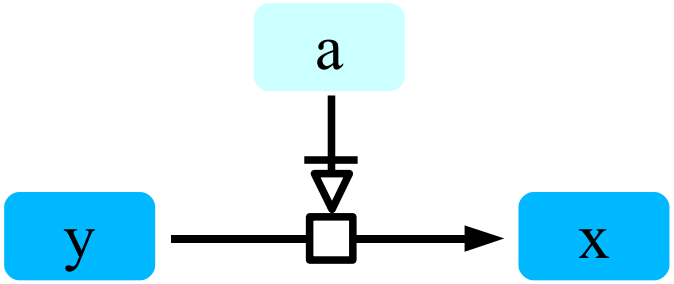
# absolute Vs relative activators

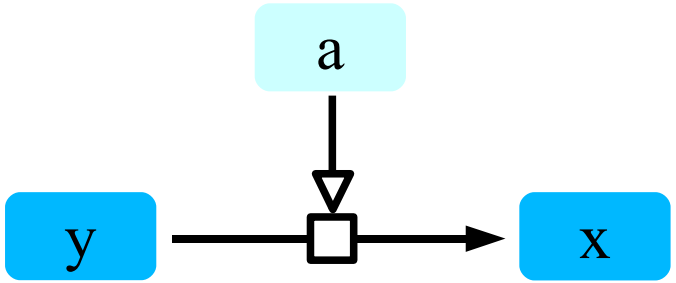



$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



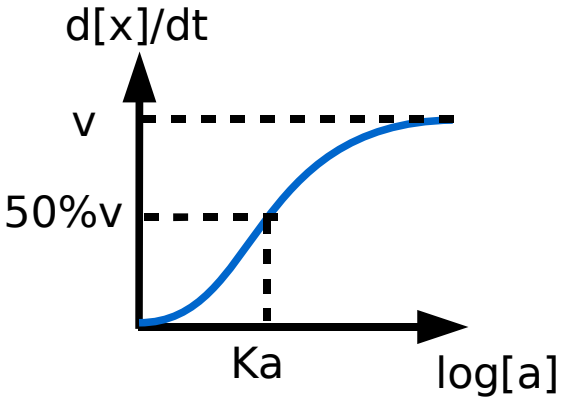
# absolute Vs relative activators

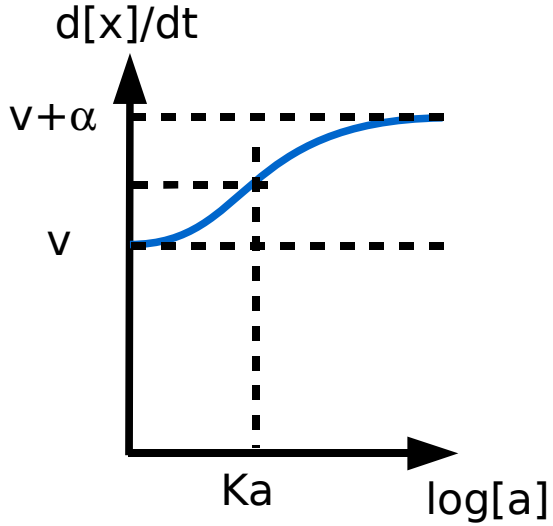



$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

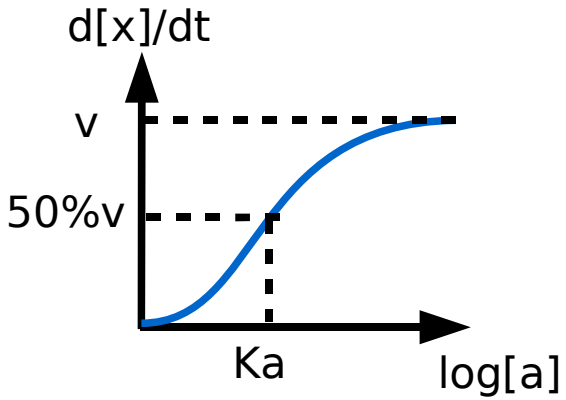
$$\frac{d[x]}{dt} = v \cdot (1 + \alpha \cdot \frac{[a]}{Ka + [a]})$$



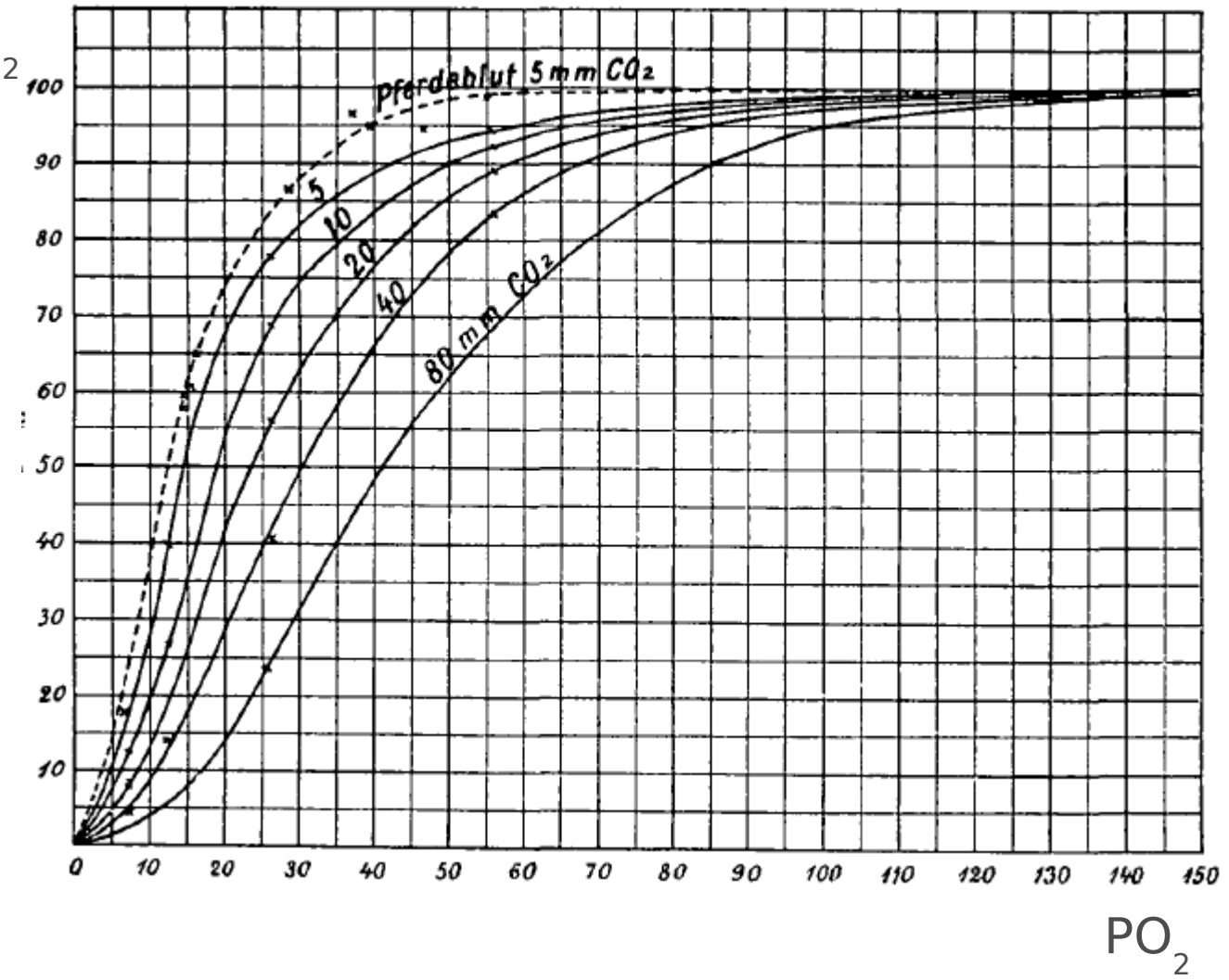



# Ultrasensitivity

$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$



# Origins of cooperativity: Bohr




Bohr C (1903) Theoretische behandlung der quantitativen verhältnisse bei der sauerstoff aufnahme des hämoglobins *Zentralbl Physiol* 17: 682

# Origins of cooperativity: Hill



**The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves.** By A. V. HILL.

In a previous communication Barcroft and I gave evidence which seemed to us to prove conclusively that dialysed hæmoglobin consists simply of molecules containing each one atom of iron. The molecular weight is therefore Hb = 16,660. These experiments have not been published yet, but I shall assume the results.

Other observers (Reid, Roaf, Hüfner and Gansser) working on different solutions have obtained divergent results. The method used by all of them was the direct estimation of the osmotic pressure, by means of a membrane permeable to salts, but not to hæmoglobin. The method involves a relatively large error, because the quantity measured is small. It is doubtful however whether this can explain the discordant results.

Our work led me to believe that the divergence between the results of different observers was due to an aggregation of the hæmoglobin molecules by the salts present in the solution, a consequent lowering of the number of molecules, and an increase in the average molecular weight as observed by the osmotic pressure method. To test this hypothesis I have applied it to several of the dissociation curves obtained by Barcroft and Camis with hæmoglobin in solutions of various salts, and with hæmoglobin prepared by Bohr's method.

The equation for the reaction would be

$$\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2},$$
$$\mathrm{Hb}_n + n\mathrm{O_2} \rightleftarrows \mathrm{Hb}_n\mathrm{O}_{2n},$$

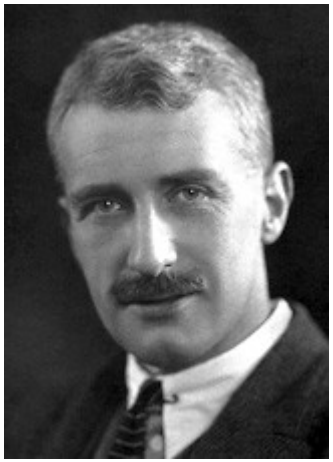
where $\mathrm{Hb}_n$ represents the aggregate of $n$ molecules of Hb. I have supposed that in every solution there are many different sized aggregates, corresponding to many values of $n$.

