Introduction to Computational Systems Biology

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The Holy Grail

Theory

A Whole-Cell Computational Model Predicts Phenotype from Genotype

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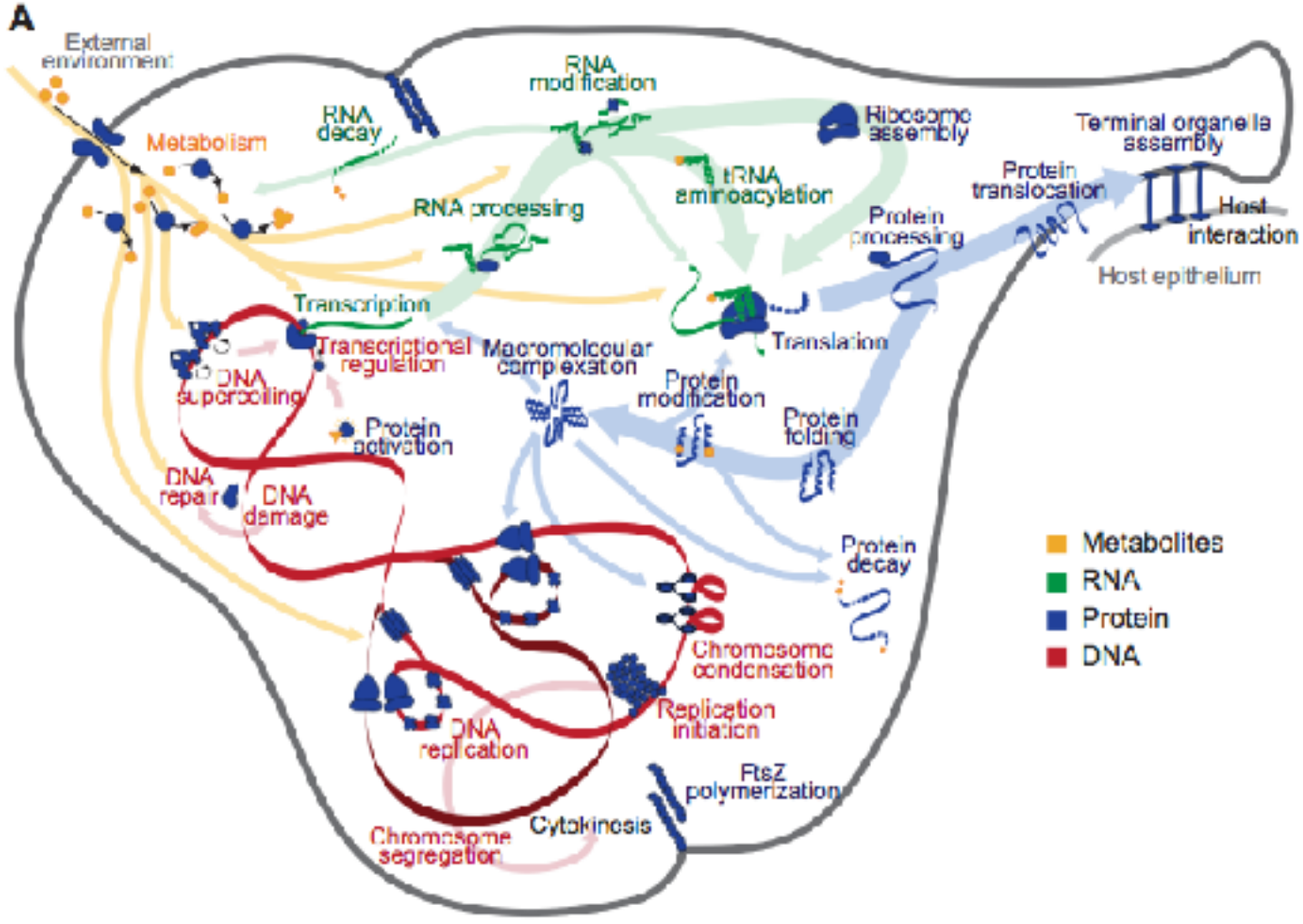
Mycobacterium with 600 genes.
Scaling to Eucaryotes is highly non-trivial.

Biological systems

A cell is made of many subsystems, performing different tasks and interacting among them.

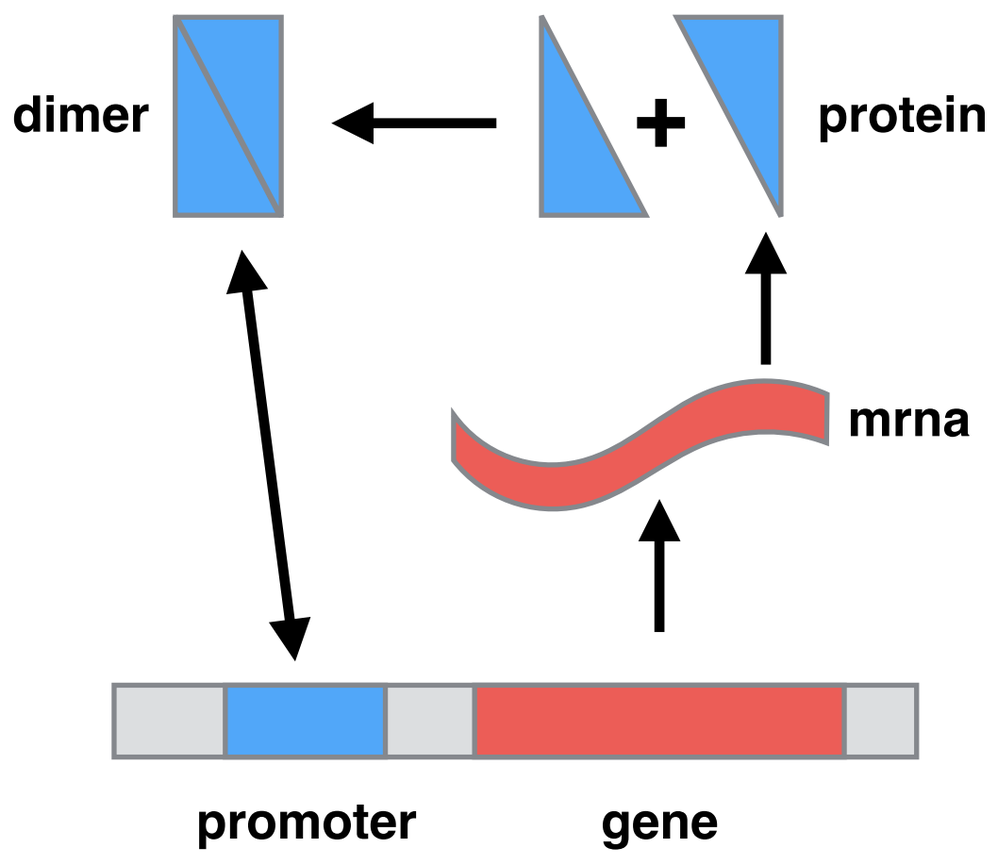
We have several *classes* of subsystems

sensor networks
signalling networks
gene networks
transport networks
metabolic networks
…



Bio-chemical networks

Most biological systems can be described as a set of bio-chemical reactions, to be intended as a modelling language.
(warning: not suited for systems involving large protein complexes)



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gene —>$_{kp}$ gene + mrna

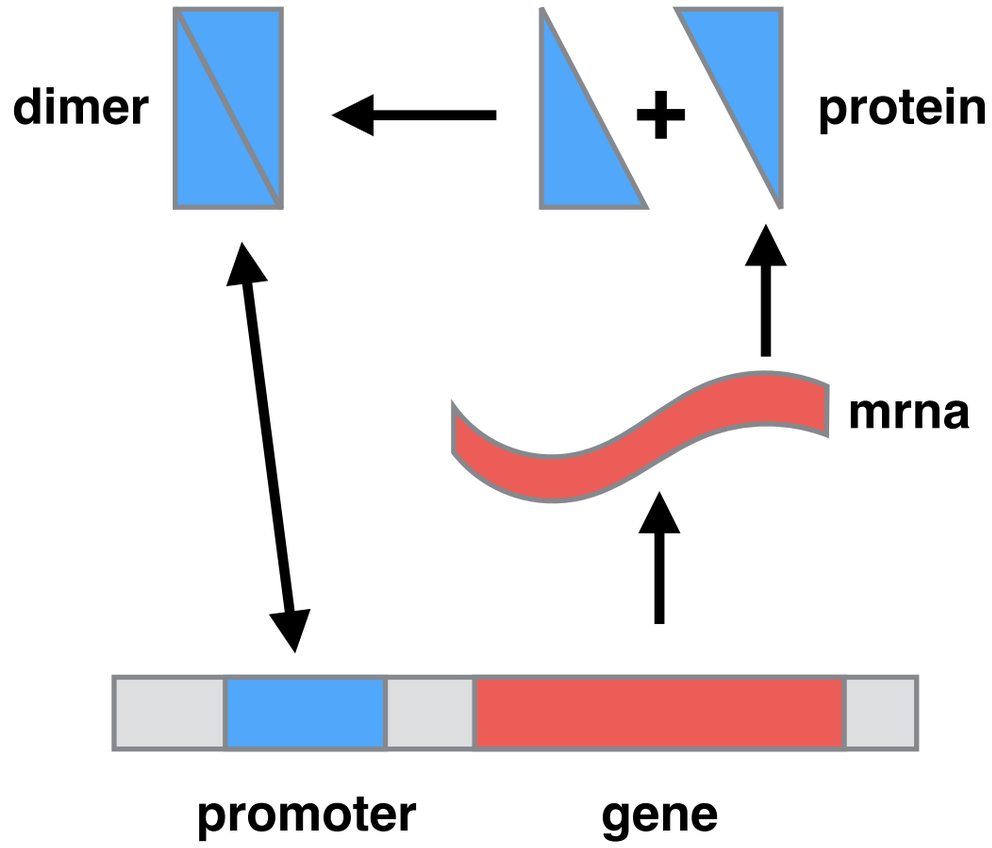
mrna —>$_{kt}$ mrna + protein

protein + protein —>$_{k1}$ dimer

dimer —>$_{k0}$ protein + protein

dimer + gene —>$_{kb}$ gene_repr

gene_repr —>$_{ku}$ dimer + gene



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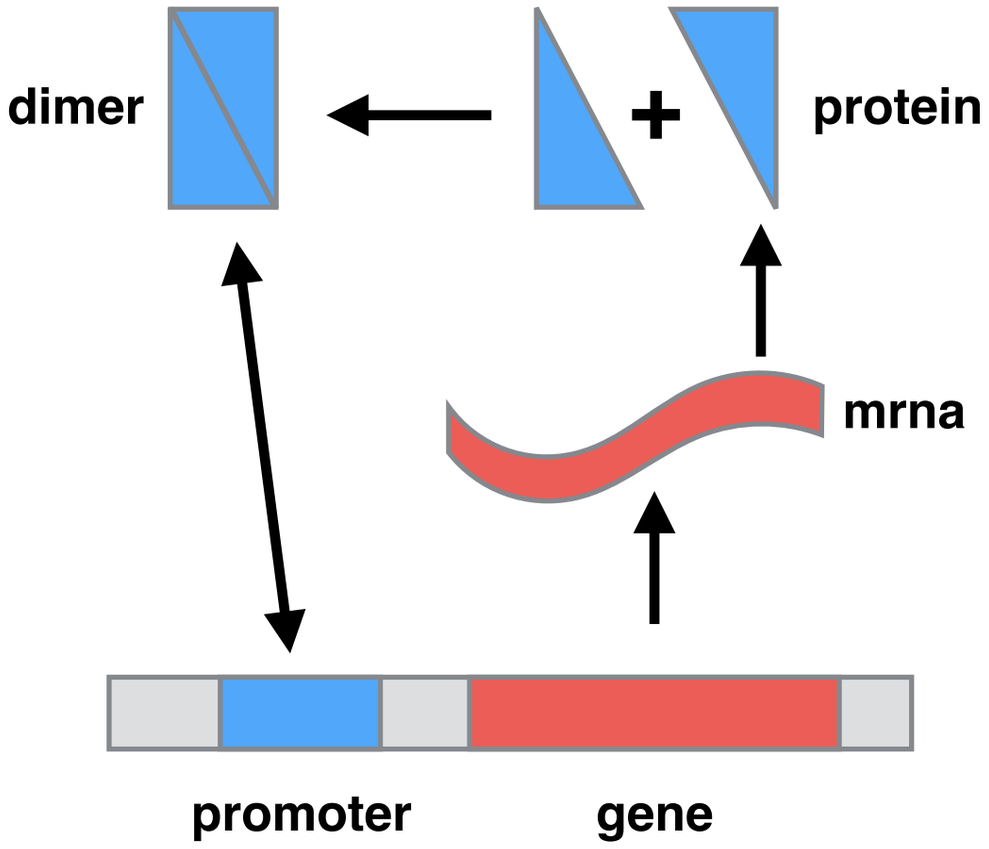

We are typically interested in the dynamic behaviour.
Kinetic constants are crucial for this, but are hard to measure or infer.

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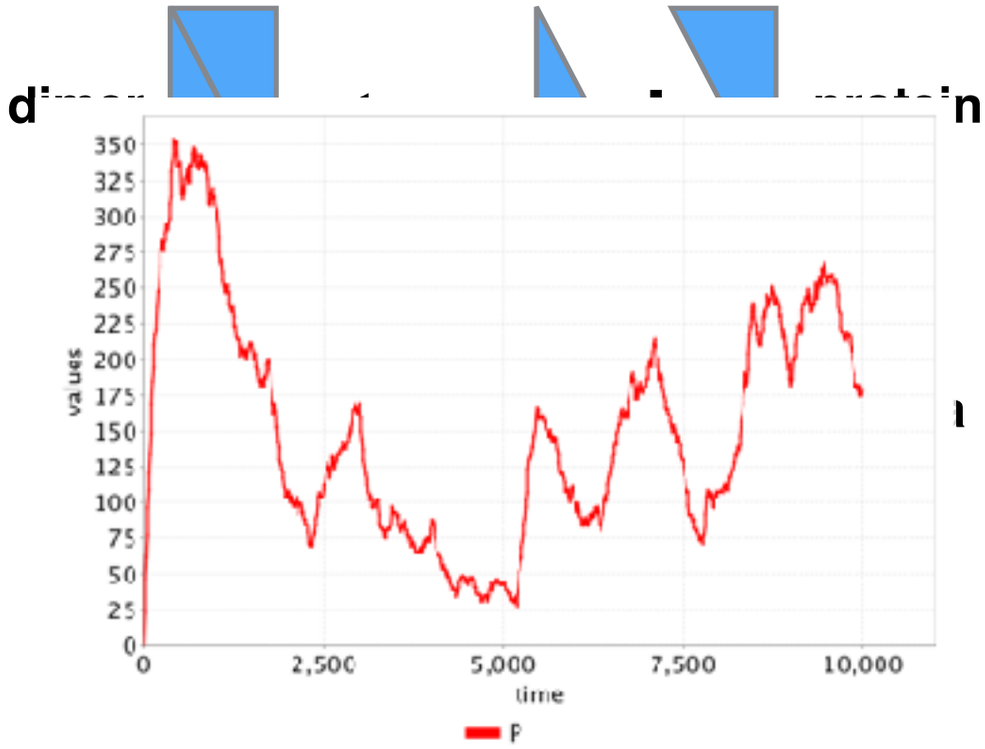

