Supplementary information part

Enhanced Photo-Responsiveness in a Photoswitchable System Model: Emergent Hormetic Catalysis

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1)- Irreversible Michaelis-Menten model

The most elementary kinetic scheme of a catalyzed reaction is the Michaelis Menten (MM) irreversible model (scheme 1S). The catalytic reaction consists of two main steps, the formation of catalyst–substrate complex AS and the following catalytic action to produce the reaction product P.

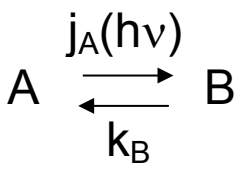
$$A + S \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} AS \xrightarrow{k_{21}} A + P$$

Scheme 1S: Skeleton of the MM model of the catalyzed S → P reaction; A is the catalyst and AS the catalytic complex. k_{11} is the second-order rate constant for the substrate catalyst binding; k_{-11} is the first order rate constant for the splitting of the catalytic complex; k_{21} is the first order rate constant for the product formation and catalyst regeneration.

The system is characterized by the Michaelis-Menten constant $K_m = (k_{21} + k_{-11})/k_{11}$, the catalyst loading $[A]_0/[S]_0$, and the initial substrate concentration $[S]_0$. Maximum initial rate (when the catalyst is completely saturated) is $v_M = k_{21}[S]$. K_M is also the value of substrate concentration to have the initial rate $v_i = v_M/2$. The setting up the reaction defines two kinetic regimes: first-order like when $[S] \ll K_M$ and zero-order like when $[S] \gg K_M$. Catalyst efficiency is further measured by the magnitude of the ratio k_2/K_M. In our approach, the binding and unbinding rate constants were considered independently and the substrate/catalyst reversible binding was not assumed to be fast. Since numerical integration was privileged, this lack of simplification was managed without insuperable difficulties[1] .

2)- T-photochromism[2]

Thermally reversible photochromism (T-photochromism) can be described by scheme 2S:

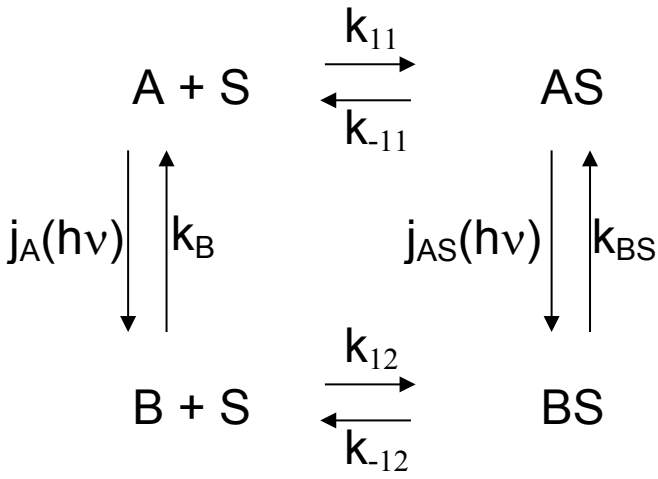


Scheme 2S: Skeleton model of a T-photochromic system where A is the stable form. j_A is the photochemical apparent rate constant.

The rigorous expression of the photochemical rate of a A→ B (hν) reaction is given by: $d[B]/dt = \Phi_A I_0 \varepsilon_A l F[A]$ where Φ_A is the quantum yield, I_0 the irradiation photon flux, ε_A the molar absorption coefficient of the compound A at the irradiation wavelength, *l* the irradiation optical path (*l* = 1cm), F is the photokinetic factor and [A] the concentration. When the total absorbance Abs_T is low, $F = (1-10^{-AbsT})/Abs_T \rightarrow 2.3$, therefore $-d[A]/dt = 2.3\Phi_A I_0 \varepsilon_A l\,[A]$ *i.e.* $-d[A]/dt \approx j_A[A]$ where $j_A \approx \Phi_A I_0 \varepsilon_A$. In presence of the thermal back reaction B → A, the evolution of [A] can be written as: $d[A]/dt = -\Phi_A I_0 \varepsilon_A l F[A] + k_B[B] \approx -\Phi_A I_0 \varepsilon_A [A] + k_B[B]$. For a single T-photochromic compound, mass balance equation: $[A] + [B] = [A]_0$ always applies, therefore assuming that $(\Phi_A I_0 \varepsilon_A / k_B) = j/k$, we have at the PSS:
$[A]_{PSS} = [A]_0[k/(k + j)]$.