If there were in the solution only Hb and $\mathrm{Hb_2}$ the dissociation curve would be

$$y = \lambda \frac{K'x^2}{1+K'x^2} + (100-\lambda)\frac{Kx}{1+Kx} \quad \ldots\ldots\ldots\ldots\ldots\ldots (\mathrm{A}),$$

where $\lambda$ % is as $\mathrm{Hb_2}$, $(100-\lambda)$ % as Hb, $K'$ is the equilibrium constant of the reaction $\mathrm{Hb_2} + 2\mathrm{O_2} \rightleftarrows \mathrm{Hb_2O_4}$ and $K$ that of $\mathrm{Hb} + \mathrm{O_2} \rightleftarrows \mathrm{HbO_2}$: $K$ has the value ·125 (Barcroft and Roberts).

Hill AV (1910) The possible effects of the aggregation of the molecules of hæmoglobin on its dissociation curves. *J Physiol* 40: iv-vii.



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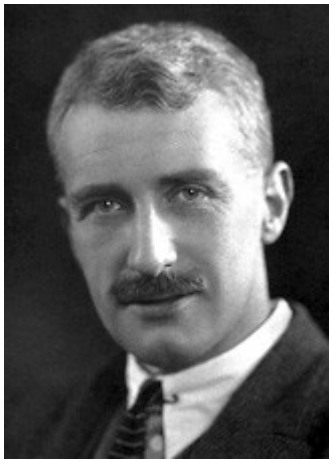
$$y = 100\frac{Kx^n}{1+Kx^n} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (\mathrm{B})$$

would satisfy the observations.



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iv PROCEEDINGS OF THE PHYSIOLOGICAL

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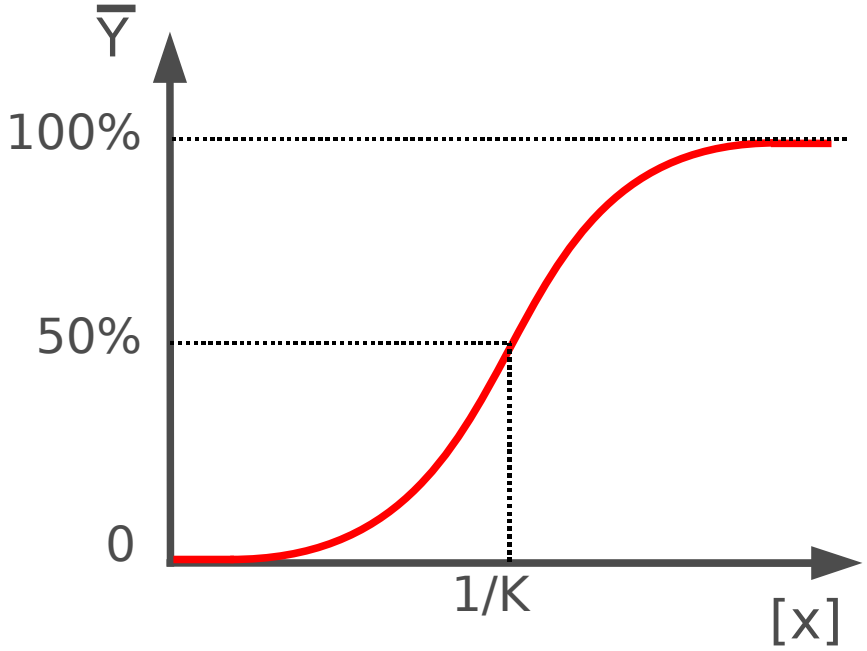

# Ultrasensitivity

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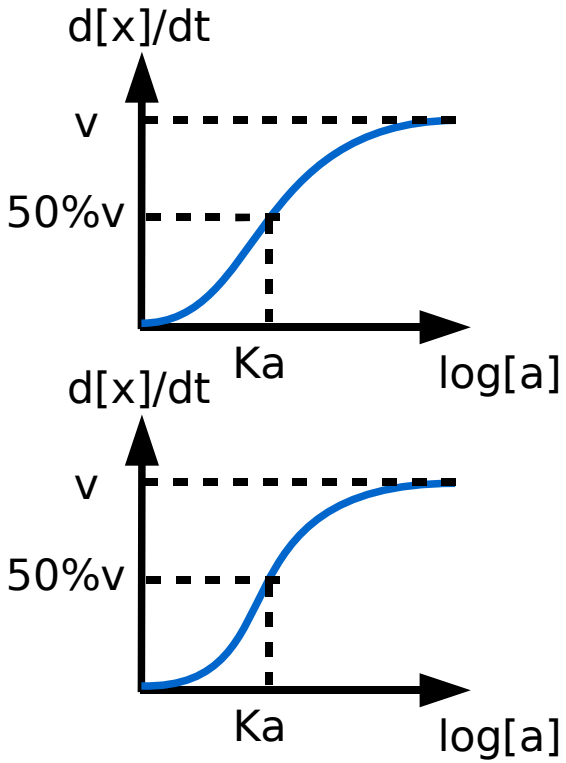
$$\frac{d[x]}{dt} = v \cdot \frac{[a]^2}{Ka^2 + [a]^2}$$



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$$\frac{d[x]}{dt} = v \cdot \frac{[a]}{Ka + [a]}$$

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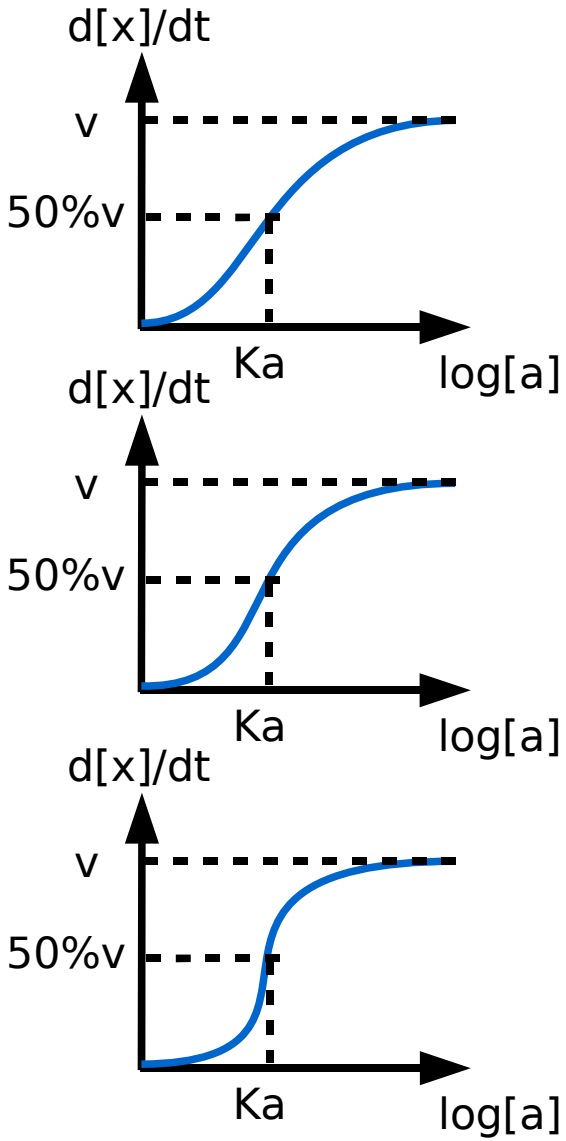
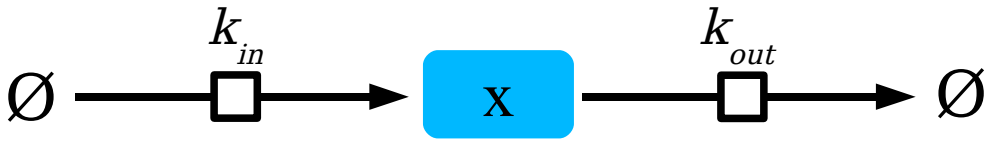
$$\frac{d[x]}{dt} = v \cdot \frac{[a]^n}{Ka^n + [a]^n}$$



# Homeostasis

How can-we maintain a stable level with a dynamic system?



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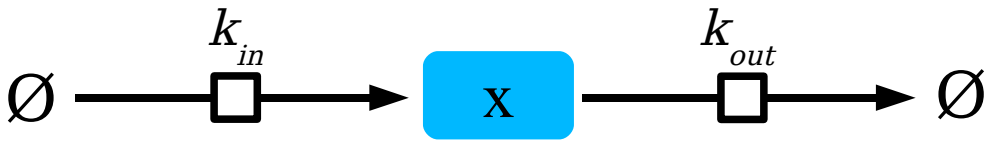


$$\frac{d[x]}{dt} = k_{in} - k_{out} \cdot [x]$$

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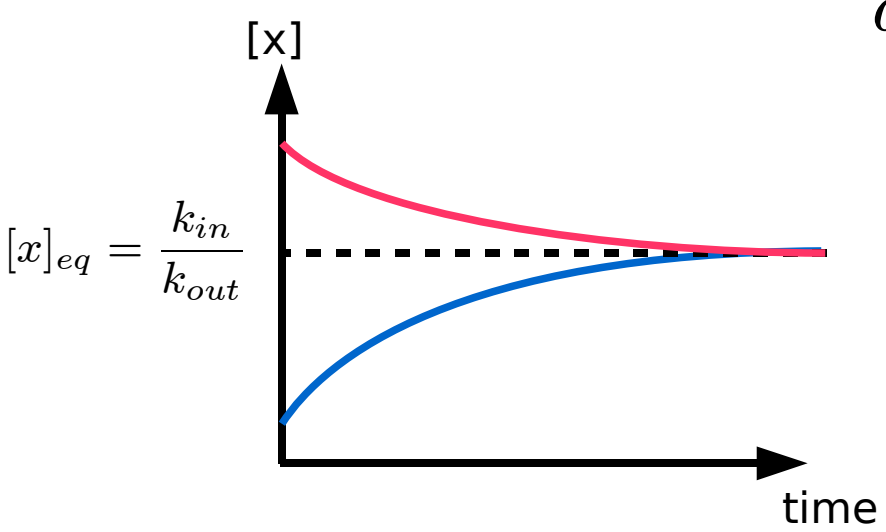


# Encoding models

# SBML.org — The Systems Biology Markup Language



The **Systems Biology Markup Language** (**SBML**) is a computer-readable format for representing models of biochemical reaction networks in software. It's applicable to models of metabolism, cell-signaling, and many others. SBML has been evolving since mid-2000 thanks to an international community of software developers and users. This website is the portal for the global SBML development effort; here you can find information about all aspects of SBML.