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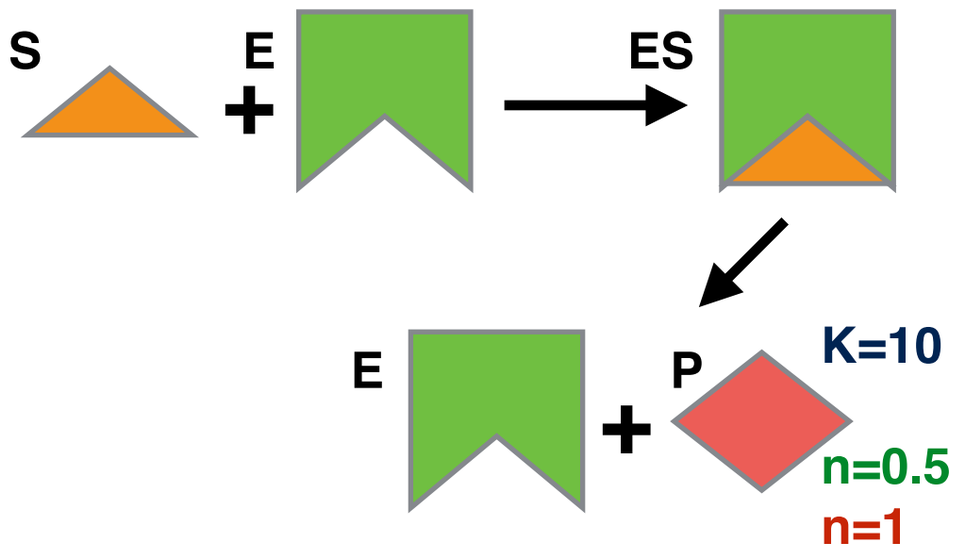
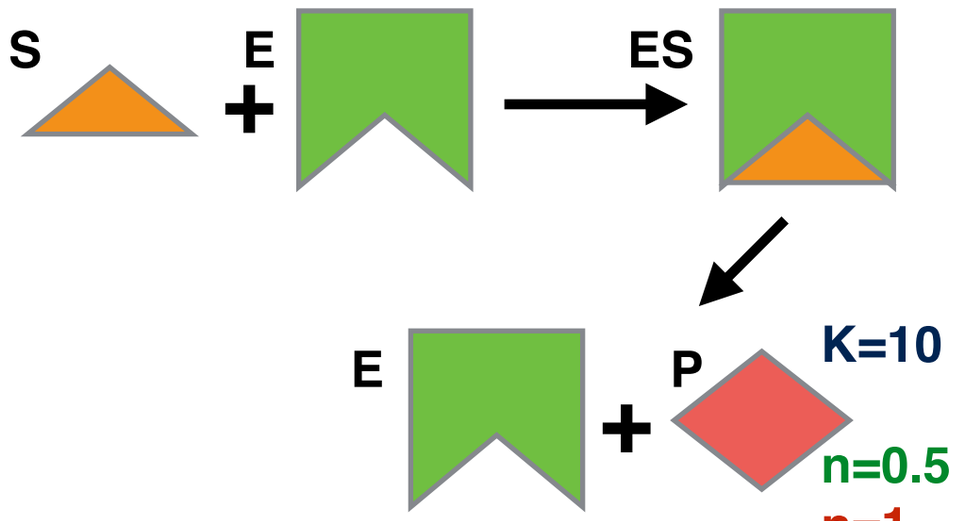
Dynamic Modelling



$$S + E \underset{k0}{\overset{k1}{\leftrightarrow}} ES$$

$$ES \xrightarrow{k} P + E$$

Dynamic Modelling



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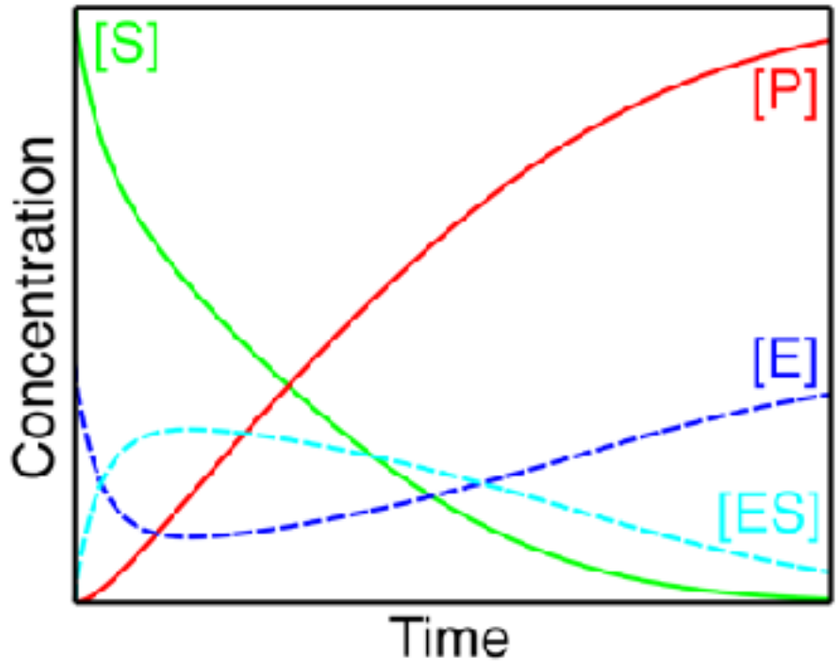

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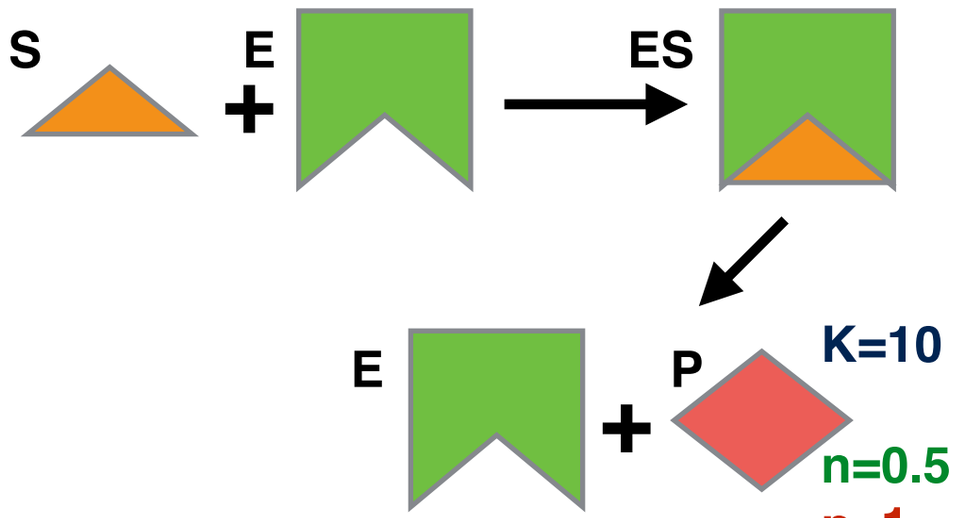

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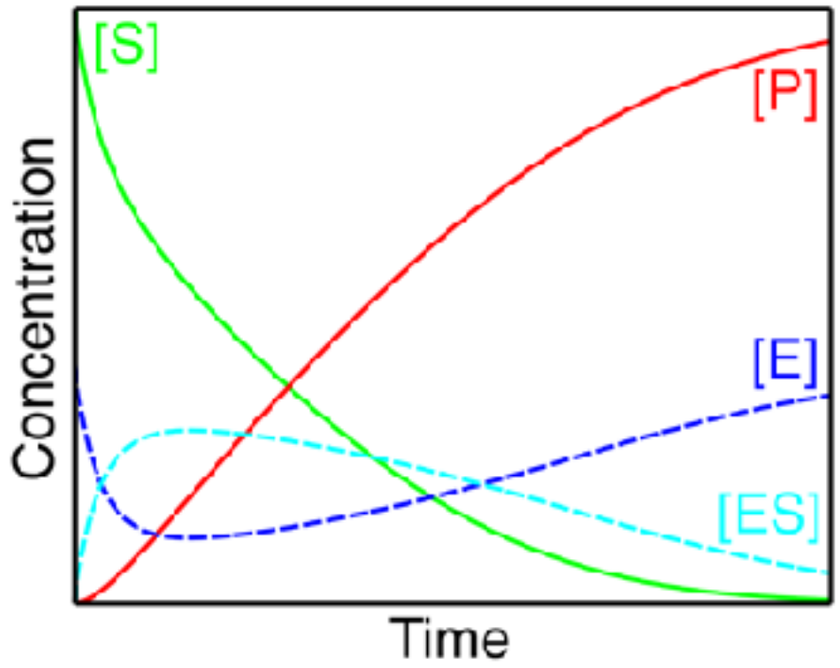

Under time-scale separation, we can assume d[ES]/dt = 0, getting the classic Michaelis Menten kinetics:

$$d[P]/dt = V_{max}\,[S]/(K + [S])$$

Cooperation/competition between enzyme and substrate results in the Hill kinetics:

$$d[P]/dt = V_{max}\,[S]^n/(K^n + [S]^n)$$

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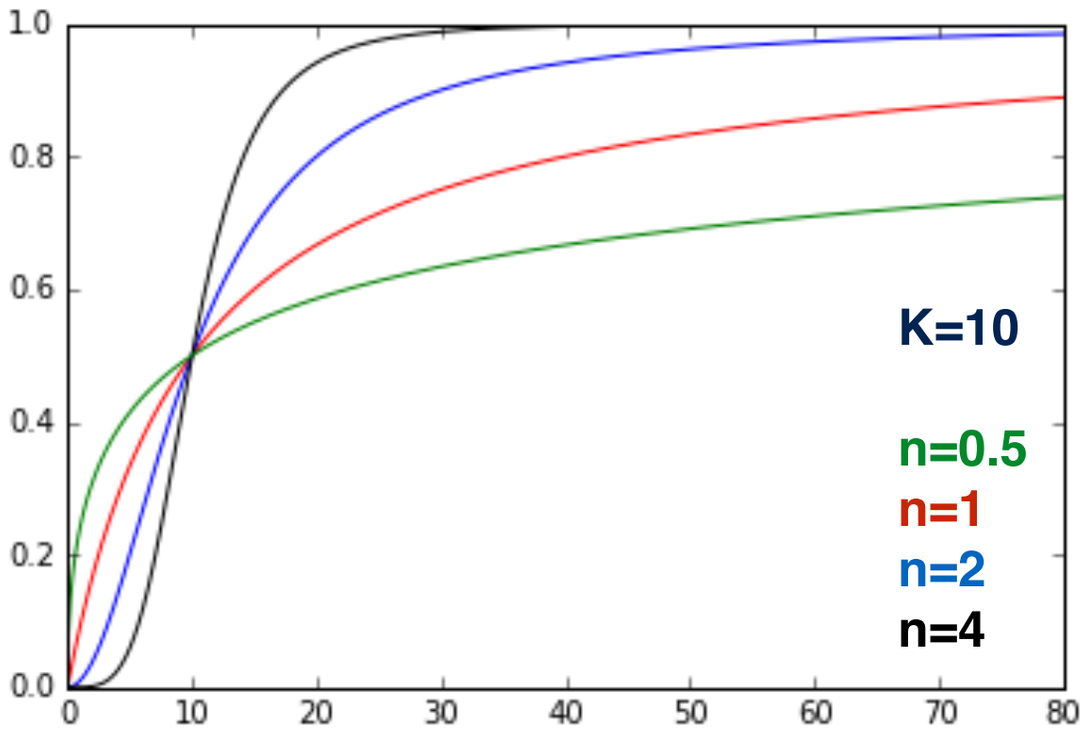

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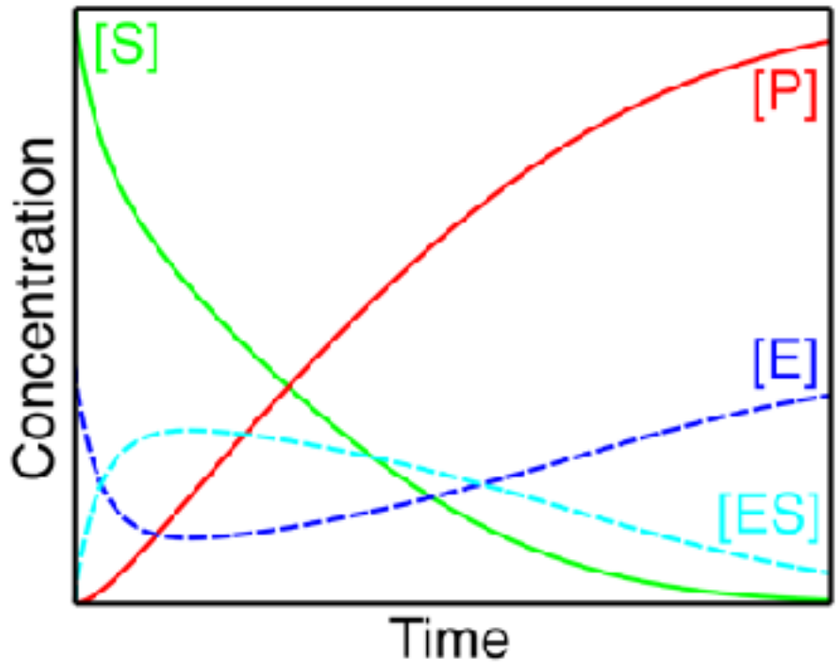

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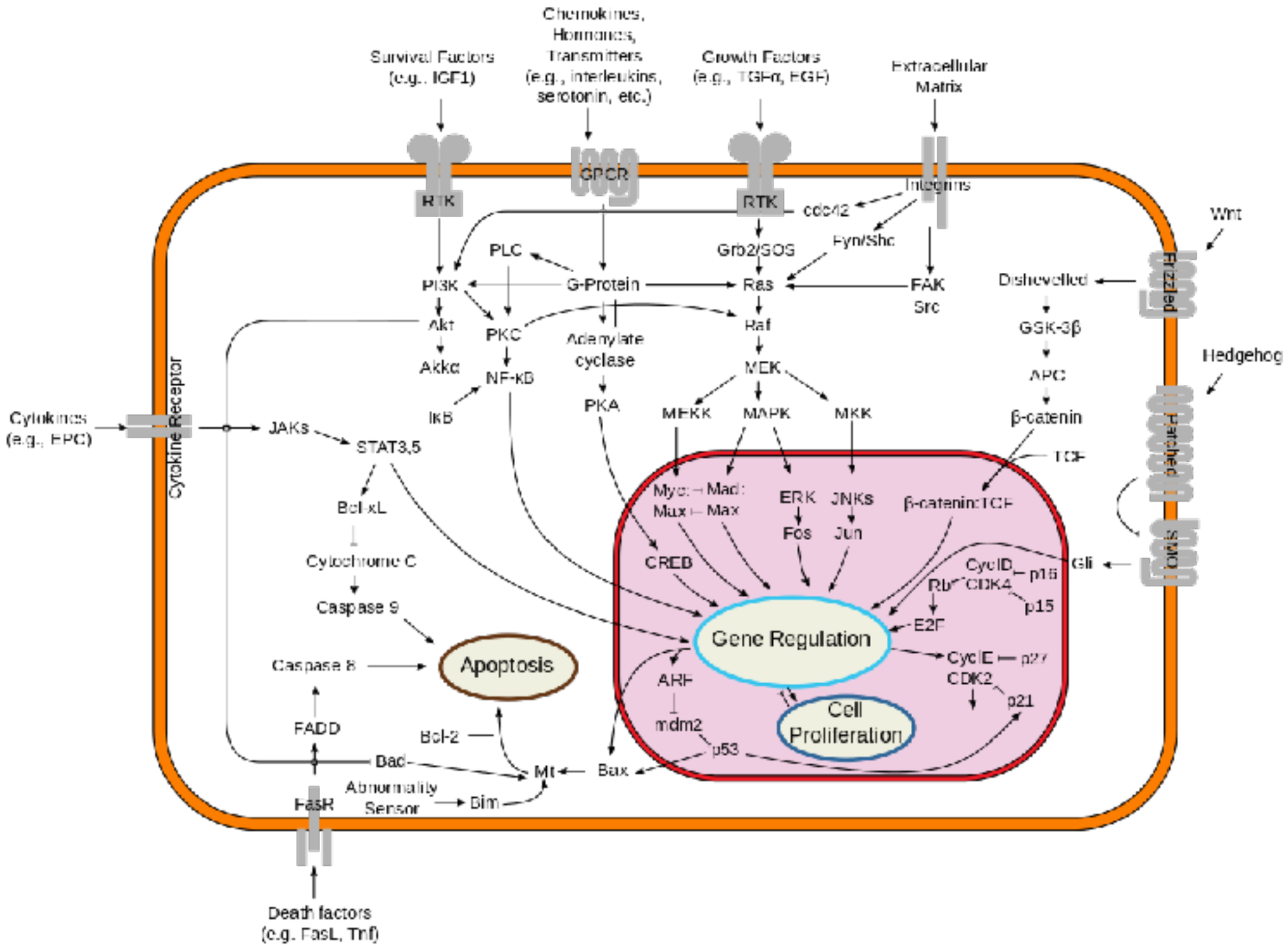
Signal transduction networks