3)- Gated-photochromism and photo-modulation

Gated photochromism and photo-modulation appear in the so-called 5 species, square scheme (Scheme 3S).



Scheme 3S: Phomodulation / gated photochromism kinetic model.

Four dye-derived species, two free A and B and two bound AS and BS T-photochroms interact with a guest S.

Gated photochromism corresponds to the variations of quantum yields or thermal relaxation rate constants on reversible association (*i.e* $j_A \neq j_{AS}$ and $k_B \neq k_{BS}$). Photo-modulation is related to the change in the reversible association-dissociation rate constants with the guest S under irradiation (*i.e.* $k_{11} \neq k_{12}$ and $k_{-11} \neq k_{-12}$).

4)- Analysis of the directional rotation in two literature examples:

The product of the clockwise rate constants (or apparent rate constants) is: $k_{11}.j_{AS}.k_{-12}.k_B$ while the anti-clockwise product is $k_{-11}.j_A.k_{12}.k_{BS}$. The r criterion (from [R2] inequality) for directional rotation is:

$r = (k_{11}.j_{AS}.k_{-12}.k_B) / (k_{-11}.j_A.k_{12}.k_{BS}) > 1$ (clockwise) or < 1 (anticlockwise).

rate constants	Jullien *et al.* [3]	*Ragazzon et al.*[4]
k_{11}	$1x10^{10}$	*54*
j_{AS}	$5.5x10^{-3}$	*$1.8x10^{-3}$*
k_{-12}	$3.1x10^{8}$	*$4.7x10^{-6}$*
k_B	$3.0x10^{-5}$	*$8.0x10^{-5}$*
clockwise product	$5.12x10^{11}$	*$3.65x10^{-11}$*
k_{-11}	$1.0x10^{8}$	*$8.6x10^{-5}$*
j_A	$2.6x10^{-3}$	*$1.6x10^{-3}$*
k_{12}	10^{10}	*0.81*
k_{BS}	$2.0x10^{-3}$	*$1.8x10^{-6}$*
anti-clockwise product	$5.2x10^{12}$	*$2.01x10^{-13}$*
r criterion	*9.8e-2 (anti-clockwise)*	*182 (clockwise)*

Table 1S: Numerical check of the directional rotation in two literature examples. r criterion allows to deduce the direction of rotation.

5)- Differential equations describing the full model displayed on scheme 1 (main text):

$d[A]/dt = - k_{11}[A][S] + k_{-11}[AS] - \Phi_A I_0 \varepsilon_A[A] + k_B[B] + k_{21}[AS];$

$d[AS]/dt = k_{11}[A][S] - k_{-11}[AS] - \Phi_{AS} I_0 \varepsilon_{AS}[AS] + k_{BS}[BS] - k_{21}[AS];$

$d[B]/dt = - k_{12}[B][S] + k_{-12}[BS] + \Phi_A I_0 \varepsilon_A[A] - k_B[B] + k_{22}[BS];$

$d[BS]/dt = k_{12}[B][S] - k_{-12}[BS] + \Phi_{AS} I_0 \varepsilon_{AS}[AS] - k_{BS}[BS] - k_{22}[BS];$

$d[S]/dt = -k_{11}[A][S] + k_{-11}[AS] + k_{-12}[BS] - k_{12}[B][S];$

$d[P]/dt = k_{21}[AS] + k_{22}[BS];$

Mass balance equations:

$[A]_0 = [S]_0 + [B] + [A] – [P] – [S]$

$[S]_0 = [BS] + [AS] + [P] + [S]$

6)- Kinetic modelling software

a)-model file in C++

```
// Emergent Hormetic Catalysis.cpp

// automatically written by modan

// CAUTION: mode "reduced equations"

//-----------------------------------------------------------
#include "global.h"
//-----------------------------------------------------------
void Identification(Modele& modele)
{
   modele.Fichier = String(__FILE__);
   modele.Version = String(__DATE__) + String() + String(__TIME__);
   modele.Auteur = "unknown";
   nom_syst = "COMPMM01";
   n_diff = 4;
   first_var = 0;
   nv_mod = 6;
   nexp = 1;
}
//-----------------------------------------------------------
// Special declarations:

//-----------------------------------------------------------
void eqdiff(Sa_data x, Sa_data *y, Sa_data *dy)
{
   Sa_data     y4,y5,v0,v1,v2,v3,v4,v5,v6,v7,v8,v9;
   y4 = ca[4][0] -y[0] +ca[0][0] +y[1] -ca[1][0] +y[3] -ca[3][0];  // B
   y5 = ca[5][0] -y[1] +ca[1][0] -y[2] +ca[2][0] -y[3] +ca[3][0];  // BS

   v0 = p[0]*y[0]*y[1];       // A + S <-> AS
   v1 = p[1]*y[2];    //      inverse
   v2 = p[2]*y[2];    // AS -> P + A
   v3 = p[3]*y[0];    // A <-> B
   v4 = p[4]*y4;      //      inverse
   v5 = p[5]*y[2];    // AS <-> BS
   v6 = p[6]*y5;      //      inverse
   v7 = p[7]*y[1]*y4; // B + S <-> BS
   v8 = p[8]*y5;      //      inverse
   v9 = p[9]*y5;      // BS -> P + B

   dy[0] = - v0 + v1 + v2 - v3 + v4; // d[A]/dt
   dy[1] = - v0 + v1 - v7 + v8;      // d[S]/dt
   dy[2] = v0 - v1 - v2 - v5 + v6;   // d[AS]/dt
   dy[3] = v2 + v9;   // d[P]/dt
}
//-----------------------------------------------------------
void fappel()
{
   // suppress or modify this loop, if needed:
   for (int i = 0; i < np; i++)
      p[i] = fabs(p[i]);

   for (int k = 0; k < nexp; k++)
   {
      first_var = k*nv_mod;
      srkvi(n_diff, &ca[first_var], ind, npt, h0, tol, iset, jacob, h_compt, c_min);

      // non integrated variables:
      for (int i = 0; i < npt; i++)
      {
         Ca(k,4,i) = Ca(k,4,0) - Ca(k,0,i) + Ca(k,0,0) + Ca(k,1,i) - Ca(k,1,0) + Ca(k,3,i) -
Ca(k,3,0);     // [B]
         Ca(k,5,i) = Ca(k,5,0) - Ca(k,1,i) + Ca(k,1,0) - Ca(k,2,i) + Ca(k,2,0) - Ca(k,3,i) +
Ca(k,3,0);     // [BS]

      }
   }
}
```

b)- command file in text

```
Nom_syst:       COMPMM01
paramètres_du_système:10
k0_A+_S___      1.0000e+01      f       0.0e+00 0.0e+00
k1_AS_back      1.0000e+00      f       0.0e+00 0.0e+00
k2_AS_forw      1.0000e+00      f       0.0e+00 0.0e+00
k3_A-->Bhv      1.0000e+00      f       0.0e+00 0.0e+00
k4B->A____      1.0000e+01      f       0.0e+00 0.0e+00
k5AS->BShv      1.0000e+01      f       0.0e+00 0.0e+00
k6BS->AS__      1.0000e+00      f       0.0e+00 0.0e+00
k7B_+_S___      1.0000e+00      f       0.0e+00 0.0e+00
k8BSback__      1.0000e+01      f       0.0e+00 0.0e+00
k9BS_forwa      1.0000e+01      f       0.0e+00 0.0e+00
Précision:      1.00e-02
Min_f():        1.00e-06
Nombre_de_variables:  6
intégrer_à_partir_de: 0
post_à_partir_de:     0
Valeurs_initiales:
A_________      1.0000e-01      f       0.0e+00 0.0e+00
S_________      1.0000e+00      f       0.0e+00 0.0e+00
AS________      0.0000e+00      f       0.0e+00 0.0e+00
P_________      0.0000e+00      f       0.0e+00 0.0e+00
B_________      0.0000e+00      f       0.0e+00 0.0e+00
BS________      0.0000e+00      f       0.0e+00 0.0e+00
x0:             0.00e+00
xf:             2.50e+01
hout:           2.50e-01
h0:             1.00e-01
tol:            5.00e-03
```