## *For the curious*

What *is* SBML? Read our **basic introduction** and then perhaps browse the **mailing lists** to get a sense for what's currently going on in the world of SBML.

## *For modelers*

Are you looking for ready-to-run software that supports SBML? Take a look at our **SBML Software Guide**. Are you instead looking for ready-to-use models? Visit the **BioModels Database**, where you can find hundreds of tried and tested models.

## *For software developers*

Are you interested in developing SBML support for your software? Read our **basic introduction** and then the **SBML specifications** to understand how to use SBML. After that, you may want to look at **libSBML**, an API library supporting many programming languages.

Whether you use SBML as a modeler or a developer, we invite you to sign up for news updates either through our **RSS feed** or one of the **mailing lists**, and get involved with community efforts to help keep SBML improving. You

## *SBML News*

### *LibSBML 3.3.2 released!*

*(3 Mar.'09)* **LibSBML** is an API library for SBML. The new release fixes bugs and a memory leak in 3.3.1.

### *LibSBML 3.3.1 released!*

*(3 Feb.'09)* **LibSBML** is an API library for SBML. The new release fixes a few bugs in 3.3.0, including a potential crasher.

### *LibSBML 3.3.0 released!*

*(21 Jan.'09)* **LibSBML** is an API library for working with SBML. New features include support for SBML Level 2 Version 4.

**Older news ...**

## *Community News*

### *SBW 2.7.9 released*

*(3 Mar.'09)* The **Systems Biology Workbench** is a component-based application framework. This release improves simulator and auto-layout performance, and adds other features.

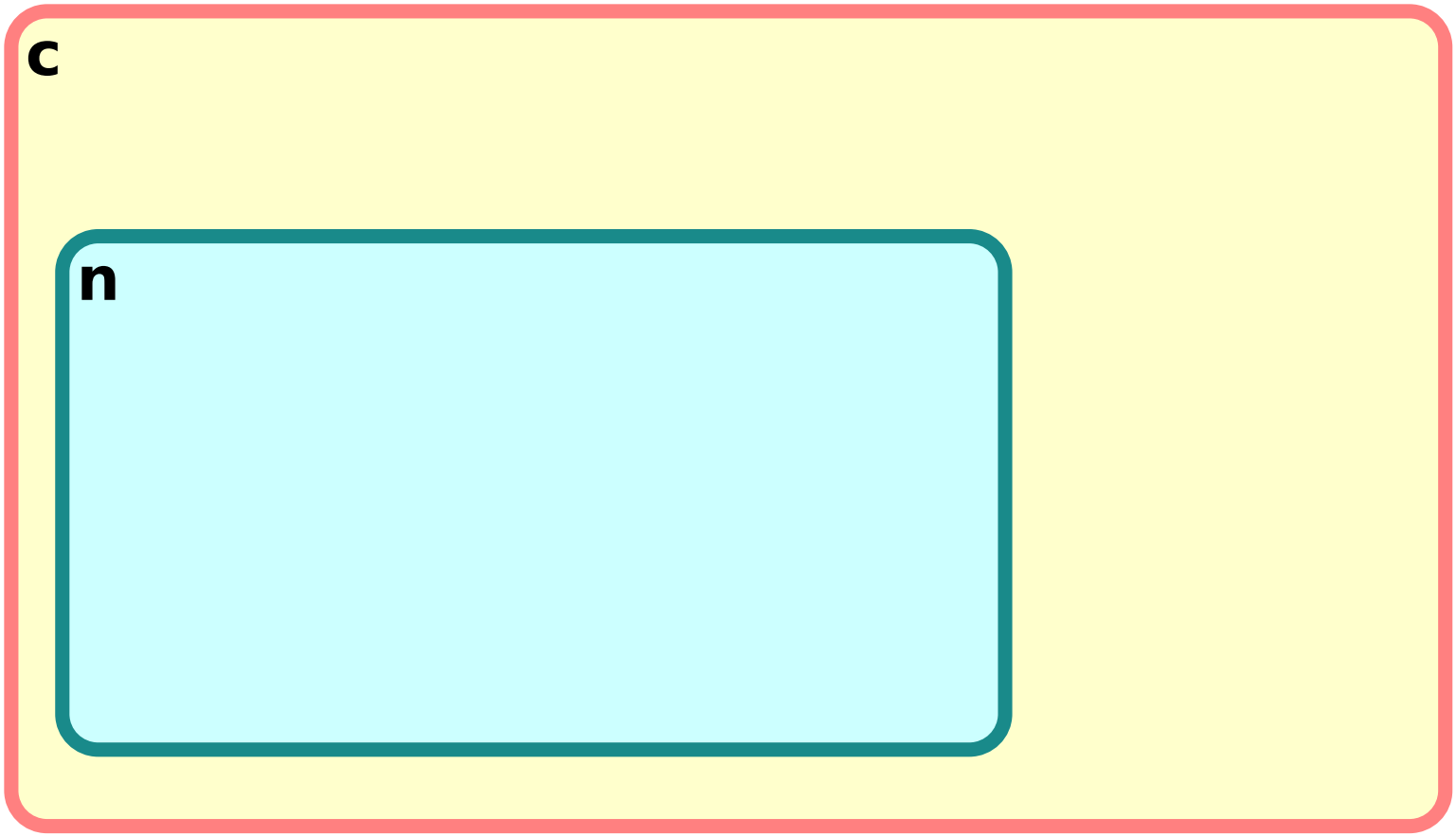
### *BioModels Database mirror @ Caltech*

*(26 Feb.'09)* **BioModels Database**, a free, public resource, now has a mirror site at Caltech for better load balancing.

### *New version of SABIO-RK*

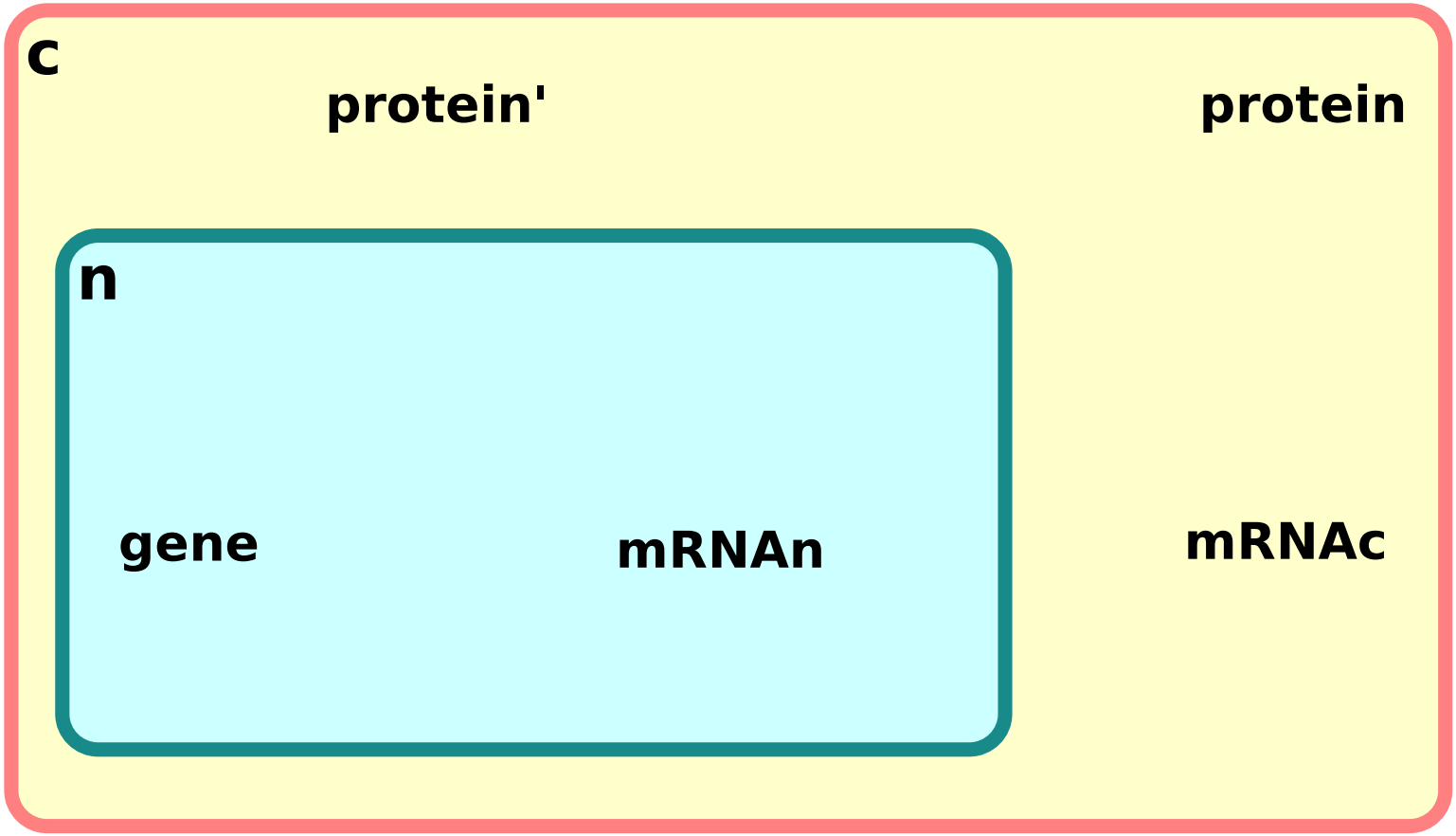
# What can we encode in SBML?