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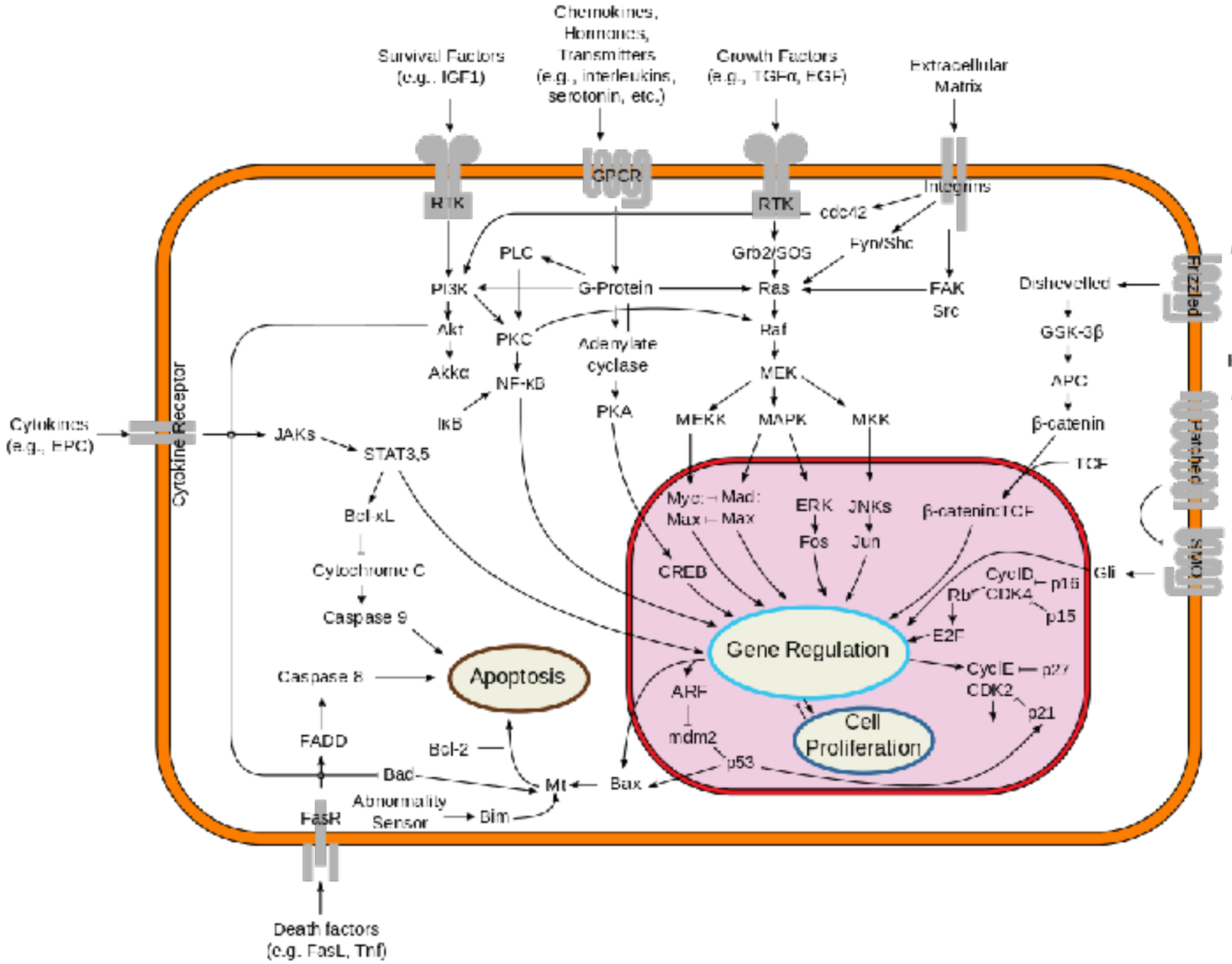


Response to external stimuli

Crucial in many diseases, including cancer

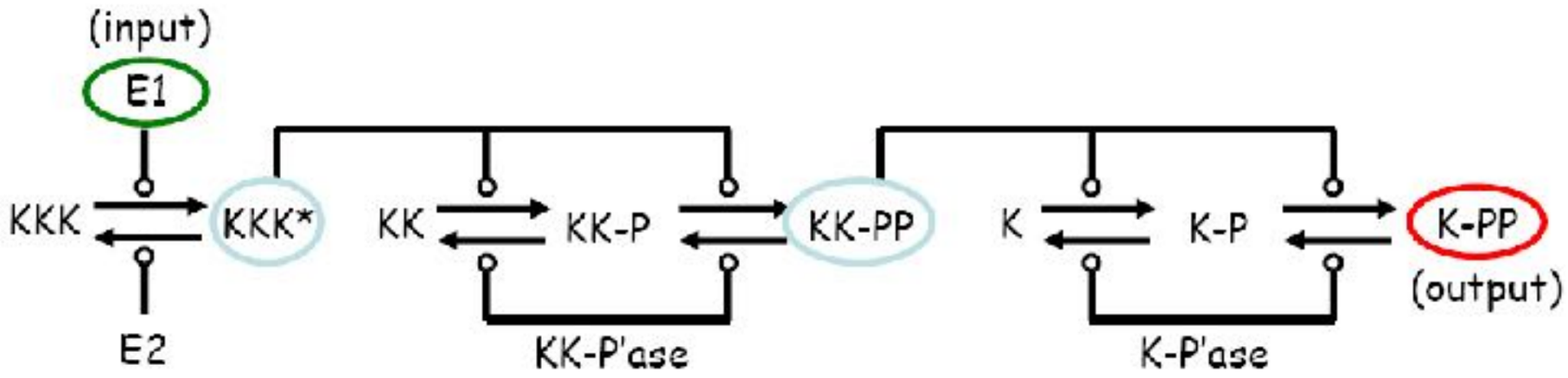
…

Signal transduction networks

Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 10078–10083, September 1996
Biochemistry

Ultrasensitivity in the mitogen-activated protein kinase cascade

CHI-YING F. HUANG AND JAMES E. FERRELL, JR.†



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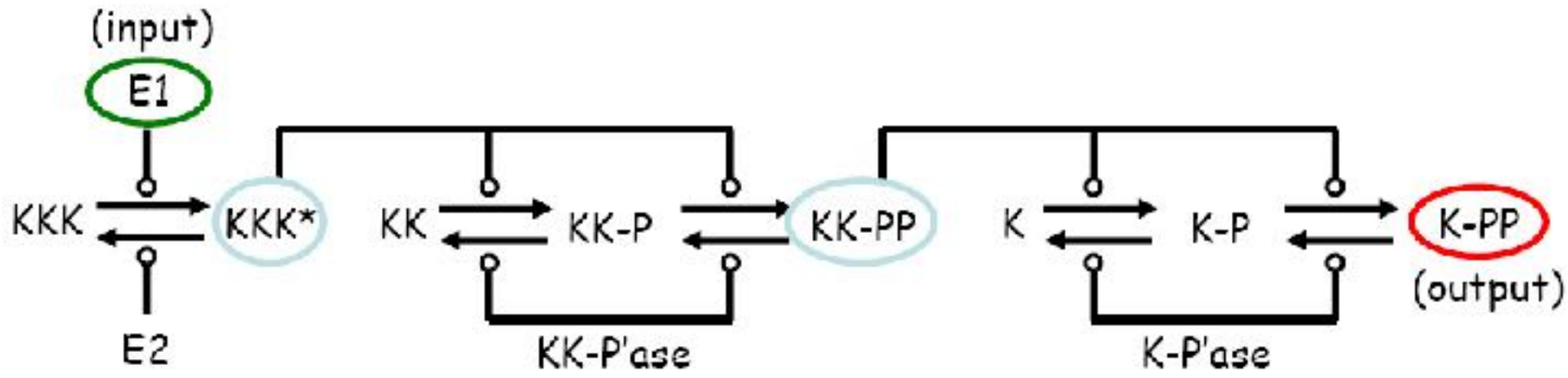
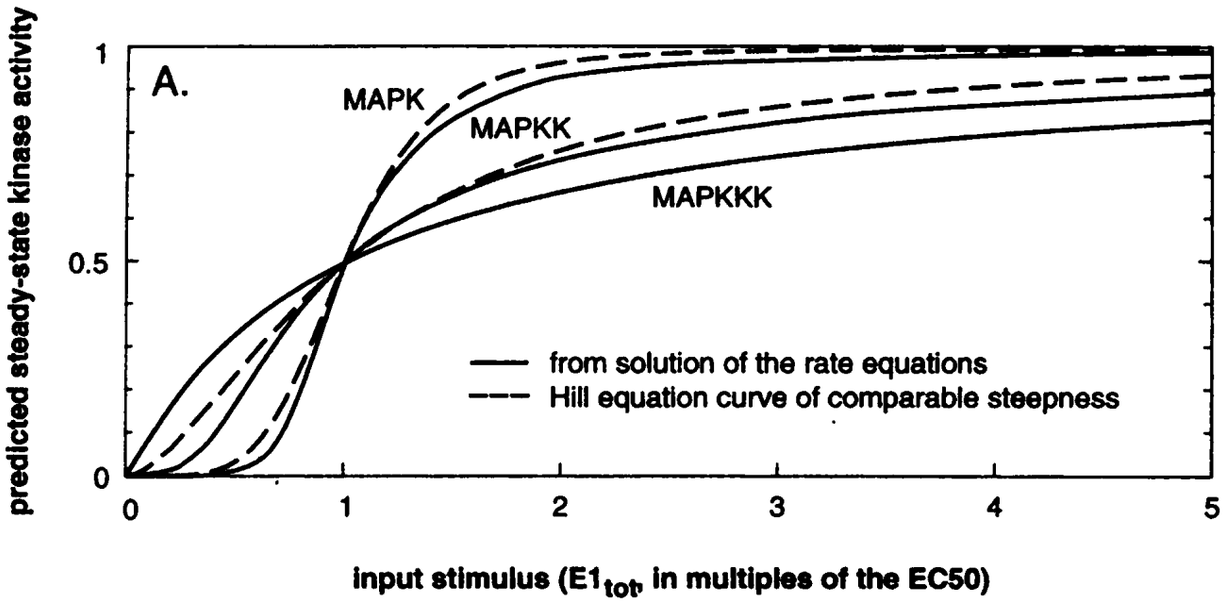




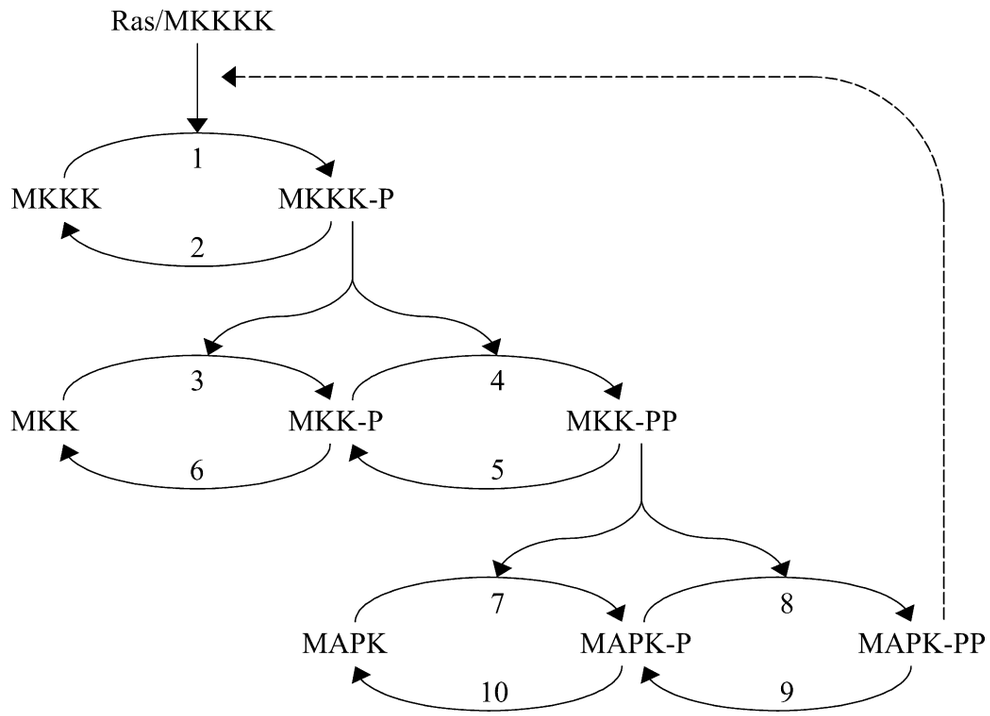
The activation cascade
gives MAPK
an ultra-sensitive response
to variations in input

Signal transduction networks

Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades

Boris N. Kholodenko

Department of Pathology, Anatomy and Cell Biology, Thomas Jefferson University, Philadelphia, PA, USA



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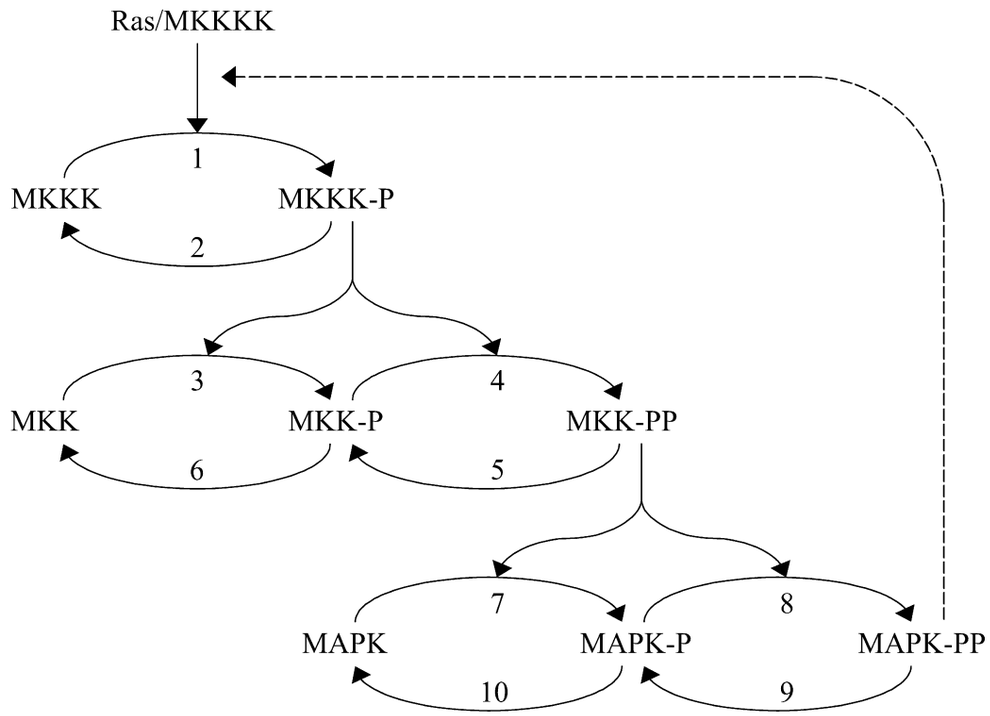

Table 1. Kinetic equations comprising the computational model of the MAPK cascade.

$d[MKKK]/dt = v_2 - v_1$
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$d[MKK]/dt = v_6 - v_3$
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$d[MKK\text{-}PP]/dt = v_4 - v_5$
$d[MAPK]/dt = v_{10} - v_7$
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Moiety conservation relations:

$[MKKK]_{total} = [MKKK] + [MKKK\text{-}P]$
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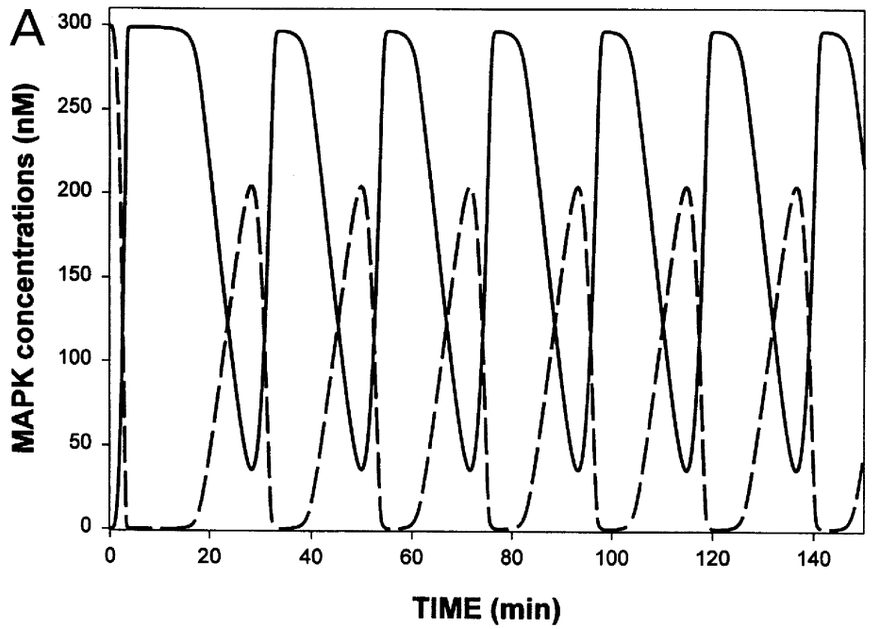