c)- example of output files in text (reduced version)

```
Time    A               S               AS              P       B               BS
0.0000  0.10000         1.0000          0.0000          0.0000  1.3878e-17      0.0000
5.0000  0.055642        0.31951         0.015695        0.65694 0.020806        0.0078567
10.000  0.081477        0.057115        0.0041714       0.93666 0.012297        0.0020543
15.000  0.089598        0.0071496       0.00057776      0.99199 0.0095400       0.00028406
20.000  0.090755        0.00083093      6.8077e-05      0.99907 0.0091439       3.3467e-05
25.000  0.090891        9.5656e-05      7.8497e-06      0.99989 0.0090970       3.8588e-06
```

Our free access software and tutorial can be downloaded at:

http://cinet.chim.pagesperso-orange.fr/index.html

A recent successful use of this software can be found in reference 5.

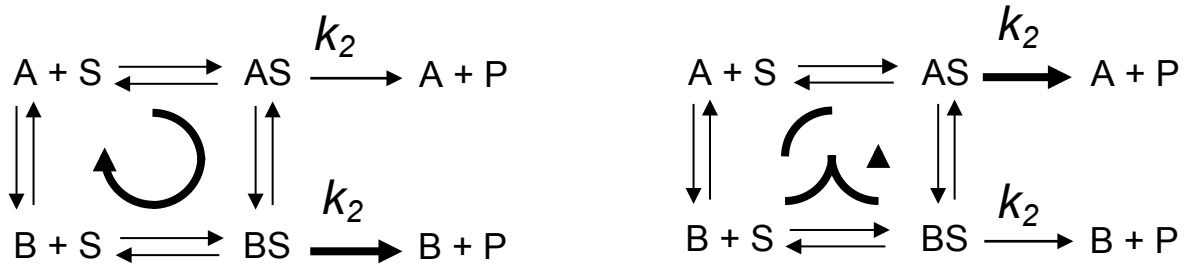
7)- Reaction net fluxes in example 1 and 2

Net fluxes (symbol: >>) have been computed according to table 1 (main text). The four positive values in example 2 indicate a fully directional clockwise rotation. Units are in concentration.time^{-1} *i.e.* 0.13/0.1 = 1.3 round per time unit.

	A+S>>AS	AS>>BS	BS>>B+S	B>>A
1:	0.074180	0.0037455	-0.0064224	-0.013286
2:	0.29626	0.28938	0.13065	0.29634

8)- Relationship between k_{21} and k_{22} for the occurrence of the collaborative catalysis

Scheme 4S shows that photo-hormesis is conditioned by a catalytic rate constants increase with the directional rotation. If the rotation is clockwise k_{21} must be $< k_{22}$, if anti-clockwise k_{22} must be $> k_{21}$.



Scheme 4S: Relative magnitude exhibited by k_{21} and k_{22}. Right order for the emergence of photo-hormesis is given by the directional rotation within the cycle. A sufficient contrast is needed.