**containers (compartments)**



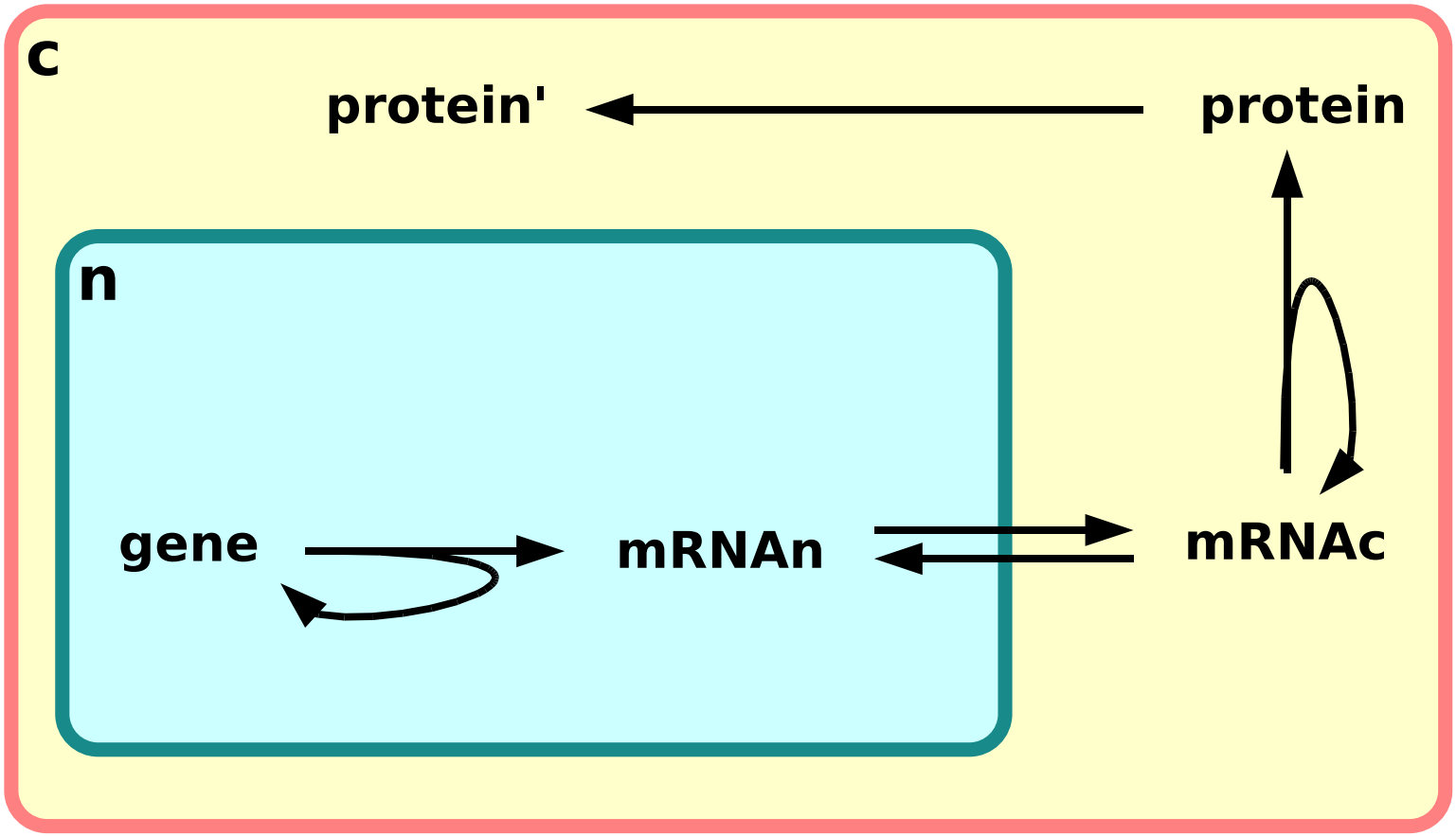
# What can we encode in SBML?

## entity pools (species)



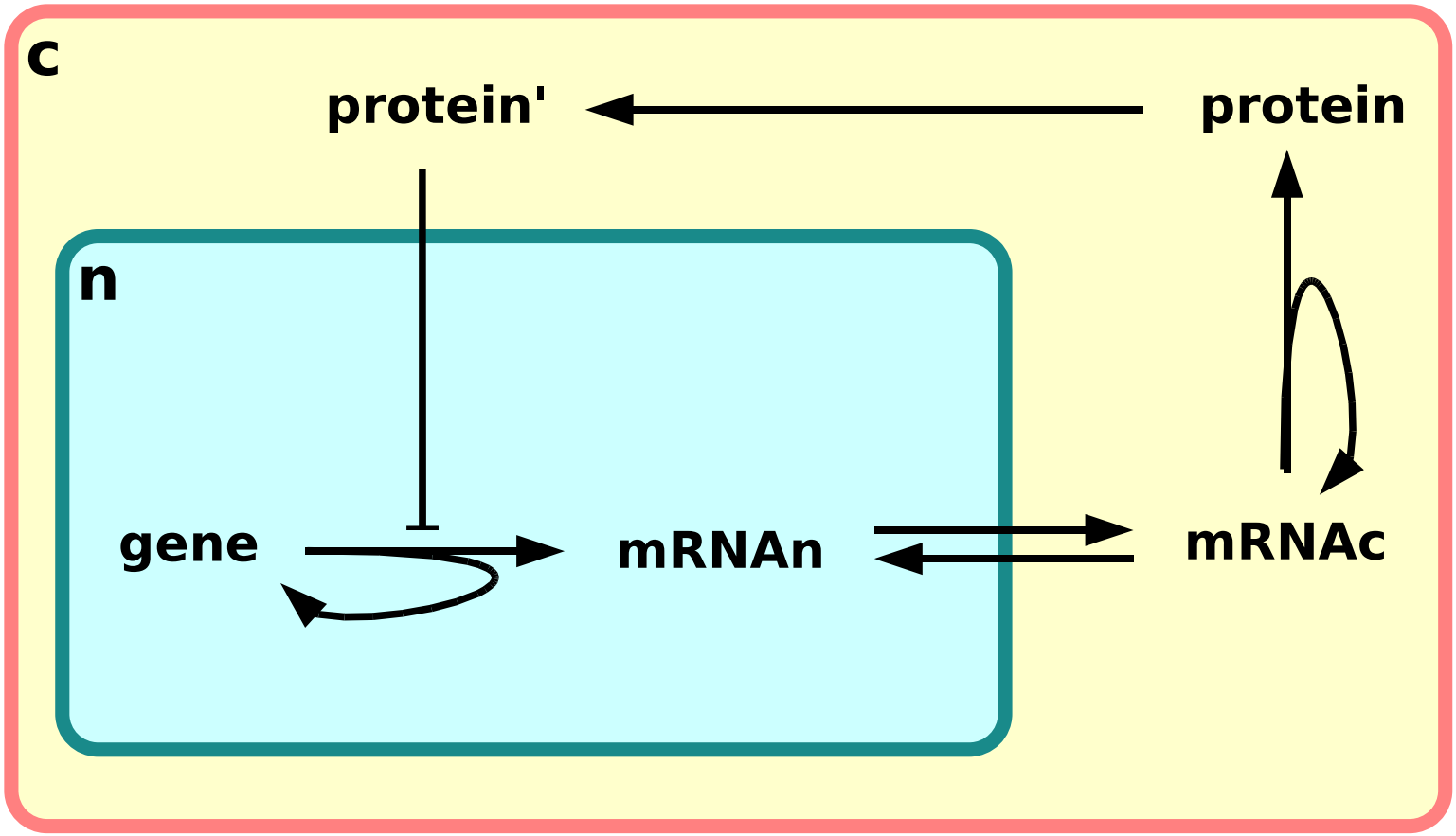
# What can we encode in SBML?

**reactions**



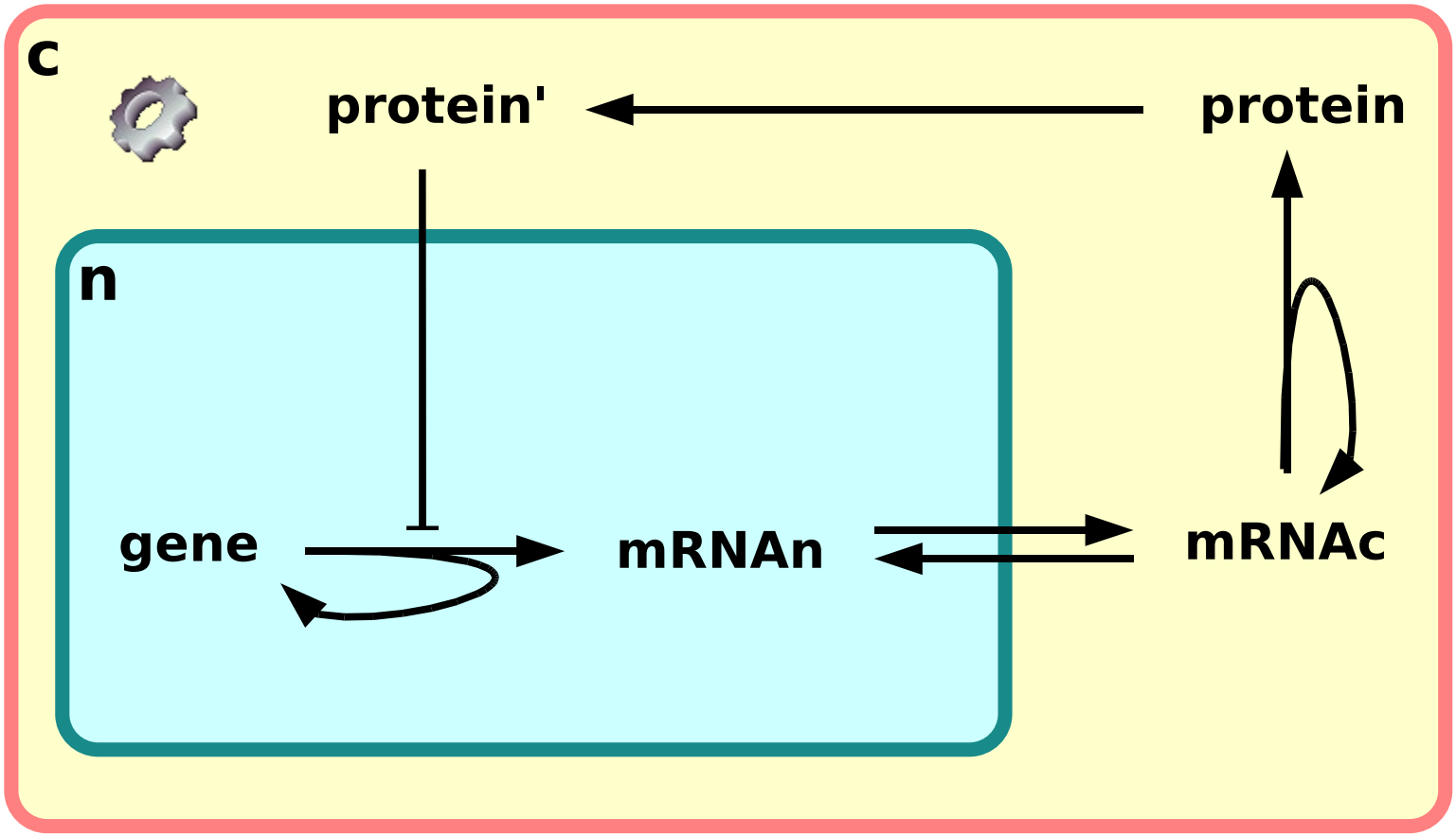
# What can we encode in SBML?