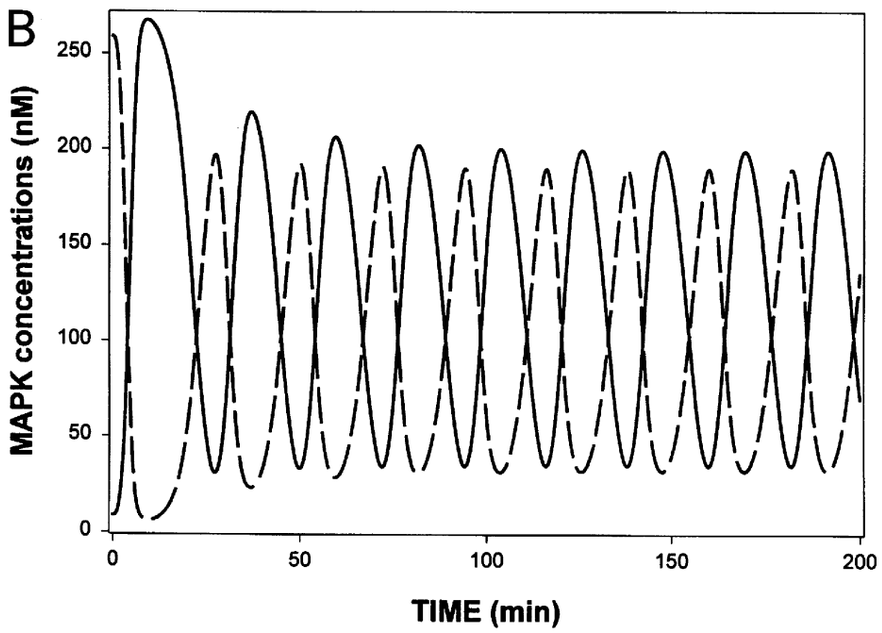

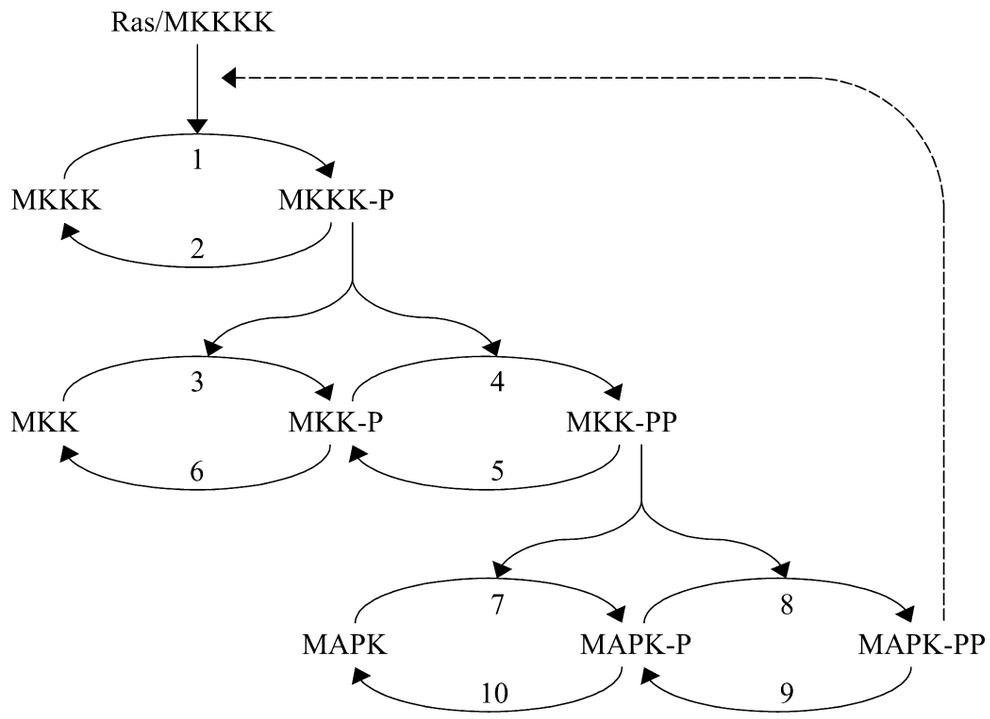

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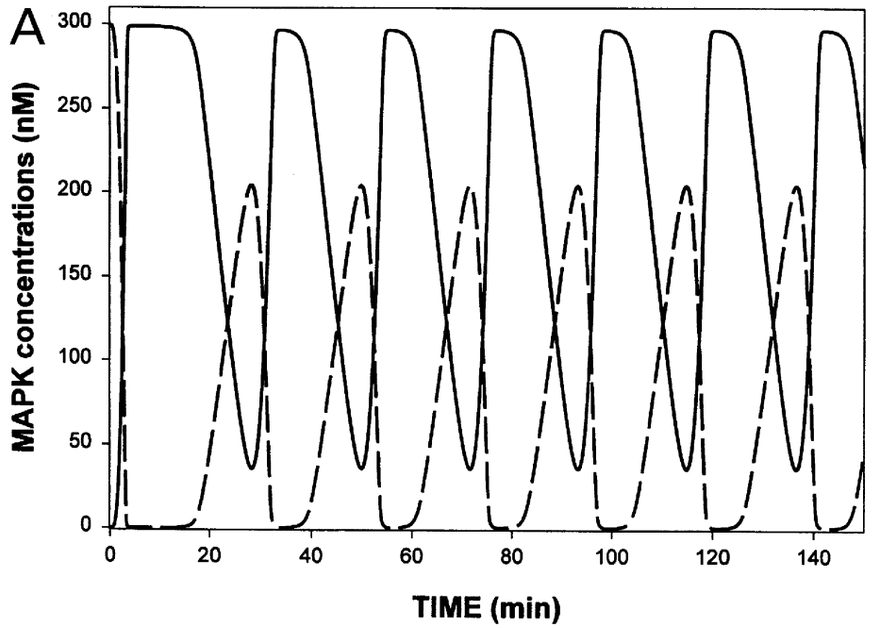

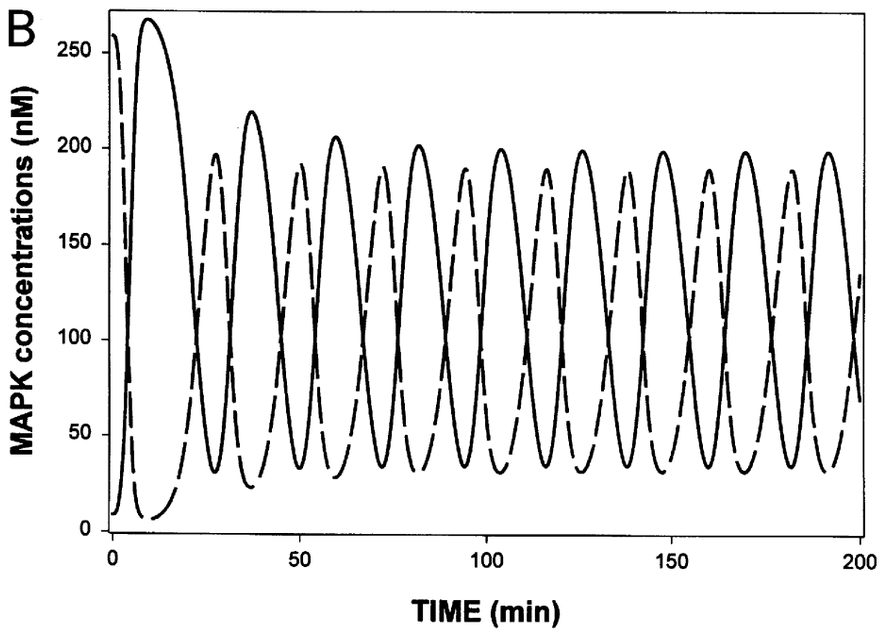

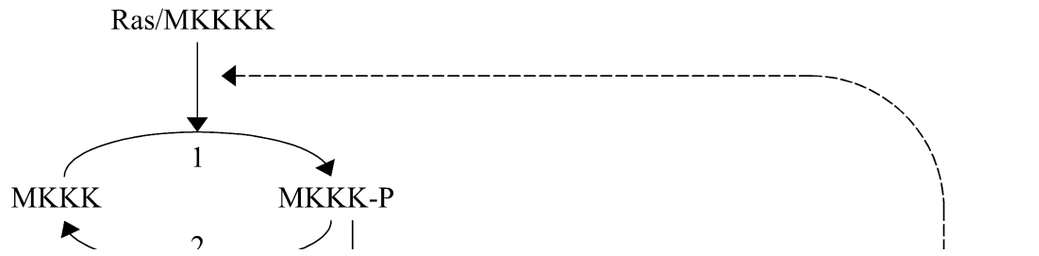

Reaction number	Rate equation	Parameter values
1	$V_1 \cdot [MKKK]/((1 + ([MAPK\text{-}PP]/K_i)^n) \cdot (K_1 + [MKKK]))$	$V_1 = 2.5$; $n = 1$; $K_i = 9$; $K_1 = 10$;
2	$V_2 \cdot [MKKK\text{-}P]/(K_2 + [MKKK\text{-}P])$	$V_2 = 0.25$; $K_2 = 8$;
3	$k_3 \cdot [MKKK\text{-}P] \cdot [MKK]/(K_3 + [MKK])$	$k_3 = 0.025$; $K_3 = 15$;
4	$k_4 \cdot [MKKK\text{-}P] \cdot [MKK\text{-}P]/(K_4 + [MKK\text{-}P])$	$k_4 = 0.025$; $K_4 = 15$;
5	$V_5 \cdot [MKK\text{-}PP]/(K_5 + [MKK\text{-}PP])$	$V_5 = 0.75$; $K_5 = 15$;
6	$V_6 \cdot [MKK\text{-}P]/(K_6 + [MKK\text{-}P])$	$V_6 = 0.75$; $K_6 = 15$;
7	$k_7 \cdot [MKK\text{-}PP] \cdot [MAPK]/(K_7 + [MAPK])$	$k_7 = 0.025$; $K_7 = 15$;
8	$k_8 \cdot [MKK\text{-}PP] \cdot [MAPK\text{-}P]/(K_8 + [MAPK\text{-}P])$	$k_8 = 0.025$; $K_8 = 15$;
9	$V_9 \cdot [MAPK\text{-}PP]/(K_9 + [MAPK\text{-}PP])$	$V_9 = 0.5$; $K_9 = 15$;
10	$V_{10} \cdot [MAPK\text{-}P]/(K_{10} + [MAPK\text{-}P])$	$V_{10} = 0.5$; $K_{10} = 15$;

Total concentrations: $[MKKK]_{total} = 100$; $[MKK]_{total} = 300$; $[MAPK]_{total} = 300$

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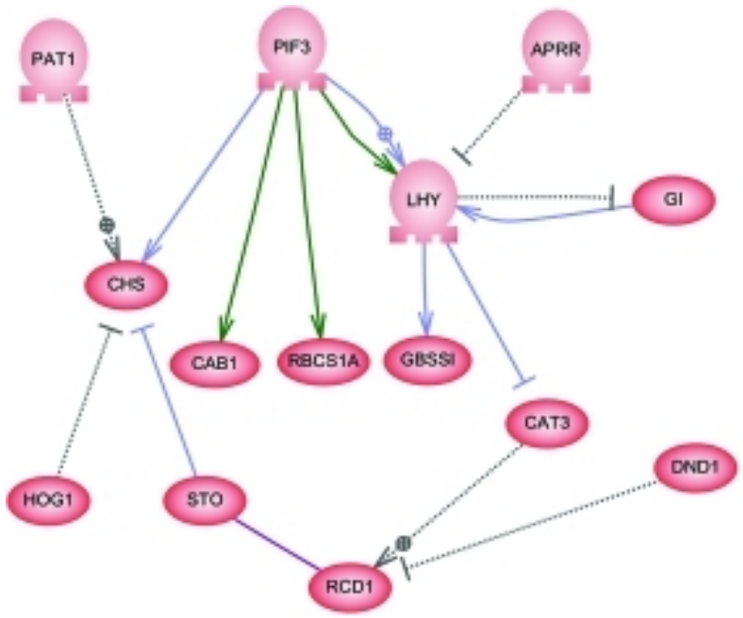
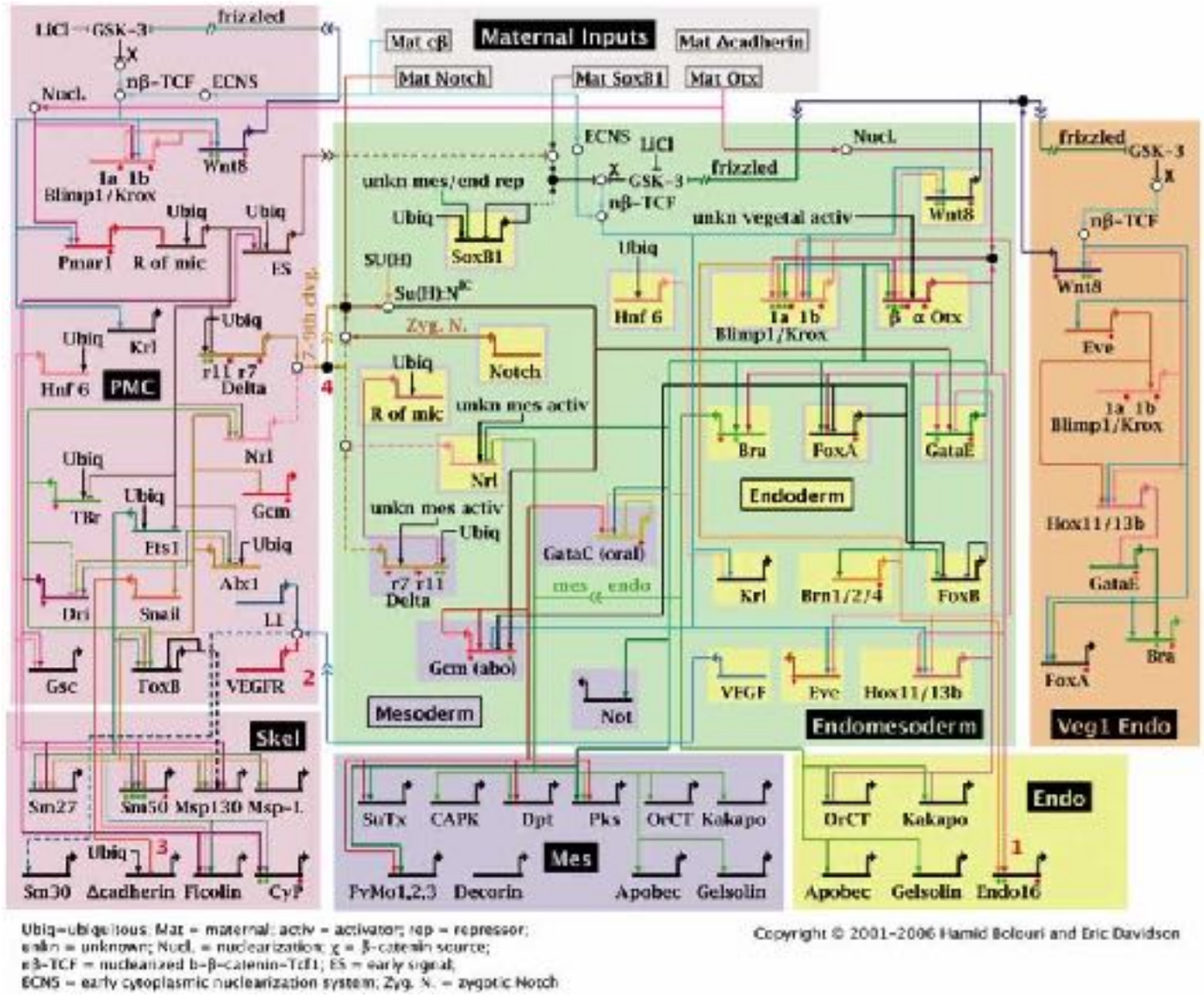
Genetic Networks