9)- Numerical simulation of representative examples of the full model

The following examples illustrate of the influence of the parameters:

$r = (k_{11}.j_{AS}.k_{-12}.k_B) / (k_{-11}.j_A.k_{12}.k_{BS})$ and $s = k_{22}/k_{21}$ (clockwise) or k_{21}/k_{22} (anti-clockwise) on the emergence of the collaborative catalysis (hormesis).

parameters	3	4	5	6	7	8
k_{11}	10	5	2	1	10	2
k_{-11}	1	2	1	10	1	1
k_{12}	1	2	1	10	1	1
k_{-12}	10	5	2	1	10	2
j_A	.1	.2	.5	1	.1	.25
k_B	1	5	2	1	10	2
j_{AS}	1	.5	1	.1	1	1
k_{BS}	10	1	1	10	1	1
k_{21}	1	2	1	10	10	1.3
k_{22}	10	5	2	1	1	1.7
r	100	78	16	10^{-4}(a)	10^4	32
s	10	2.5	2	10(a)	0.1	1.31
hormesis	yes	yes	yes	yes	no	no

Table 2S: List of examples (3 to 8) showing the influence of the kinetic parameters on the emergence of the hormesis. Photochemical apparent rate constants (j_A and j_{AS}) are given at $I_0 = 1$. (a): anti-clockwise rotation.

10)- Photo-hormesis plots

Initial rate *vs* light intensity plots show the emergence of collaborative catalysis (hormesis) in examples 3 to 6 (Figure 1Sa) and smooth response in examples 7 and 8 (Figure 1Sb). Hormesis appears if parameter r is sufficiently departed from 1 and if s is sufficiently high.

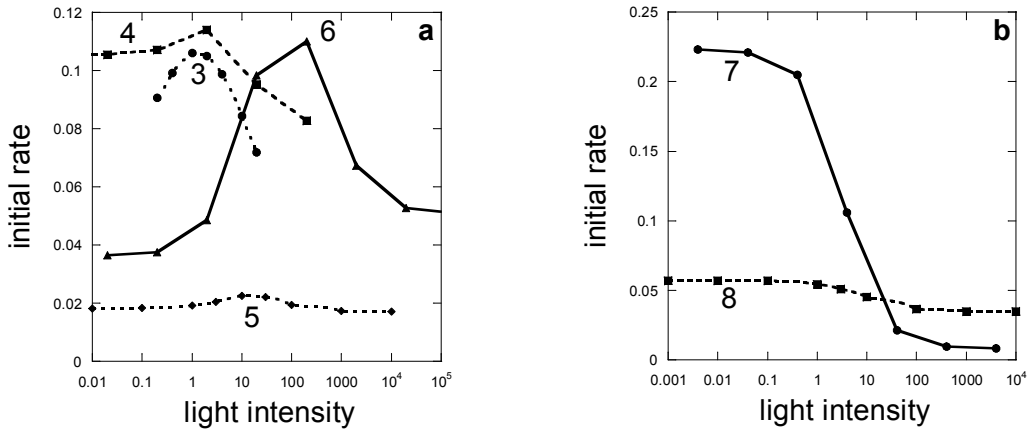


Figure 1S: Initial rate vs light intensity plot in full model; **a**: examples of hormetic responses; **b**: examples of smooth response.

11)- Gated photochromism and photo-modulation quantitative data mining

photochromic species	Guest	measured parameters	reference
spiro fused azo benzene piperidine base	H^+	$\Delta pK_a = 0.8$ on photoisomerisation (m)	6
hydroxy- azobenzene	H^+	$\Delta pK_a \approx 3$ on photoisomerisation (m)	7; 8
bis-pyridyl methyl thienyl cyclopentene	Zn^{2+}	photocyclisation quantum yield increases from 0.155 to 0.446 upon complexation (g)	9
diacid dithienyl ethene	H^+	photocyclisation quantum yield decreases from 0.9 to 0.65 upon deprotonation (g); pK_a increases from 1.2 to 2.6 on photo-cyclisation (m)	10
Merocyanine photochromic acid generator	H^+	pK_a decreases from 9.99 to 3.97 upon cyclisation (m)	11
spironaphthoxazine	H^+	protonation reaction rate constant increases under UV irradiation from 4.48e-4 (dark) to 9.57e-4s^{-1} (UV) (m)	12
hydroxyl ethyl nitro BIPS	CB8	thermal back reaction increases from complexed: 1.45e-5 to free at 8.3e-5s^{-1} (g)	13
spiro pyrane reversible photo acid	H^+	pK_a decreases from 7.75 to 4.3 on photocyclisation (m)	14

Table 3S: List of papers where quantitative parameters related to gated photochromism (g) and /or photomodulation (m) have been determined. MC: macrocycle for 1:1 pseudorotaxane-type complexes ; Zn^{2+} = (4eq.) ; CB8 = cucurbit[8]uril.