**modulations**



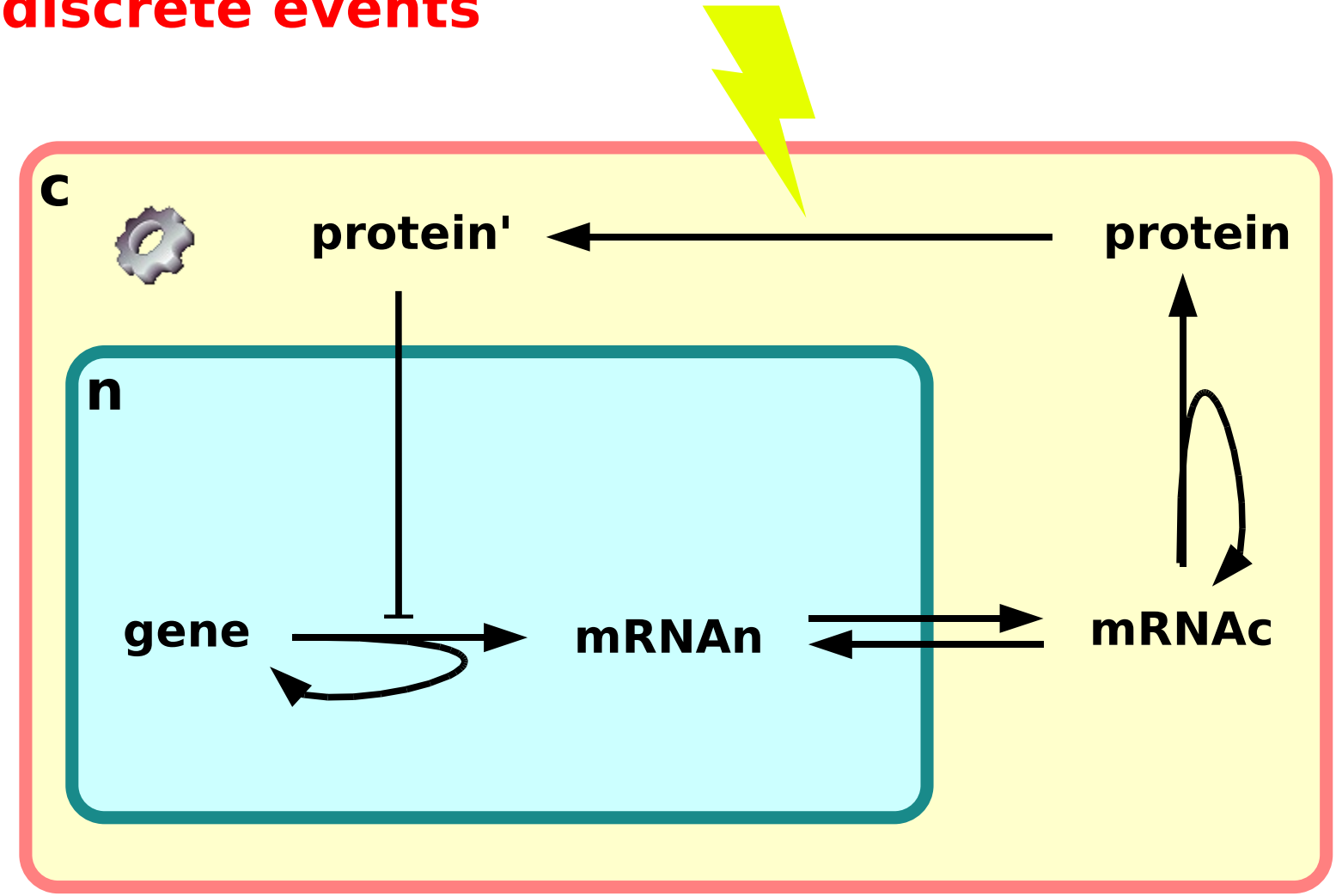
# What can we encode in SBML?

**arbitratry rules**



# What can we encode in SBML?

**discrete events**



# A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>

  </model>
</sbml>
```

# A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>









  </model>
</sbml>
```

# A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>









  </model>
</sbml>
```

# A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>









  </model>
</sbml>
```

# A → B

```
<?xml version="1.0" encoding="UTF-8"?>
<sbml level="2" version="1" xmlns="http://www.sbml.org/sbml/level2">
  <model>
    <listOfCompartments>
      <compartment id="cell" />
    </listOfCompartments>
    <listOfSpecies>
      <species id="A" compartment="cell" initialConcentration="1"/>
      <species id="B" compartment="cell" initialConcentration="0"/>
    </listOfSpecies>
    <listOfParameters>
      <parameter id="kon" value="1"/>
    </listOfParameters>
    <listOfReactions>
      <reaction>
        <listOfReactants>
          <speciesReference species="A" />
        </listOfReactants>
        <listOfProducts>
          <speciesReference species="B" />
        </listOfProducts>
        <kineticLaw>
          <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
              <times />
              <ci>kon</ci>
              <ci>A</ci>
              <ci>cell</ci>
            </apply>
          </math>
        </kineticLaw>
      </reaction>
    </listOfReactions>
  </model>
</sbml>
```

# A more realistic example ...

```
<species
    id="A"
    name="α-tubulin"
    compartment="cell"
    initialAmount="1000"
    substanceUnits="item"
    hasOnlySubstanceUnits="true"
    boundaryCondition="true"
    constant="false"
    charge="0"
    metaid="PX"
    sboTerm="SBO:0000245" >
  <notes>
    <body xmlns="http://www.w3.org/1999/xhtml">
      <p>One of the components of a microtubule</p>
    </body>
  </notes>
  <annotation>
    <rdf:RDF
        xmlns:bqbiol="http://biomodels.net/biology-qualifiers/"
        xmlns:bqmodel="http://biomodels.net/model-qualifiers/"
        xmlns:rdf="http://www.w3.org/1999/02/22-rdf-syntax-ns#">
      <rdf:Description rdf:about="#PX">
        <bqbiol:is>
          <rdf:Bag>
            <rdf:li rdf:resource="urn:miriam:uniprot:P68370"/>
            <rdf:li rdf:resource="urn:miriam:obo.go:GO%3A0045298"/>
          </rdf:Bag>
        </bqbiol:is>
      </rdf:Description>
    </rdf:RDF>
  </annotation>
</species>
```

# And SBML is richer than that

| | |
|---|---|
| **Function definition** | mathematical function that may be used throughout the rest of a model. |
| **Unit definition** | new unit of measurement, or redefinition of an existing SBML default unit. |
| **Compartment Type** | type of container |
| **Species type** | type of entity that can participate in reactions. |
| **Compartment** | well-stirred container of finite size where species may be located. |
| **Species** | pool of entities of the same species type located in a specific compartment. |
| **Parameter** | named quantity, whether constant or variable, global to the model |
| **Initial Assignment** | mathematical expression to determine the initial conditions of a model. |
| **Rule** | mathematical expression added to the set of equations constructed based on the reactions |
| **Constraint** | means of detecting out-of-bounds conditions during a dynamical simulation |
| **Reaction** | statement describing some transformation, transport or binding process that can change the amount of one or more species |
| **Event** | statement describing an instantaneous change in a set of variables |

# SBML is not limited to biochemistry!

Rate Rules can describe the temporal evolution of any quantitative parameter, e.g. transmembrane voltage;

Events can describe any discontinuous change, e.g. neurotransmitter release or repolarisation;

A species is an entity participating to a reaction, **not always** a **chemical** entity:

- It can be a molecule
- It can be a cell
- It can be an organ
- It can be an organism

➔ Systems Biology is scale-free!