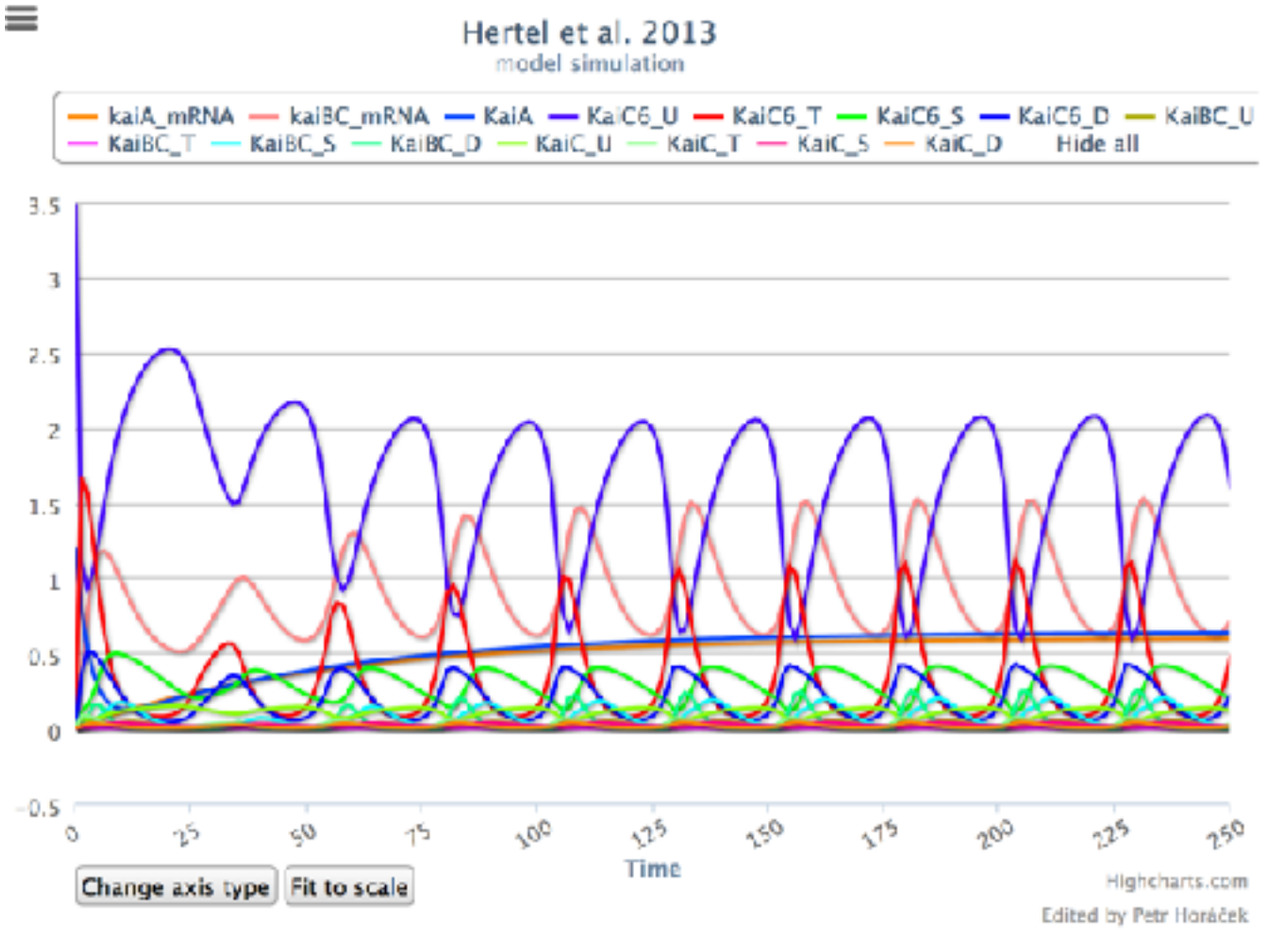


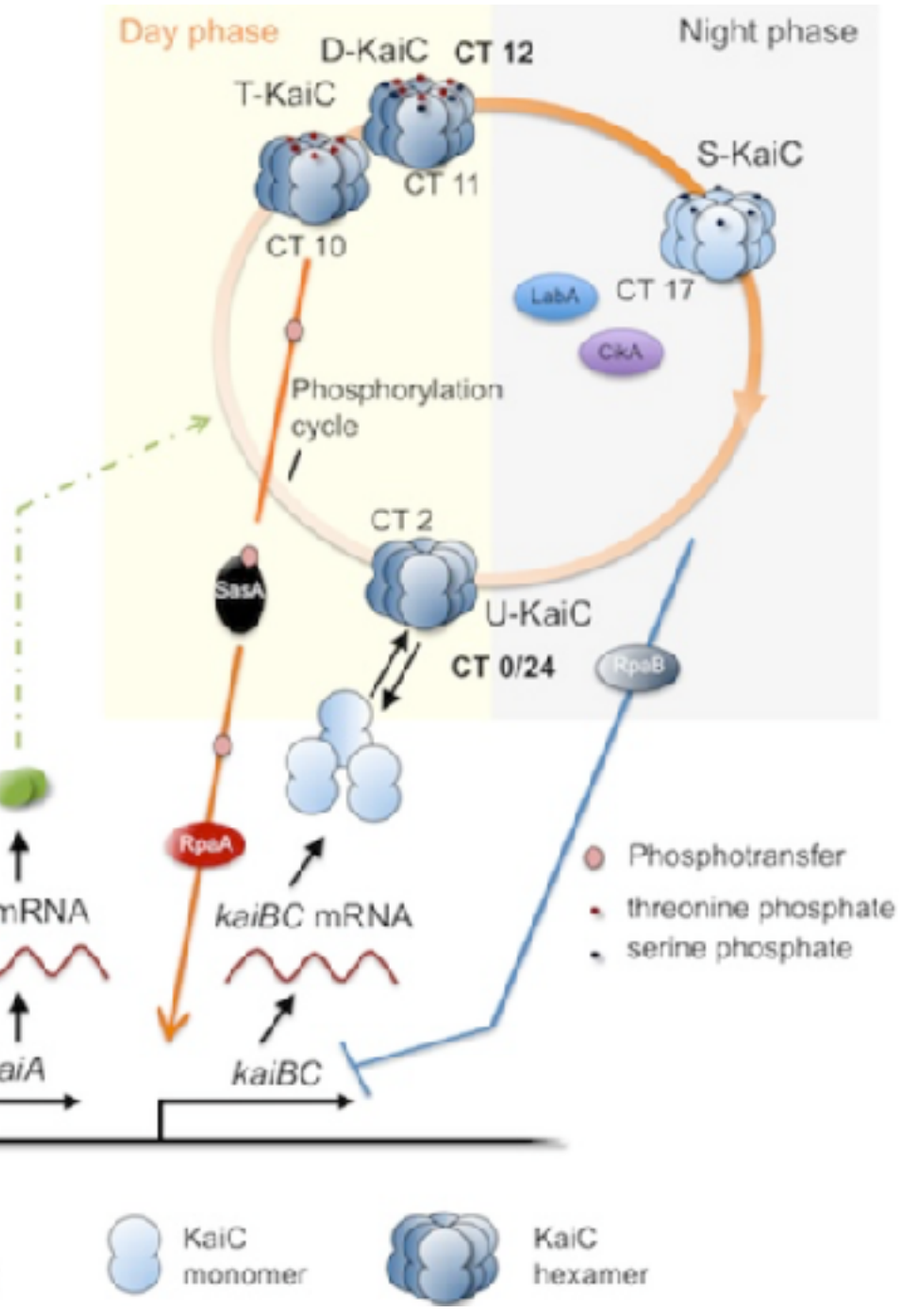


Genetic regulatory networks describe the complex regulation of gene expression, which is the “software of life”

Genetic Networks

A typical example of genetic regulatory network is the circadian clock (here in cyanobacteria, peculiar), an oscillatory module regulated by alternation of light and dark.





Revealing a Two-Loop Transcriptional Feedback Mechanism in the Cyanobacterial Circadian Clock

Stefanie Hertel, Christian Brettschneider, Ilka M. Axmann

Published: March 14, 2013 • http://dx.doi.org/10.1371/journal.pcbi.1002966

A Noisy Life

A Noisy Life

Stochastic Gene Expression in a Single Cell
Michael B. Elowitz, *et al.*
Science **297**, 1183 (2002);
DOI: 10.1126/science.107(

Molecular interactions and gene expression in single cells are **random events**, the fewer the molecules involved, the more the effect of **noise**.
Models have to account for this.

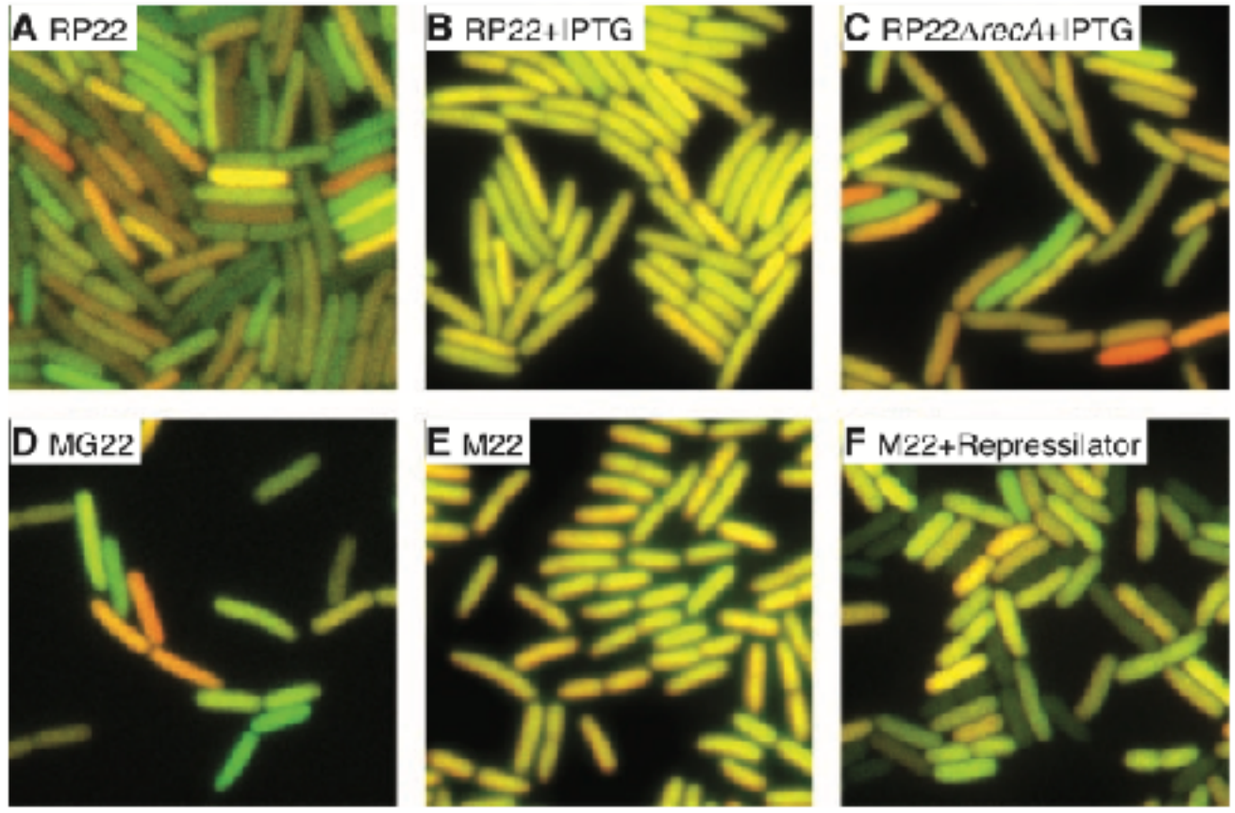


Fig. 2. Noise in *E. coli*. CFP and YFP fluorescence images were combined in the green and red channels, respectively. (**A**) In strain RP22, with promoters repressed by the wild-type *lacI* gene, red and green indicate significant amounts of intrinsic noise. (**B**) RP22 grown in the presence of lac inducer, 2 mM IPTG. Both fluorescent proteins are expressed at higher levels and the cells exhibit less noise. (**C**) As in (B), except the *recA* gene has been deleted, increasing intrinsic noise. (**D**) Another wild-type strain, MG22, shows noise characteristics similar to those of RP22. (**E**) Expression levels and noise in unrepressed *lacI*$^-$ strain M22 are similar to those in *lacI*$^+$ strains induced with IPTG (B). (**F**) M22 cells regulated by the Repressilator (*16*), an oscillatory network that amplifies intrinsic noise.

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What are the **sources of noise** in cells?

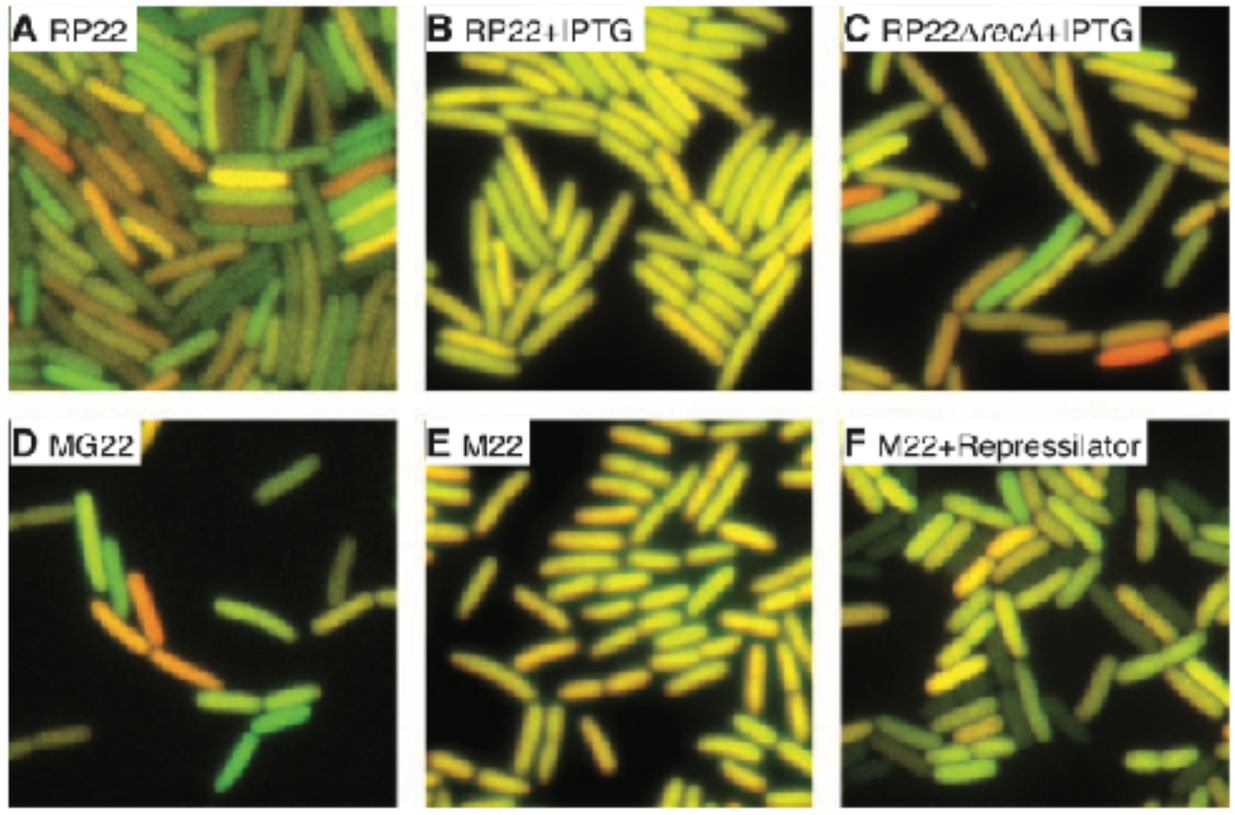

Fig. 2. Noise in *E. coli*. CFP and YFP fluorescence images were combined in the green and red channels, respectively. **(A)** In strain RP22, with promoters repressed by the wild-type *lacI* gene, red and green indicate significant amounts of intrinsic noise. **(B)** RP22 grown in the presence of lac inducer, 2 mM IPTG. Both fluorescent proteins are expressed at higher levels and the cells exhibit less noise. **(C)** As in (B), except the *recA* gene has been deleted, increasing intrinsic noise. **(D)** Another wild-type strain, MG22, shows noise characteristics similar to those of RP22. **(E)** Expression levels and noise in unrepressed *lacI*⁻ strain M22 are similar to those in *lacI*⁻ strains induced with IPTG (B). (F) M22 cells regulated by the Repressilator (*16*), an oscillatory network that amplifies intrinsic noise.

Intrinsic and extrinsic contributions to stochasticity in gene expression

Peter S. Swain*†‖, Michael B. Elowitz*§, and Eric D. Siggia*

Is Noise Always Detrimental?

What is **the role of noise** in cells?
Is it a nuisance to cope with, or it
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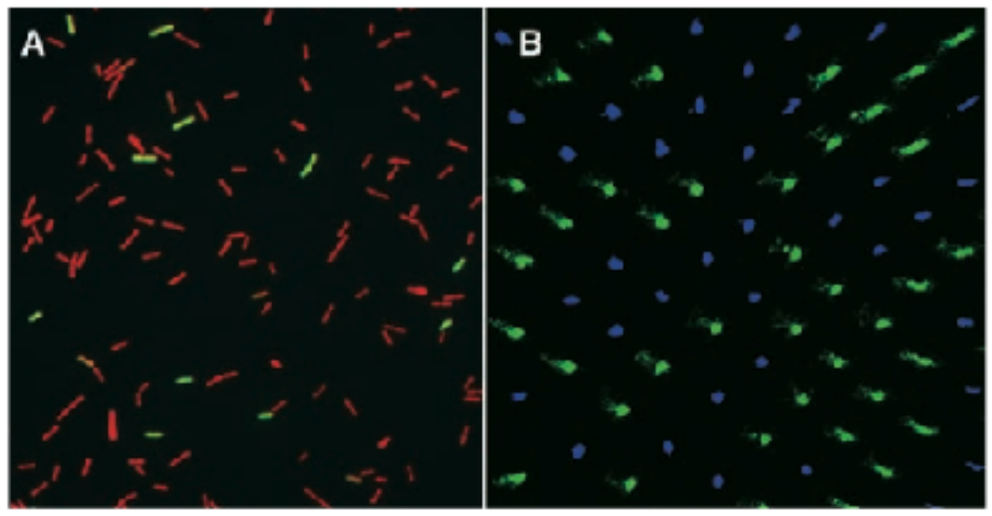

Fig. 1. Stochastic distribution of cell fates in bacteria and in insect photoreceptors. (**A**) Fluorescence micrograph of *B. subtilis* cells containing the coding sequence for GFP fused to the promoter for a gene under the control of the competence regulator ComK. The cells were visualized with a red stain; the green fluorescence reveals the subpopulation of cells that are ON for ComK. The cells are 1 to 2 μm in length. (**B**) Photograph of a whole adult *Drosophila* retina whose R8 photoreceptors were stained with antibodies to the green-sensitive photopigment Rh6 (green) and the blue-sensitive photopigment Rh5 (blue). The horizontal distance between photoreceptors is about 10 μm.