12)- Photoswitchable catalysis quantitative data mining

The criteria used were structural (the catalytic centre and the photochromic unit must be bound together) and quantitative (providing kinetic and/or thermodynamic data).

photochromic unit	catalytic system	measured parameters	catalysed reaction	note	Ref.
Azobenzene	bis-Ba complex of butterfly crown ether	quasi-cis & quasi-trans k_{obs}	basic anilides ethanolysis	(a)	15
Azobenzene	spirofused piperidine bases	k_{off}(dark) & k_{on}(UV) and ΔpK_a	Henry addition of nitroethane on nitobenzaldehyde	(b)	6; 16
Azobenzene	thiourea	conv(%) after 18h (off & on states)	Michael addition of acetyl acetone to m-bromo nitro styrene	(c)	17
Azobenzene mediated aggregation of diamide	unaggregated pyrimidinic diamide	conv(%) after 100 min (off & on states)	rearrangement of 2-acyloxy benzofuran to 3-acyl-2-benzo furanone	(d)	18
Azobenzene -receptor	acid-base	initial rates ratio	coupling between amino adenosine and p-nitro phenyl ester	(e)	19
Diarylethene	N-heterocyclic carbene	$k_{ambiant}/k_{UV}$ ratio	ROP of δ-valerolactone by BnOH	(f)	20
Diarylethene	linked imidazole	k_{open} & k_{closed}	acylation of 2-decanol with acetic anhydride	(g)	21
stilbene – based unidirectional molecular rotor	DMAP thiourea	yields after 15h and ee%	asymmetric Michael thiol addition to enone	(h)	22
stilbene – based chiral bisphosphine macrocycle	$Pd(OAc)_2$	conv(%), selectivity and ee%	asymmetric Heck reaction of DHF and aryl triflate	(i)	23
spiropyran-collagen	urease	initial rate ratio	Urea hydrolysis	(j)	24
spiropyrane-β-amylase	β-amylase	K_m's and activity	4-nitrophenyl-β-D-glucoside hydrolysis	(k)	25

Table 4S: Quantitative parameters related to photoswitchable catalytic systems. (**a**): k_{obs} for CF_3 anilide: quasi-*trans*: $1.84x10^{-2}$, quasi-*cis*: $4.89x10^{-2}$, for CHF_2 anilide: quasi-*trans*: $3.82x10^{-4}$, quasi-*cis*: $2.39x10^{-3}s^{-1}$; (**b**): k_{off}(dark) = $0.39x10^{-6}s^{-1}$, k_{on}(UV) = $13.9x10^{-6}s^{-1}$, ΔpK_a = 0.7; (**c**): conv(%) after 18h dark: 96%, UV: 21%; (**d**): conv(%) after 100 min dark: 14%, UV: 80%; (**e**): increase of initial rate *vs* uncatalysed reaction, $1.5x10^{-8}Mmin^{-1}$, E/Z (100/0), 1.2, E/Z (50/50), 10.5; (**f**): k_{amb}/k_{UV} = 59; (**g**): k_{open} = $8.8x10^{-4}$ M^{-2} s^{-1}, k_{closed} = $6.9x10^{-5}$ M^{-2} s^{-1}; (**h**): yields after 15h and *ee*%, *(P,P)-trans* = 7%, 2%, *(M,M)-cis* = 50%, 50%, *(P,P)-cis* = 83%, 54%; (**i**): aryl = naphthyl, (Z), 91(%), 72:28, 60%, (E), >99(%), 88:12, 13%, the system is less contrasted with aryl = phenyl and Trost asymmetric allylic alkylations; (**j**): dark: 7.6, visible light: 4.9μmol/min NH_3; (**k**): dark(open): K_M = 3.4, v = 1, visible light (closed): K_M = 60mM, v = 0.13 (relative units);

13)-References

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