# Neuron differentiation

```
<listOfCompartments>
  <compartment id="brain" />
</listOfCompartments>
<listOfSpecies>
  <species id="glia" compartment="brain" initialConcentration="1"/>
  <species id="neuroblast" compartment="brain" initialConcentration="1"/>
  <species id="neuron" compartment="brain" initialConcentration="0"/>
</listOfSpecies>
<listOfParameters>
  <parameter id="K" value="1"/>
</listOfParameters>
<listOfReactions>
  <reaction>
    <listOfReactants>
      <speciesReference species="neuroblast" />
    </listOfReactants>
    <listOfProducts>
      <speciesReference species="neuron" />
    </listOfProducts>
   <listOfModifiers>
      <modifierSpeciesReference species="glia" />
    </listOfModifiers>
    <kineticLaw>
      <math xmlns="http://www.w3.org/1998/Math/MathML">
        <apply>
          [...]
        </apply>
      </math>
    </kineticLaw>
  </reaction>
</listOfReactions>
```

# Hodgkin-Huxley

```
<rateRule metaid="metaid_0000048" variable="V">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">dV/dt = (I - (i_Na + i_K + i_L))/Cm</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <divide/>
      <apply>
        <minus/>
        <ci> I </ci>
        <apply>
          <plus/><ci> i_Na </ci><ci> i_K </ci><ci> i_L </ci>
        </apply>
      </apply>
      <ci> Cm </ci>
    </apply>
  </math>
</rateRule>
<assignmentRule metaid="metaid_0000042" variable="i_Na">
  <notes><p xmlns="http://www.w3.org/1999/xhtml">i_Na = g_Na * m^3.0 * h * (V - E_Na)</p></notes>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> g_Na </ci>
      <apply>
        <power/><ci> m </ci><cn> 3.0 </cn>
      </apply>
      <ci> h </ci>
      <apply>
        <minus/><ci> V </ci><ci> E_Na </ci>
      </apply>
    </apply>
  </math>
</assignmentRule>
```

rate rule:

dx/dt = f (x,y,z)

assignment rule:

x = f (y,z)

# An example of piecewise assignment

calcium flux depends on glutamate concentration

```
<listOfRules>
    <assignmentRule variable="calcium_influx">
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <piece>
                    <cn>15</cn>
                    <apply>
                        <gt/>
                        <ci>glutamate</ci>
                        <cn>1</cn>
                    </apply>
                </piece>
                <otherwise>
                    <cn>0</cn>
                </otherwise>
            </apply>
        </math>
    </assignmentRule>
</listOfRules>
```

if glutamate > 1

then calcium_influx = 15

else  calcium_influx = 0

# >170 tools supporting SBML

Parent pages: SBML.org / SBML Software Guide

## SBML Software Matrix

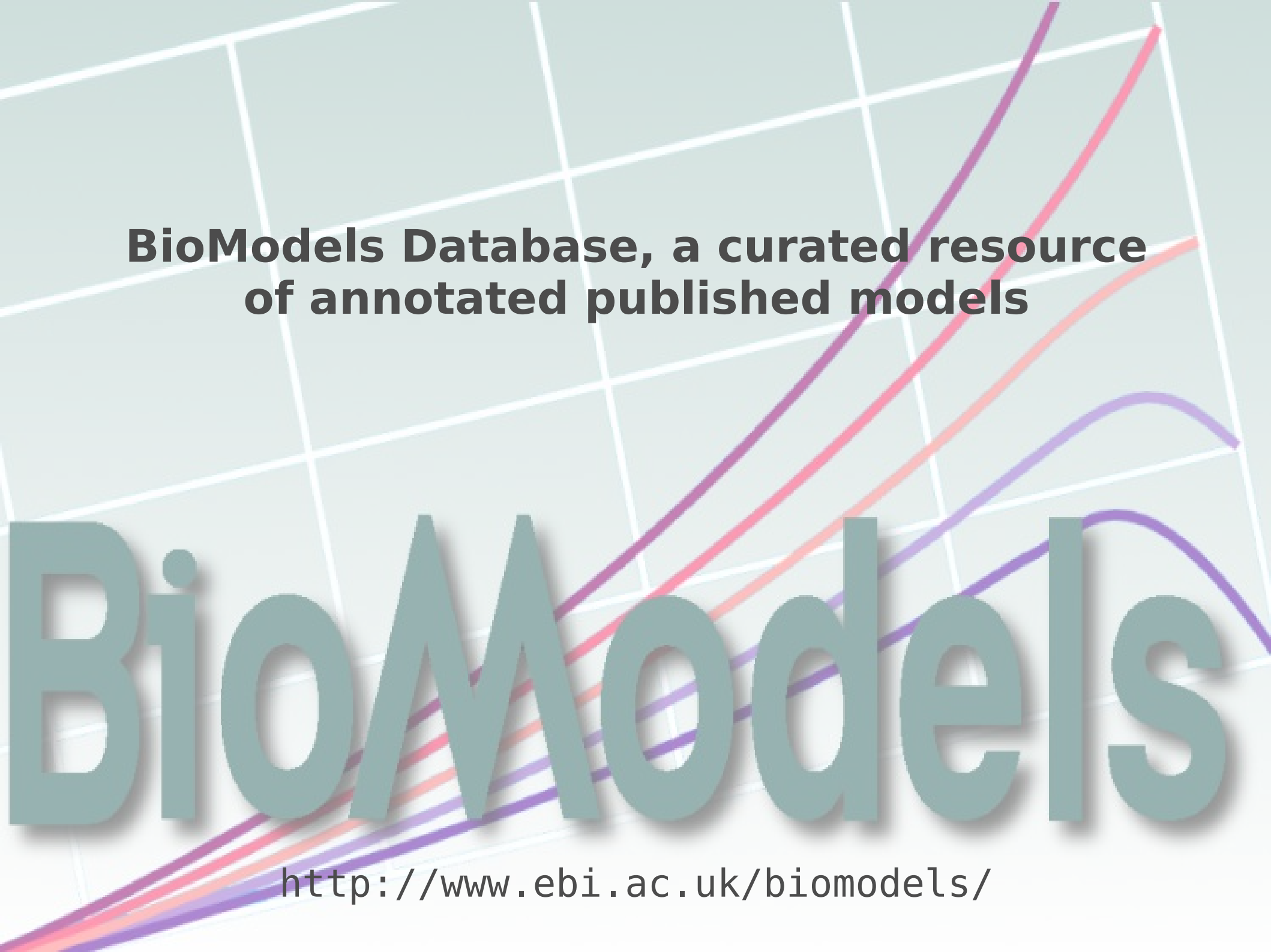
This matrix provides an at-a-glance summary of software known to us to provide some degree of support for reading, writing, or otherwise working with SBML. The columns' meanings are explained below. For a list of longer descriptions grouped into themes, please see our **SBML Software Summary** page.

| | Capabilities | | | | | Frameworks | | | | | | | API | Dep. | Platforms | SBML | | Availabil. | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Creation | Simulation | Analysis | Database | Utility | ODE | DAE | PDE | Stochastic | Events | Logical | Other | | | | Import | Export | Open source | Academic use | Commercial use |
| **acslXtreme** | • | | | | | | | | | | | | | | W | • | | | $ | $ |
| **ALC** | • | | | | | • | • | | • | | | • | | | L, W, M, B | | • | • | F | F |
| **Asmparts** | • | | | | • | • | | | | | | | | | L,W | • | • | • | F | F |
| **Antimony** | • | | | | • | | | | | | | | C, C++ | | L, W, M | • | • | • | F | F |
| **AutoSBW** | | | • | | | • | | | | | | | SBW | SBW | L, W, M | • | • | • | F | F |
| **AVIS** | | | | | | | | | | | | • | | various | L | • | | • | F | F |
| **BALSA** | • | | | | | | | | | | | | | Sigtran | | | | | | |
| **BASIS** | • | • | | • | | | | | • | • | | | WS | | B | • | • | • | F | F |
| **BetaWB** | • | • | • | | | | | | • | • | | | | | L,W,M | | • | | F | F |
| **BiNoM** | • | | • | | • | | | | | | | • | | | L, W, M | • | • | • | F | F |
| **BiNoM Cytoscape Plugin** | • | | • | | • | | | | | | | • | | Cytoscape | L, W, M | • | • | • | F | F |
| **BIOCHAM** | | • | | | • | • | | | | | | | | | L,W,M | | • | • | F | F |
| **BioCharon** | • | • | • | | • | • | | | | | | | | CHARON | | | | | | |
| **Biological Networks** | • | | • | | • | | | | | | | | | | L,W,M | • | • | | F | $ |
| **BioCyc** | | | | • | | | | | | | | | | | | | • | | F | $ |
| **BioGrid** | | | | | | | | | | | | | | | | | | | | |

The columns of this table should be read in the following way:

- *Capabilities* summarizes the facilities that a package provides by itself (i.e., without invoking another package) for working with SBML: "Creation" = creating/editing models, "Simulation" = performing time-series simulation of models, "Analysis" = analyzing models (e.g., sensitivity analysis, flux-balance analysis, etc.), "Database" = providing a database of models, and "Utility" = providing other utility functions (e.g., translating SBML to/from other formats).
- *Frameworks* summarizes the modeling frameworks supported by a package, regardless of whether the package

# BioModels Database, a curated resource of annotated published models




http://www.ebi.ac.uk/biomodels/

# BioModels Database - A Database of Annotated Published Models

BioModels Database is a data resource that allows biologists to store, search and retrieve published mathematical models of biological interests. Models present in BioModels Database are annotated and linked to relevant data resources, such as publications, databases of compounds and pathways, controlled vocabularies, etc.

Search | Go to the model | Advanced search

## Browse models

- Curated models (216)
- Browse models using GO
- Non-curated models (196)

## Simulate in JWS Online

## Submit a model

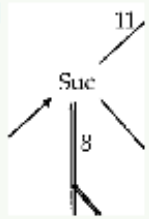
**Mirror at California Institute of Technology** http://biomodels.caltech.edu

**BioModels AT SourceForge** http://sourceforge.net/projects/biomodels/

**Web Services** http://www.ebi.ac.uk/biomodels/webservices.html

## Model of the month

May, 2009




Sucrose accumulation is accompanied by continuous synthesis and degradation processes in the developing sugar cane, *Saccharum officinarum*. Sugar cane internode maturation coincides with increased sucrose storage, but is not dependent purely on time. In addition, cane varieties accumulate sucrose to quite divergent extents.

*Read more...*

## News

16th June 2009 **Fourteenth release**
Download All Models Under SBML Format

25th March 2009 **Thirteenth release**
Download All Models Under SBML Format

28th-30th March 2009 **BioModels meeting 2009**
The Fourth BioModels Meeting will be held from March 28 to 30, 2009, at the EBI in Cambridge (United Kingdom).