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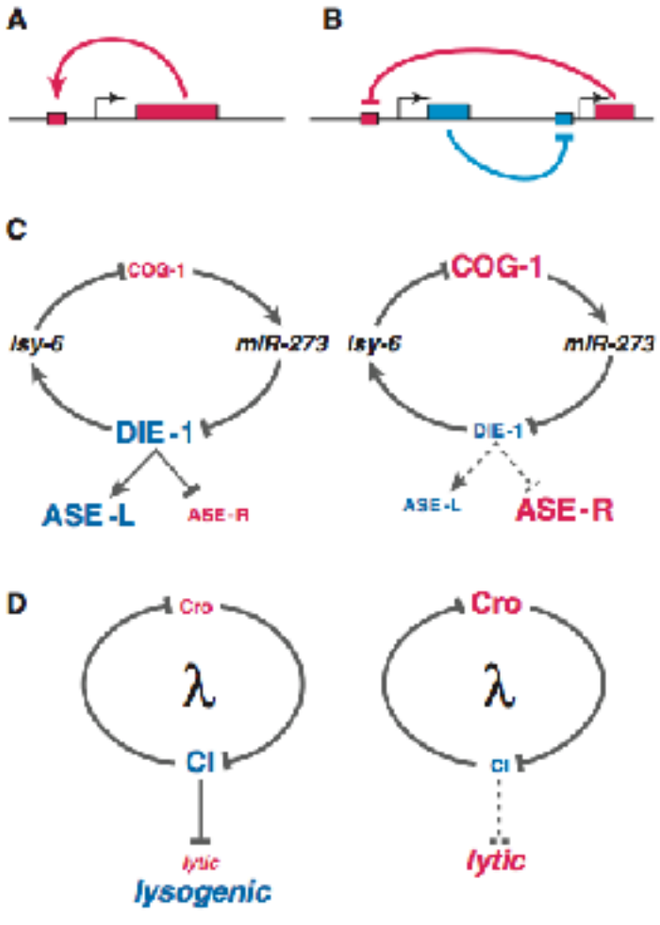

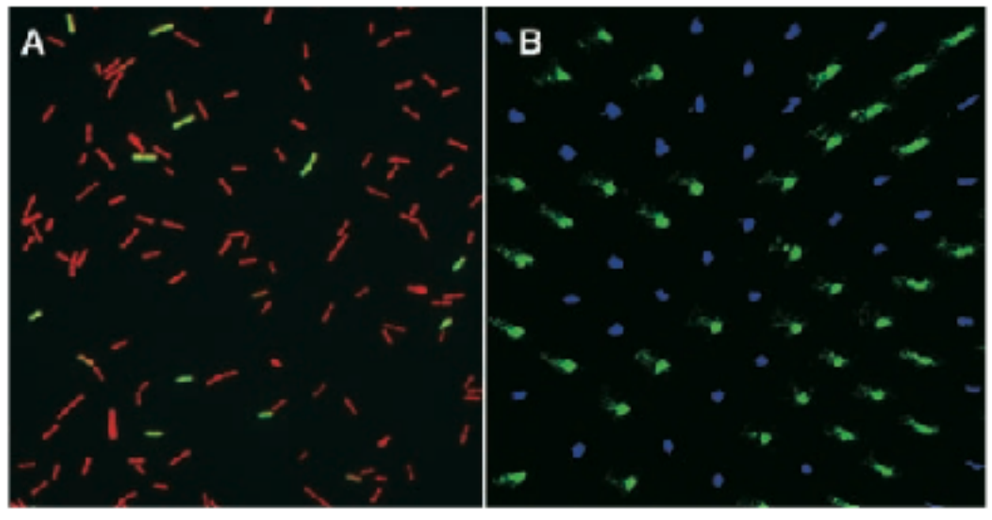

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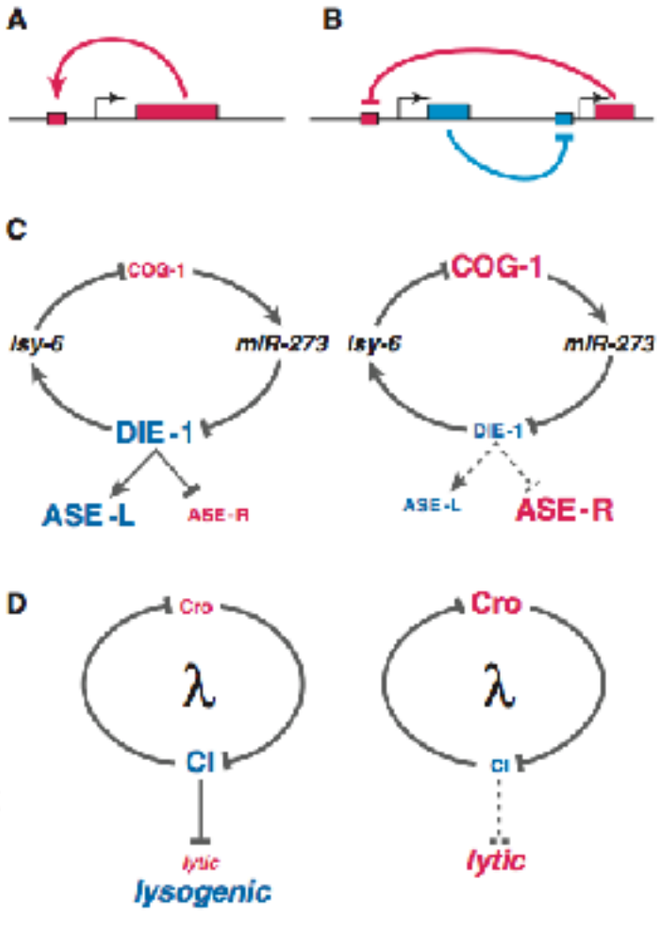

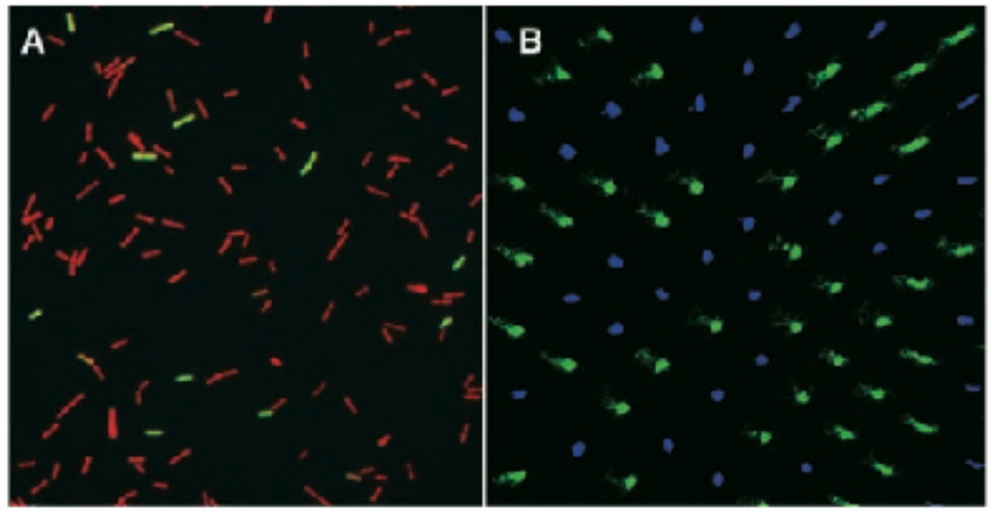

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Molecular Systems Biology 5: Article number 326; doi:10
Citation: *Molecular Systems Biology* 5:326

REVIEW

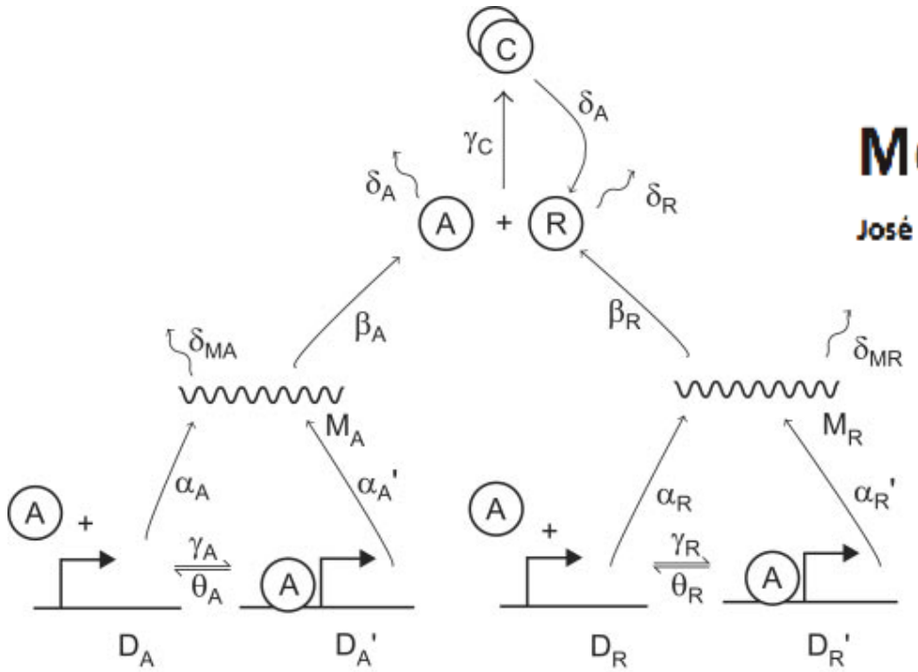
Strategies for cellular decision-making

Theodore J Perkins[1] **and Peter S Swain**[2,*]

extracellular envir

Noise-induced oscillations

Noise-induced oscillations



Mechanisms of noise-resistance in genetic oscillators

José M. G. Vilar*†, Hao Yuan Kueh*, Naama Barkai‡, and Stanislas Leibler*†§

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dA/dt &= \beta_A M_A + \theta_A D'_A + \theta_R D'_R \\
&\quad - A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A) \\
dM_R/dt &= \alpha'_R D'_R + \alpha_R D_R - \delta_{M_R} M_R \\
dR/dt &= \beta_R M_R - \gamma_C A R + \delta_A C - \delta_R R \\
dC/dt &= \gamma_C A R - \delta_A C,
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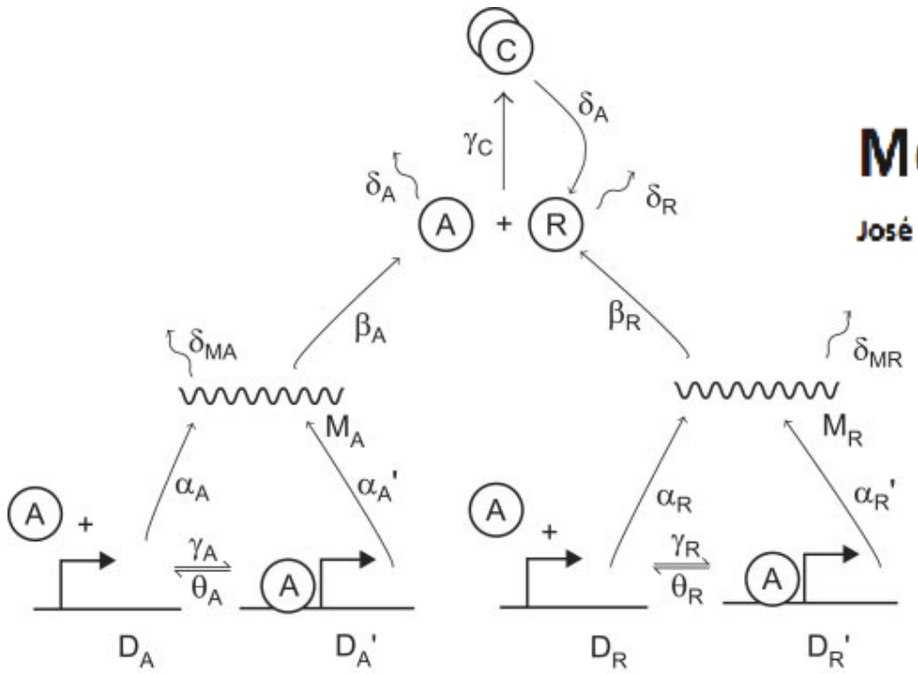
Noise-induced oscillations



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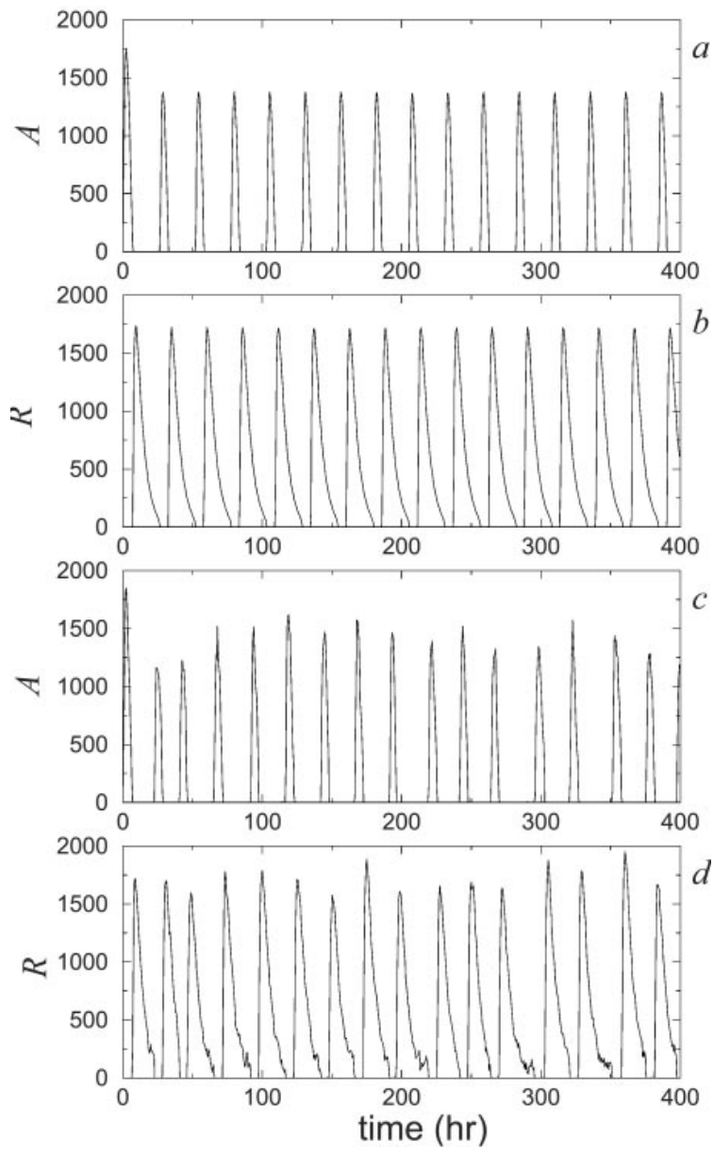

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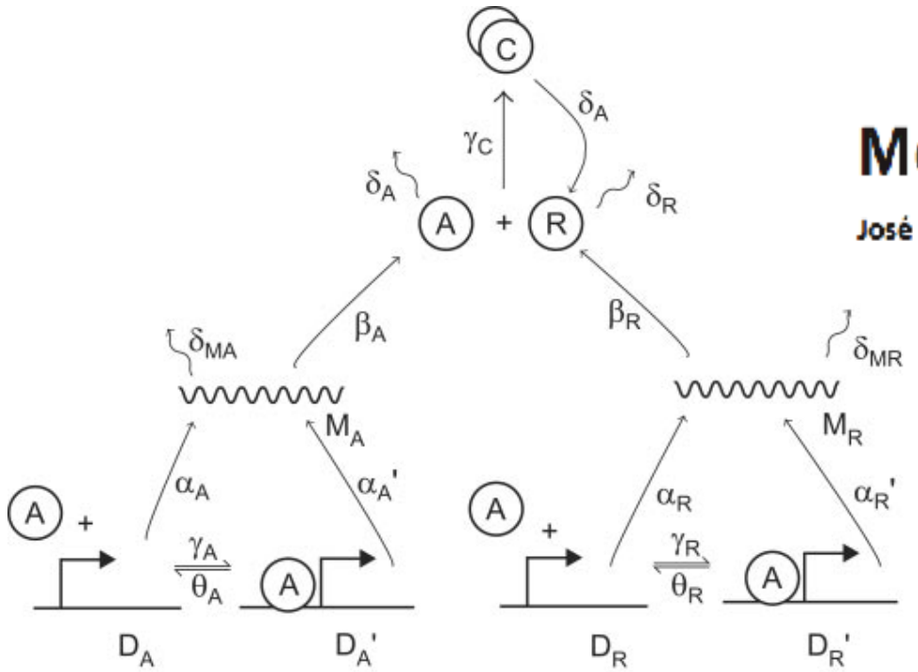