*Proc. Natl. Acad. Sci. USA*
Vol. 78, No. 11, pp. 6840–6844, November 1981
Biochemistry

# An amplified sensitivity arising from covalent modification in biological systems

(protein modification/metabolic regulation/switch mechanism/enzyme cascades)

ALBERT GOLDBETER† AND DANIEL E. KOSHLAND, JR.

Department of Biochemistry, University of California, Berkeley, California 94720

*Contributed by Daniel E. Koshland, Jr., August 11, 1981*

**ABSTRACT** **The transient and steady-state behavior of a reversible covalent modification system is examined. When the modifying enzymes operate outside the region of first-order kinetics, small percentage changes in the concentration of the effector controlling either of the modifying enzymes can give much larger percentage changes in the amount of modified protein. This amplification of the response to a stimulus can provide additional sensitivity in biological control, equivalent to that of allosteric proteins with high Hill coefficients.**

Biological systems must respond to internal and external variations such as the depletion of nutrients, the variations in hormone levels, and the reception of sensory signals. The stimuli are processed to change the activities of enzymes controlling pathways in the biological system. Two basic phenomena play a large role in this processing: allosteric changes in protein conformation and covalent modification of proteins.

Since the findings of Cori and Green (1) and Krebs and

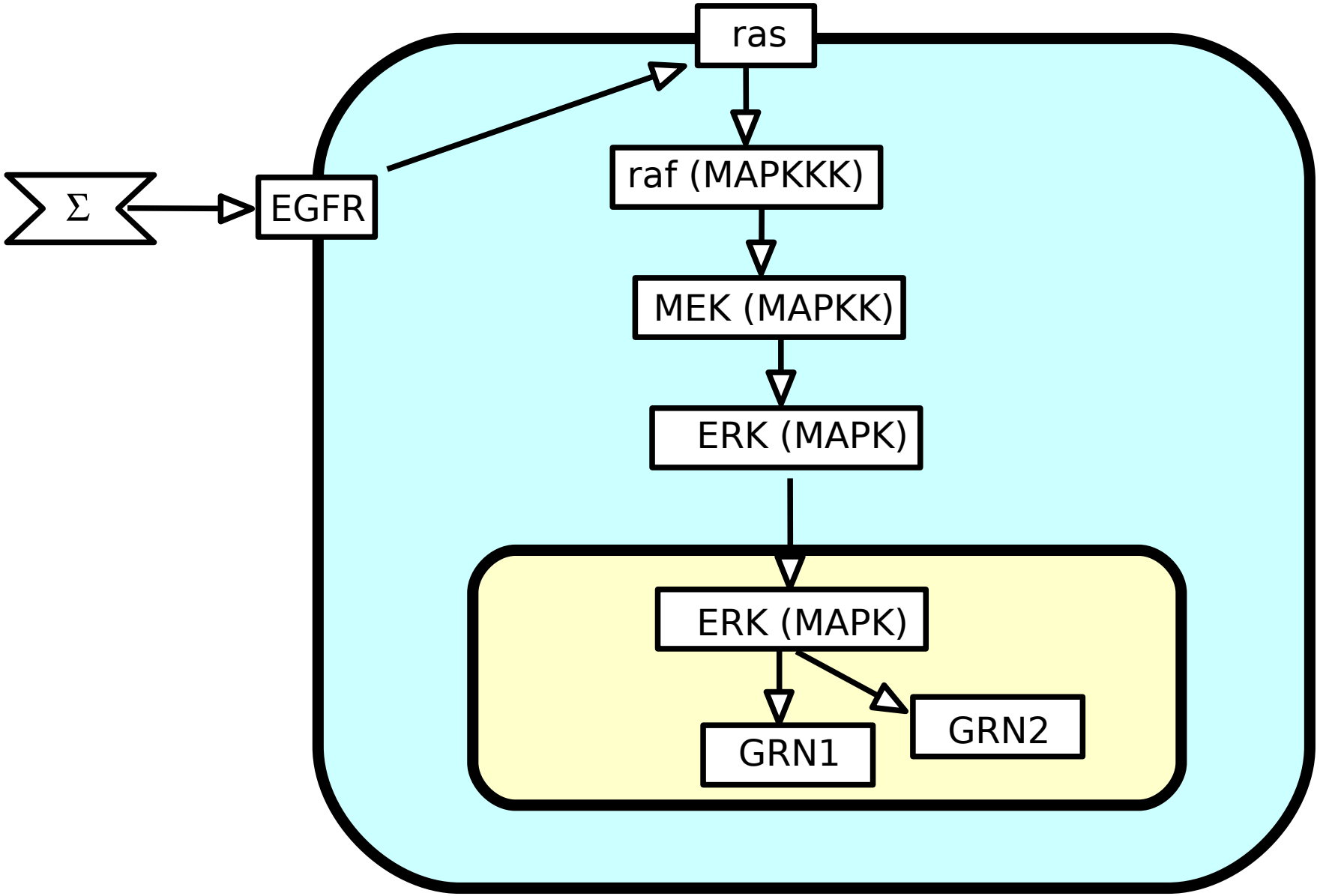
ture of covalent regulation was possible, if the differential equations could be solved analytically outside the first-order region.

This analysis has been achieved, and the results reveal that there is an added sensitivity inherent in covalent modification schemes when one or more of the converter enzymes operate in the "zero-order" region—i.e., region of saturation with respect to protein substrate. Thus there is a property of covalent systems that, in the absence of allosteric cooperativity and multiple inputs, can generate sensitivity equivalent to cooperative enzymes with high Hill coefficients. The derivations leading to and the implications of this finding are discussed below. For convenience, we shall use the term "ultrasensitivity" to describe an output response that is more sensitive to change in stimulus than the hyperbolic (Michaelis–Menten) equation.

## Steady-state behavior of modification system

We shall consider a covalent modification system in which a

# MAPK cascade



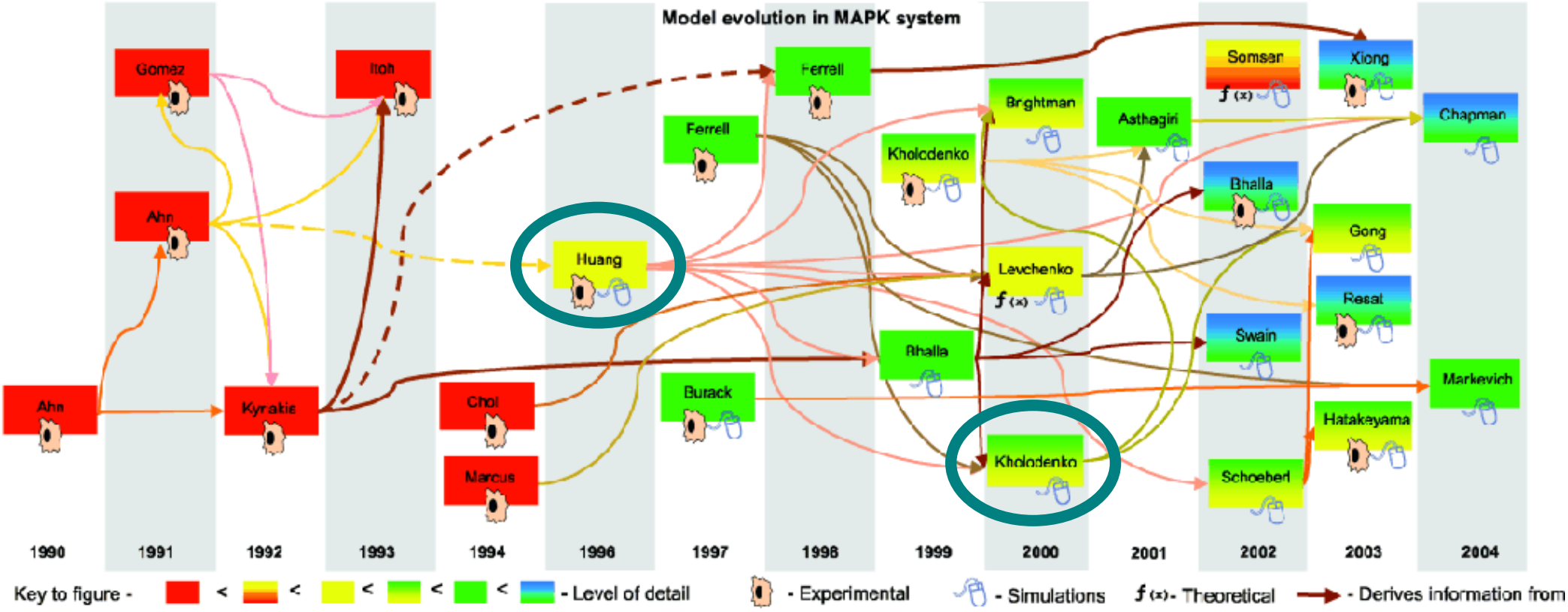
# MAPK cascade

- Mitogen Activated Protein kinase:

  mitosis, differentiation, cell survival, apoptosis

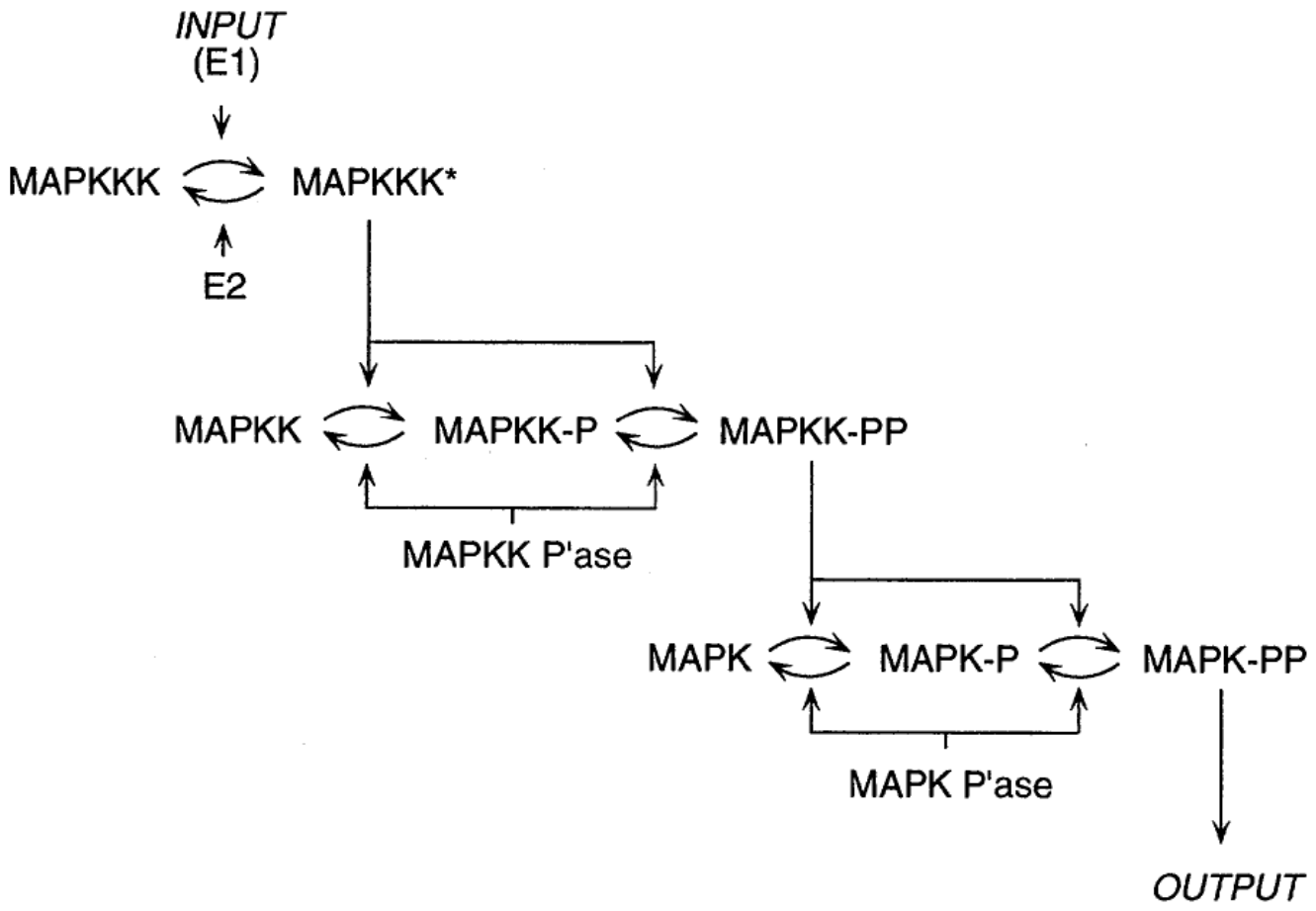
  ☞ CANCER
- Integration of many signalling pathways
- Activation of many regulatory networks
- Model systems in computational biology

# Early history of MAPK models



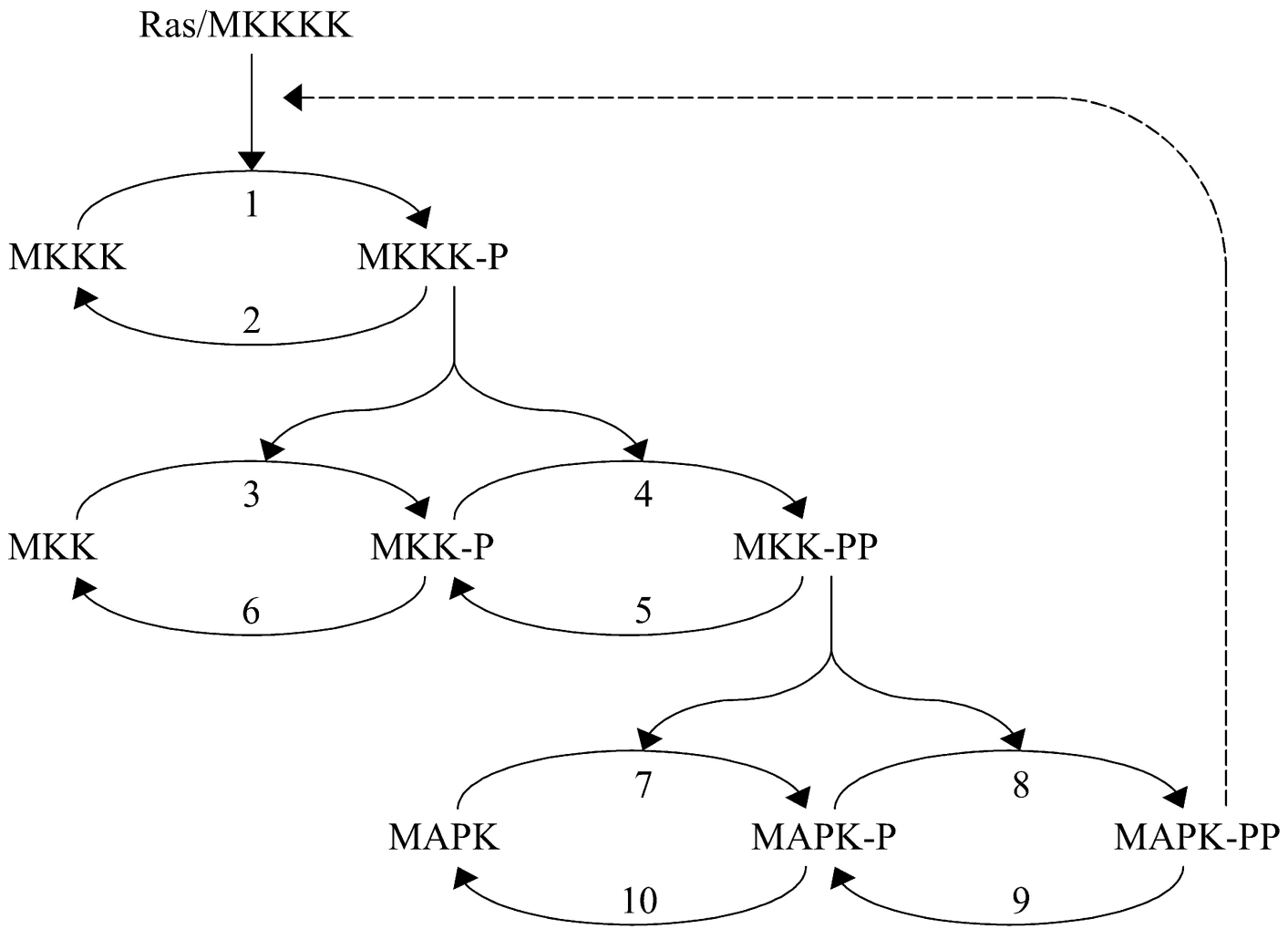

Vayttaden, Ajay, Bhalla (2004) A spectrum of models of signalling pathways. *Chembiochem* 5: 1365-1374.

# Huang and Ferrell

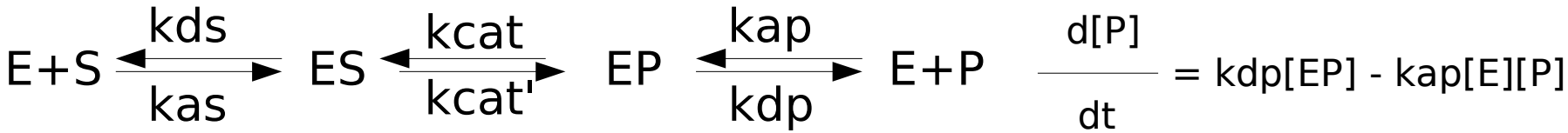



Huang and Ferrell (1996) Ultrasensitivity in the mitogen-activated protein kinase cascade. *Proc Natl Acad Sci USA* 93: 10078-10083.

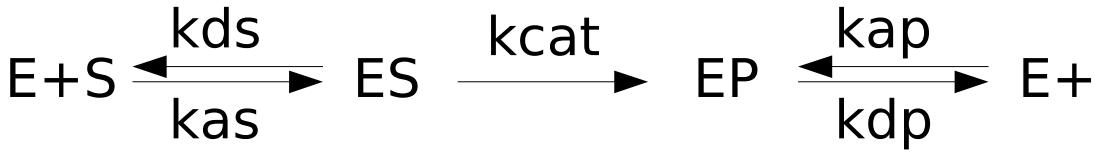
# Kholodenko




Kholodenko (2000) Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. *Eur J Biochem* 267: 1583-1588.

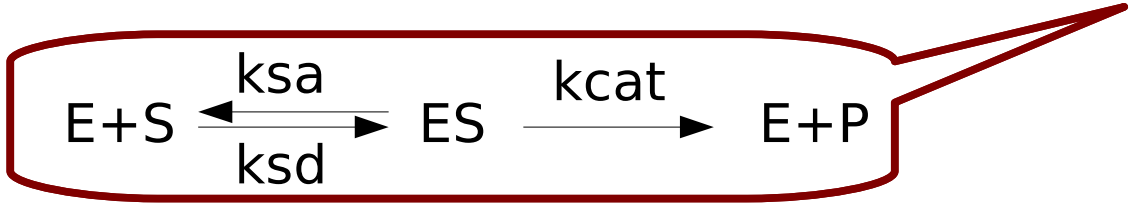



$$\frac{d[P]}{dt} = kdp[EP] - kap[E][P]$$




catalysis irreversible

## Huang and Ferrell




product is consumed before rebinding


## Kholodenko

$$\frac{d[P]}{dt} = \frac{[E]\,kcat}{1 + \frac{Km}{[S]}}$$

We will use COPASI, developed by:
Virginia Bioinformatics Institute
European Medial Laboratory

http://www.copasi.org/

Download:
http://www.copasi.org/tiki-index.php?page=DownloadNonCommercial

documentation:
http://www.copasi.org/tiki-index.php?page=DocumentationNew