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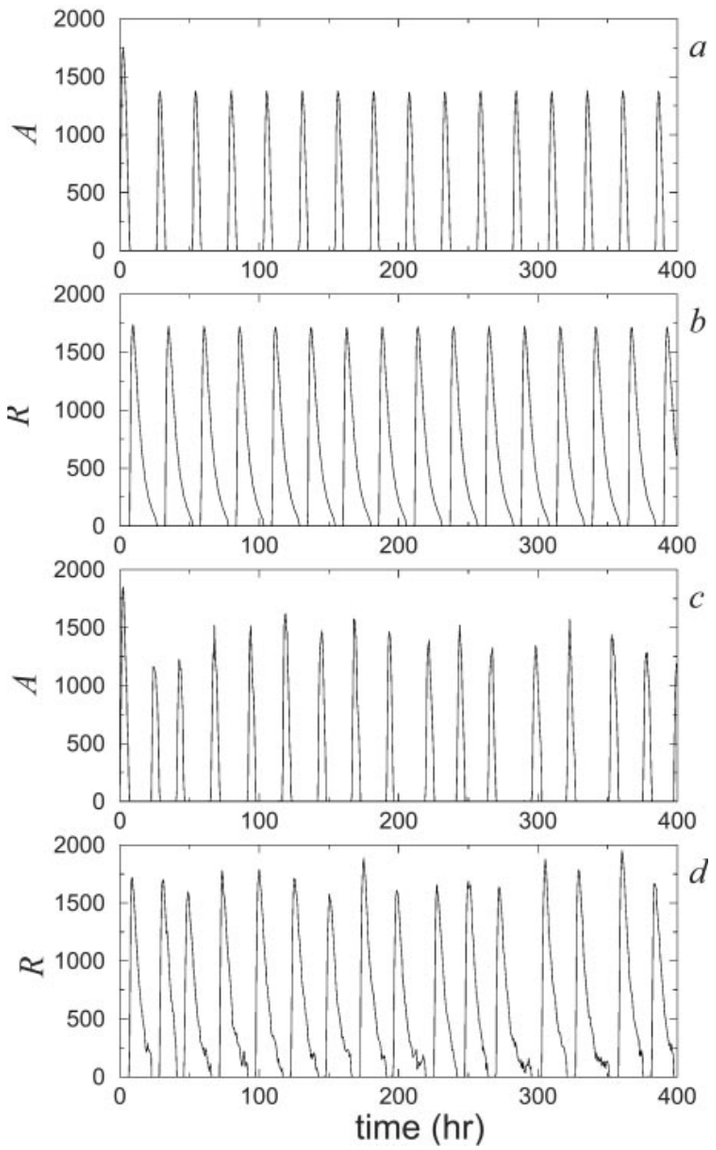

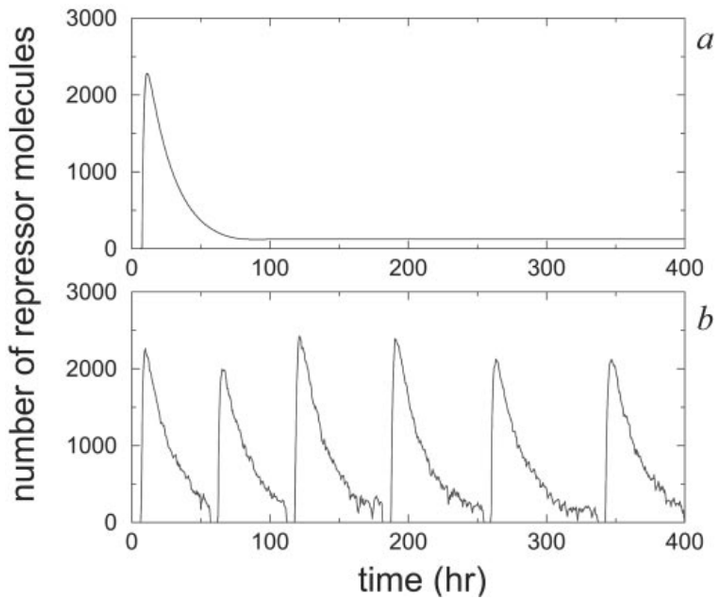

Noise can have a stabilising effect:
it makes oscillations persistent
near critical points.

Stochastic Modelling

Chemical Reaction Networks can be modelled as **Markov Population Processes**. Variables count the amount of molecules per each species. Update vectors are defined by reactions. Rates depend on the total population (mass action, Hill).

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gene $\xrightarrow{k_p}$ gene + mrna

mrna $\xrightarrow{k_t}$ mrna + protein

protein + protein $\xrightarrow{k_1}$ dimer

dimer $\xrightarrow{k_0}$ protein + protein

dimer + gene $\xrightarrow{k_b}$ gene_repr

gene_repr $\xrightarrow{k_u}$ dimer + gene

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protein + protein —>$_{k1}$ dimer

dimer —>$_{k0}$ protein + protein

dimer + gene —>$_{kb}$ gene_repr

gene_repr —>$_{ku}$ dimer + gene

Counting variables:

x_{gene}, x_{gene_repr}, x_{mrna}, $x_{protein}$, x_{dimer}

Propensity of a reaction (expected frequency) follows the mass action law:

$a_1(\mathbf{x}) = k_p\, x_{gene}$; $a_5(\mathbf{x}) = k_b\, x_{dimer}\, x_{gene}$;

$a_3(\mathbf{x}) = k_1\, x_{protein}\, (x_{protein} - 1)/2$;

Update of a reaction: net variation of each species

$\mathbf{v_1} = (0,0,1,0,0)$, $\mathbf{v_3} = (0,0,0,-2,1)$, $\mathbf{v_5} = (-1,1,0,0,-1)$

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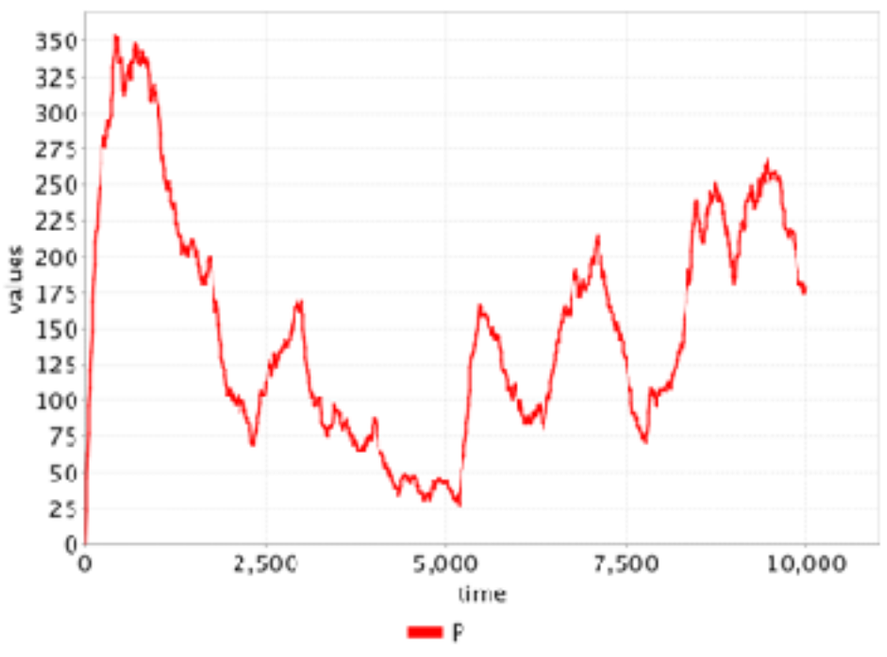

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Typical rate functions

- **Mass Action**: rate proportional to concentration/ numbers. The only one having a physical interpretation.

- **Hill Kinetics**. Typically used for enzymatic reactions or to implicitly model gene expression.

Rates and Scaling

Biochemical reactions happen in a volume V. We can convert molecule numbers into concentrations (often micro or nano-molar) dividing by V.

Molecule numbers: variables X count the number of molecules. Updates are integers.
Concentrations: variable x are concentrations. Updates are multiple of 1/V.

How do rates change while passing from numbers to concentrations?

Example: dimerisation (P monomer, P_2 dimer)

Rates and Scaling

If we express the model in terms of concentrations, by multiplying rate and update vector of each transition and adding them up, we obtain the standard deterministic model of chemical kinetic, as a set of ODEs, the **reaction rate equations**.

Example: dimerisation.

Relation between stochastic and deterministic rate constants.

Example: gene networks

Self repressing gene module

Bistable switch

Example: gene networks

Repressilator

Feed Forward Loops

What about data?

Most of classic modelling approaches in systems biology (5-20 years ago) make a **limited use of data**, mostly because there was not much usable data available back then.

Kinetic rates were inferred from dedicated experiments (in vitro) and by exploration of biological literature to make educated guesses.
This is a painstakingly time consuming and error prone process, impossible for large models.

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With the data revolution we are living in, more and more experimental techniques are capable of producing data that is good to fit dynamic models.

Typically, one needs **time series data.**

Examples of such technologies are flow cytometry, RNAsec, imaging techniques…

Circadian Clock in O. Tauri

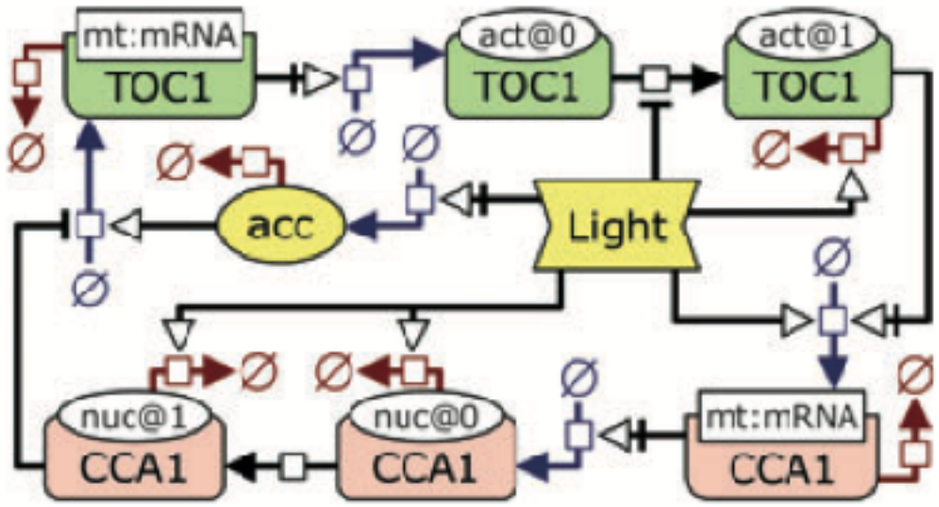
the plant journal

SEB Society for Experimental Biology

The Plant Journal (2011) **66**, 375–385

doi: 10.1111/j.1365-313X.2011.04489.x

Multiple light inputs to a simple clock circuit allow complex biological rhythms



ODE model with 7 variables/ species

Data: luciferase time series, both transcriptional (LUC attached to CCA1 and TOC1), and translational (LUC attached to promoters of CCA1 and TOC1),

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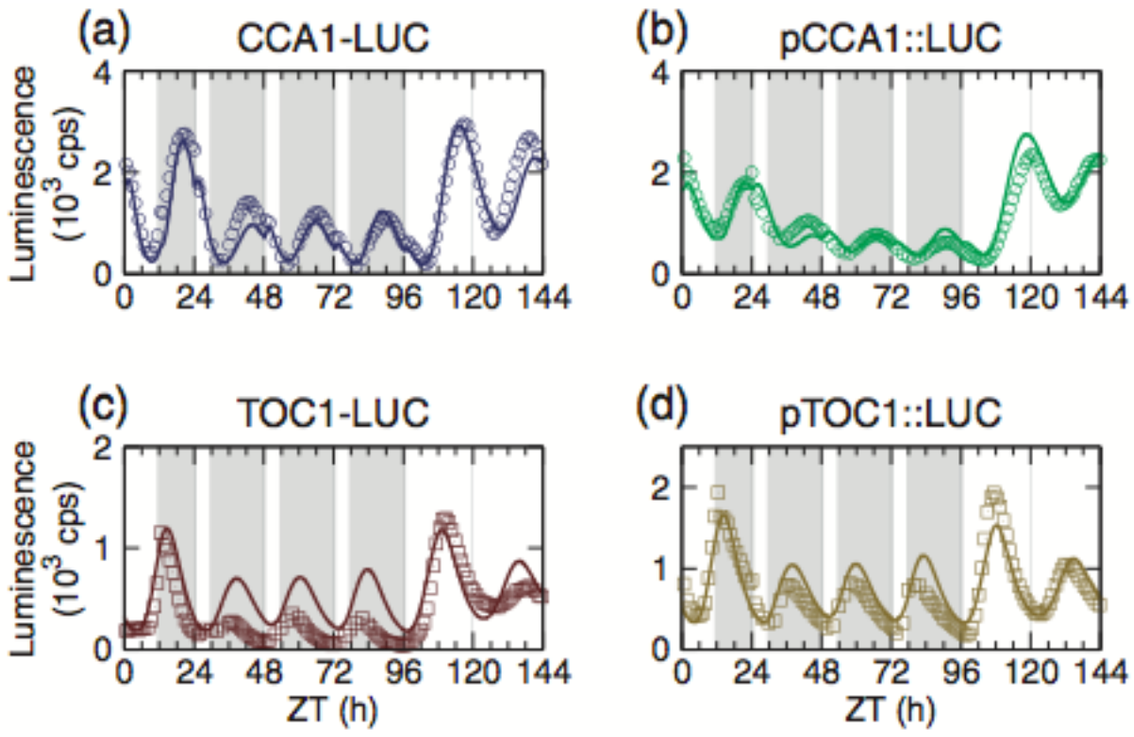

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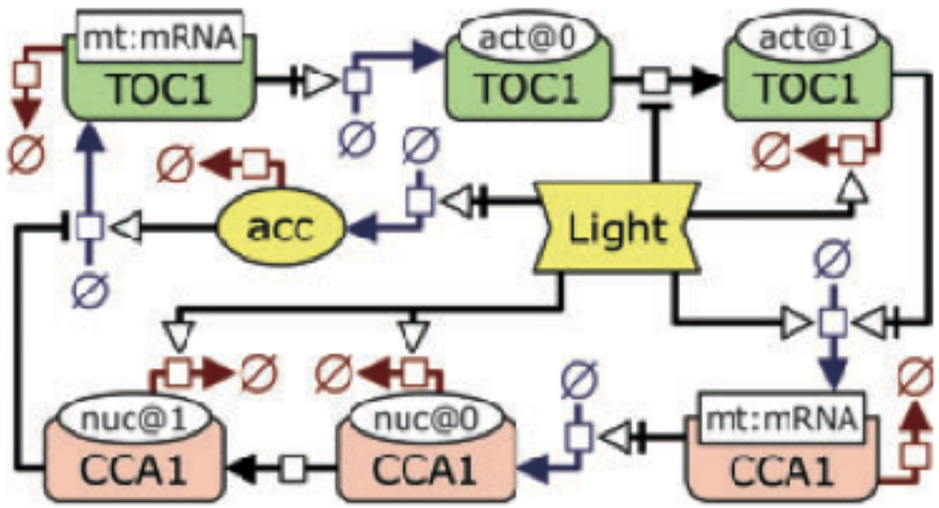

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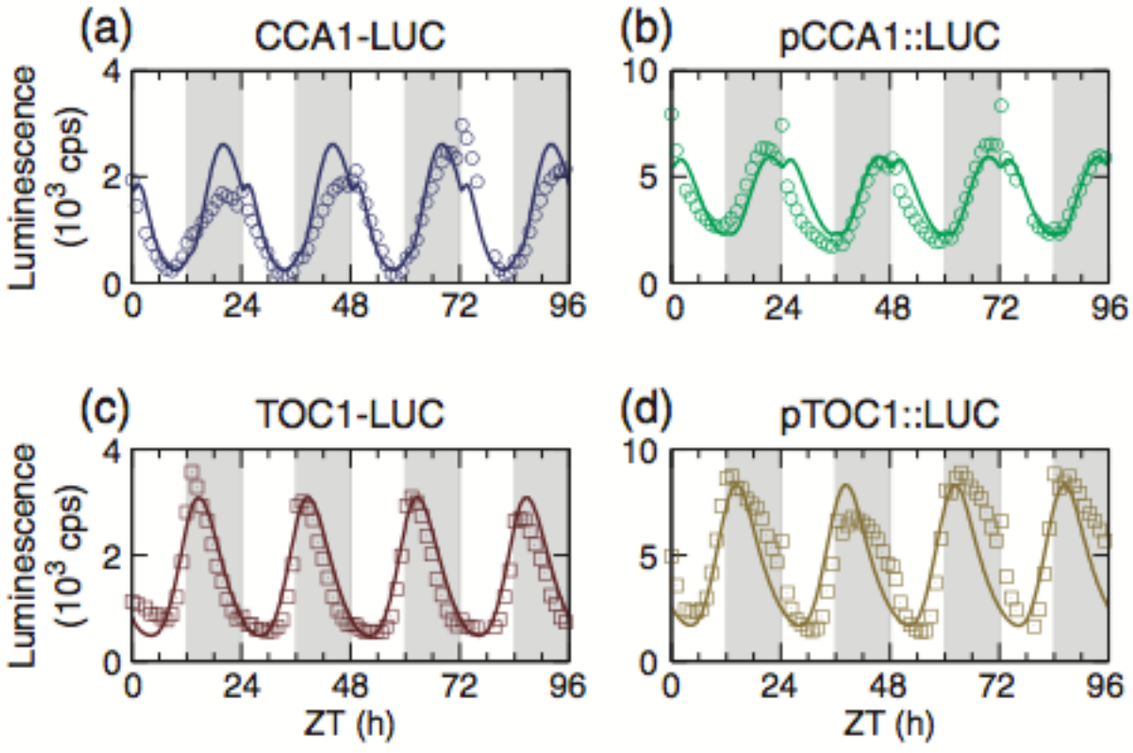

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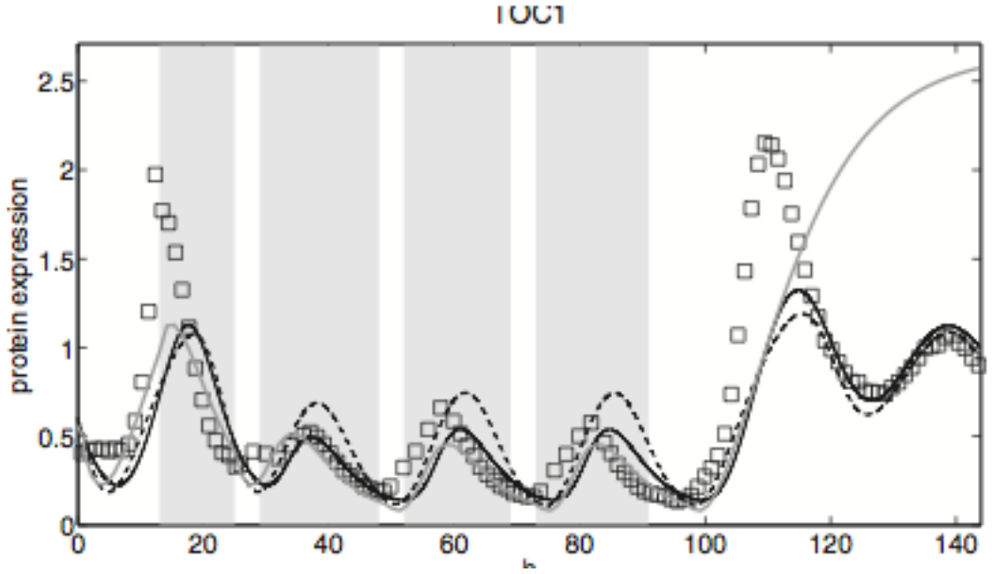

When the ODE model is trained on 12:12 LD data, it fails to predict the behaviour of irregular light patterns.

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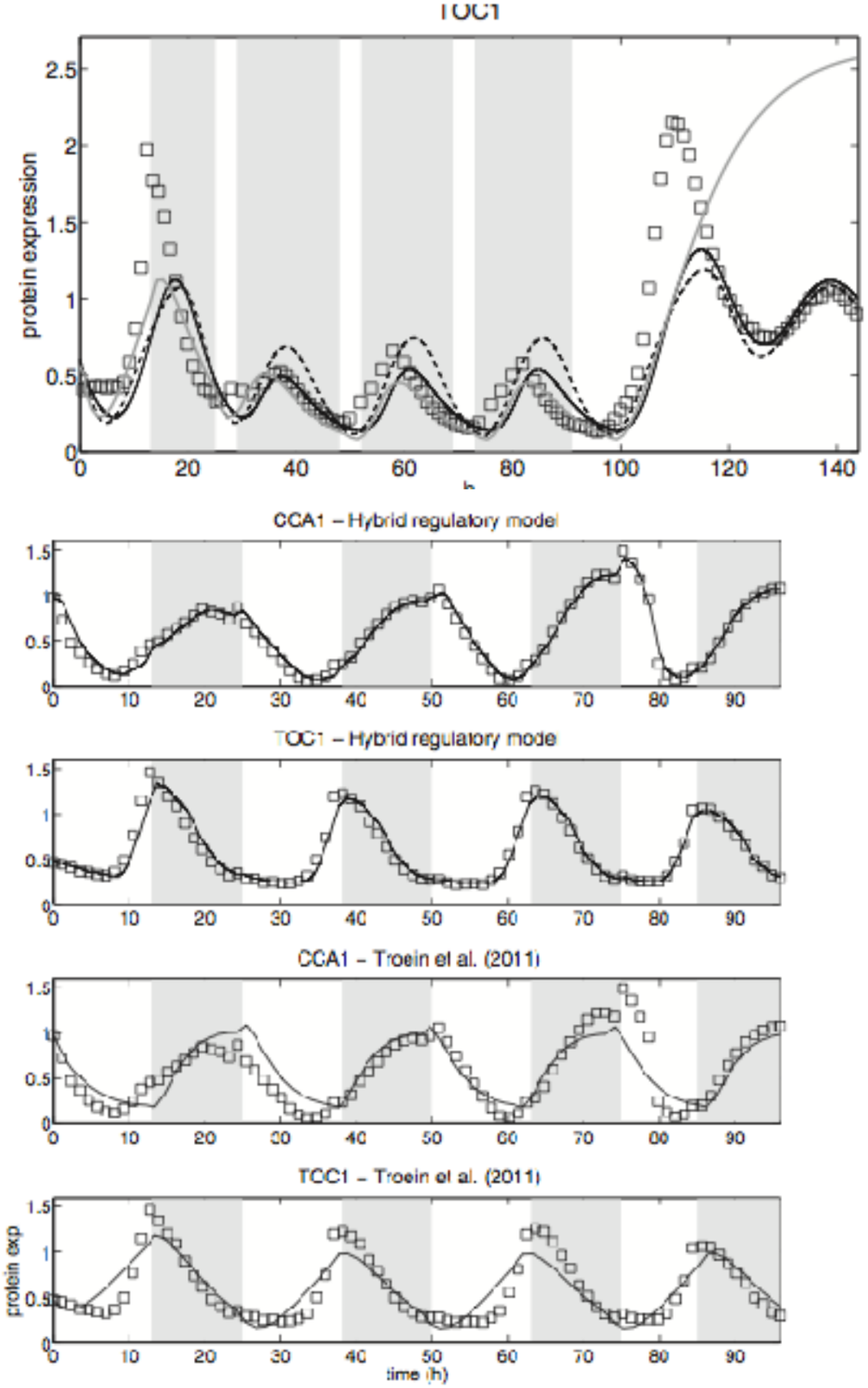

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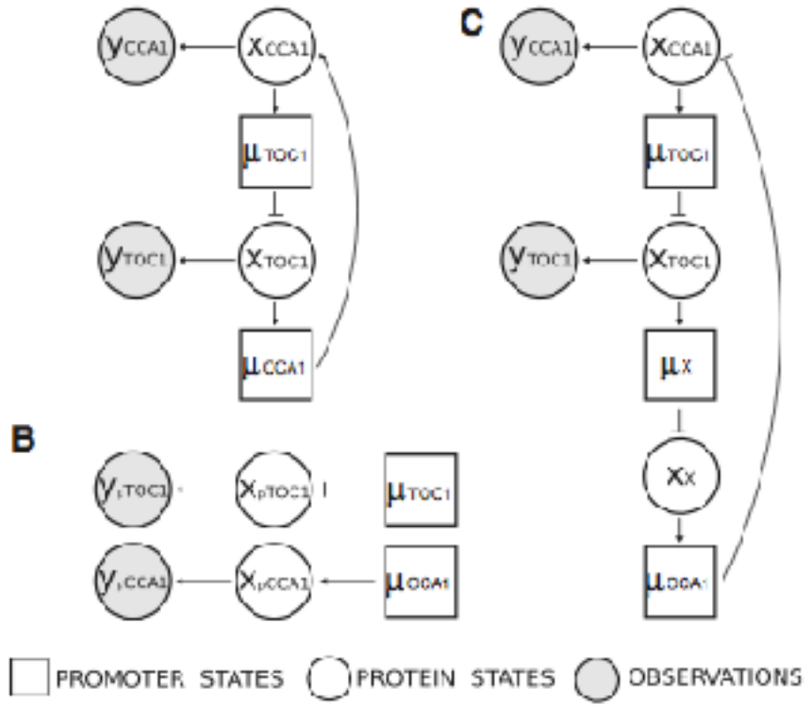

A switching diffusion stochastic model (2 species) can predict behaviour more accurately.

Systems biology Advance Access publication February 19, 2013

Hybrid regulatory models: a statistically tractable approach to model regulatory network dynamics

Andrea Ocone[1], Andrew J. Millar[2,3] and Guido Sanguinetti[1,2,*]

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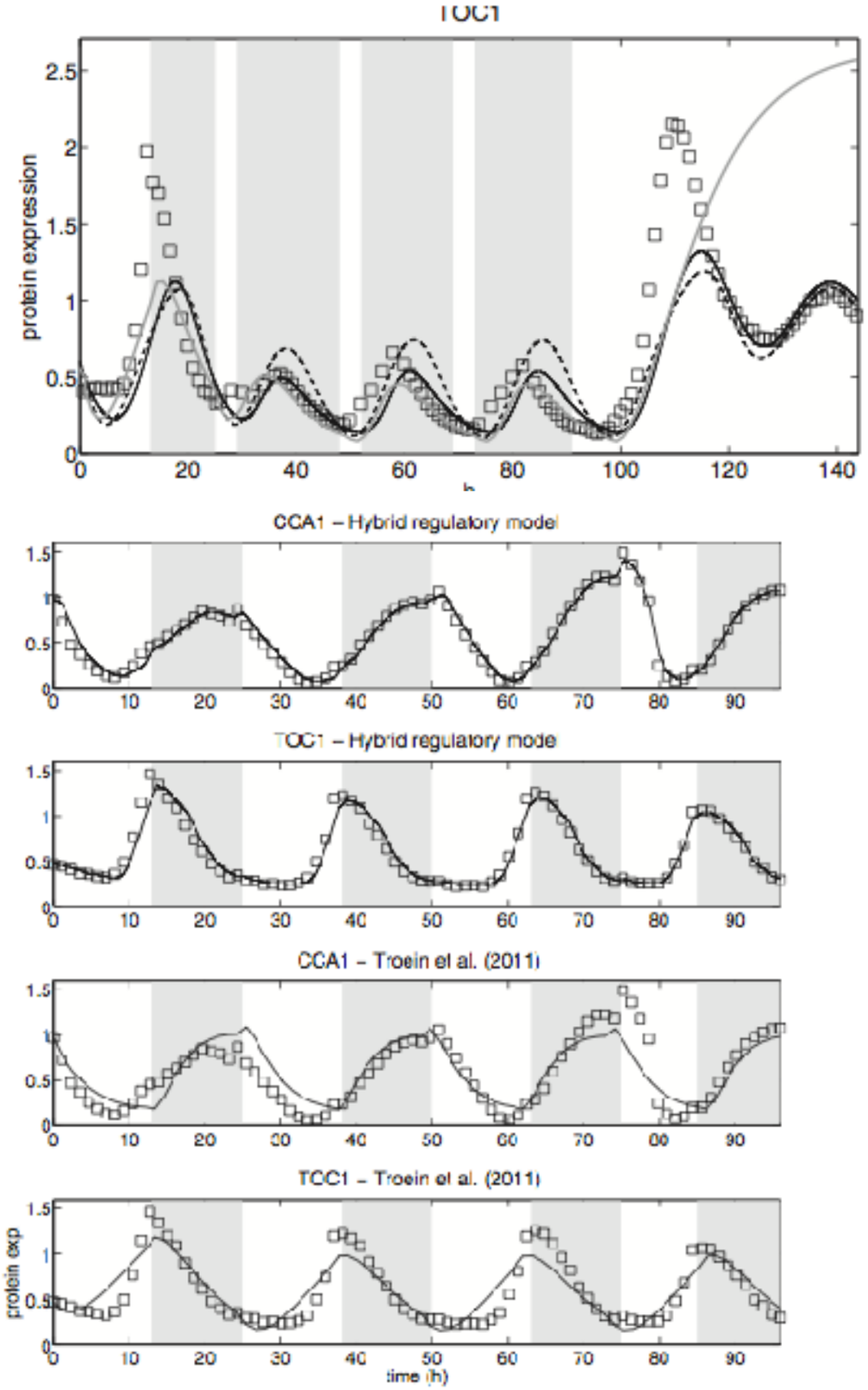

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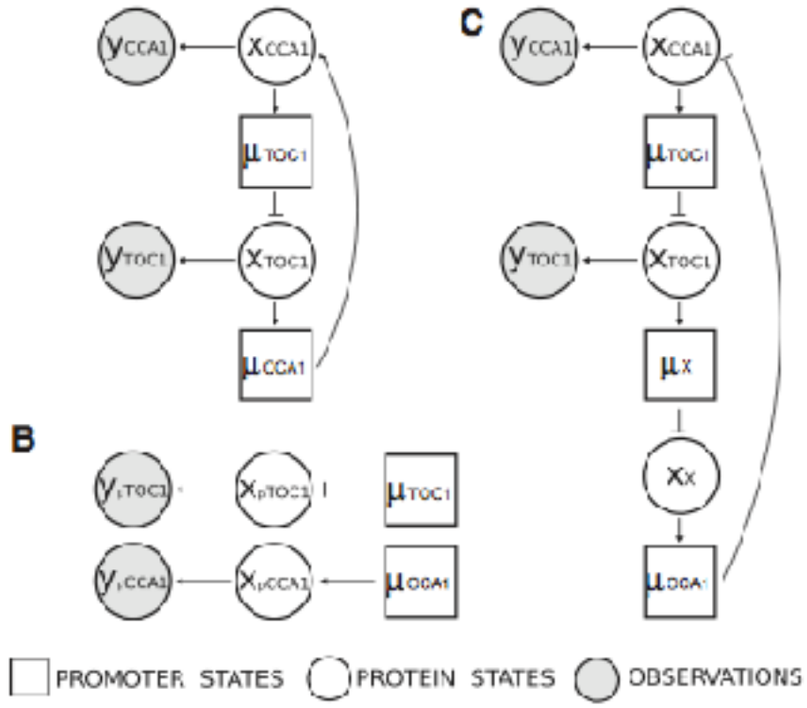

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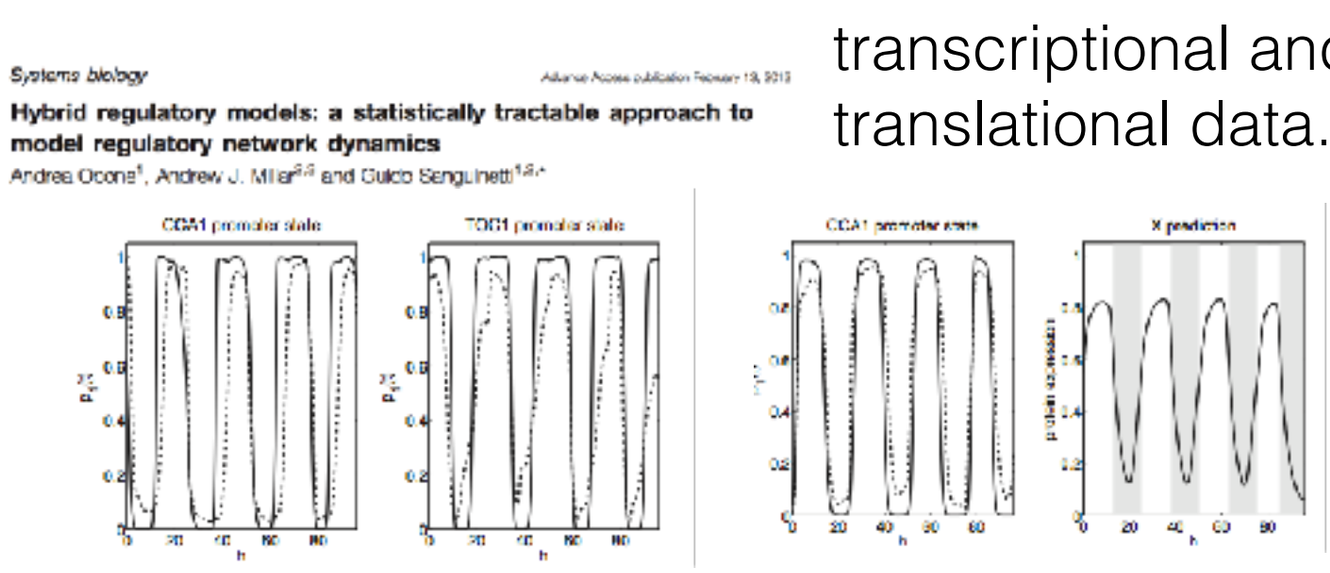
New protein required to correctly capture the behaviour of both transcriptional and translational data.



Take home messages

Modelling can help **elucidating the role and functioning** of cellular components.
Multi scale modelling can deal with tissues, organs, and so on.
It also tests if current knowledge is **consistent**.

Modelling large scale systems (e.g. whole cell) can provide a cheap **in silico experimentation environment** (e.g. for drug testing)

Modelling is a **key enabling technology** in **synthetic biology**: it allows cheap and fast exploration of the design space.

Modelling requires **time-series data** to estimate model parameters. High quality data is required for proper model identification.