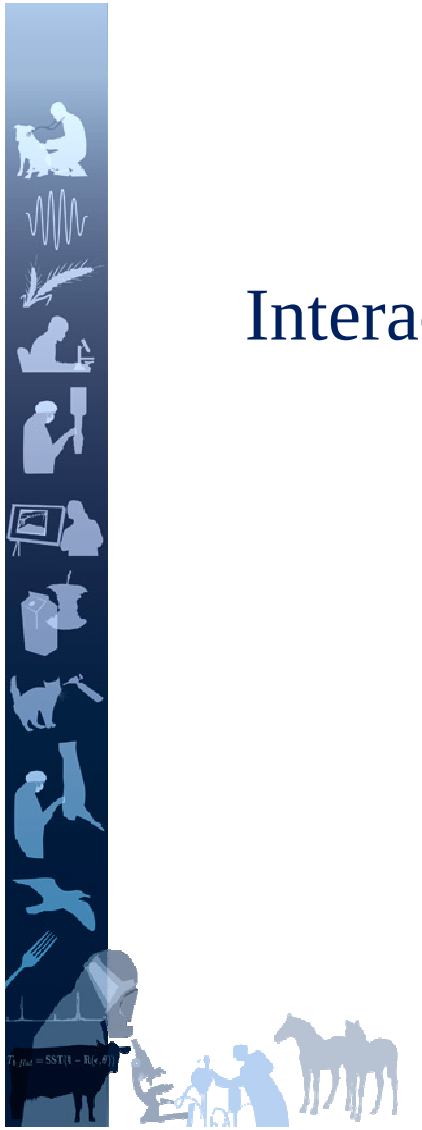
Journées du GDR Statistique et Santé
20 et 21 Septembre 2012
Rennes



Interactions drogue – récepteurs évaluées par un modèle de cinétique des effets

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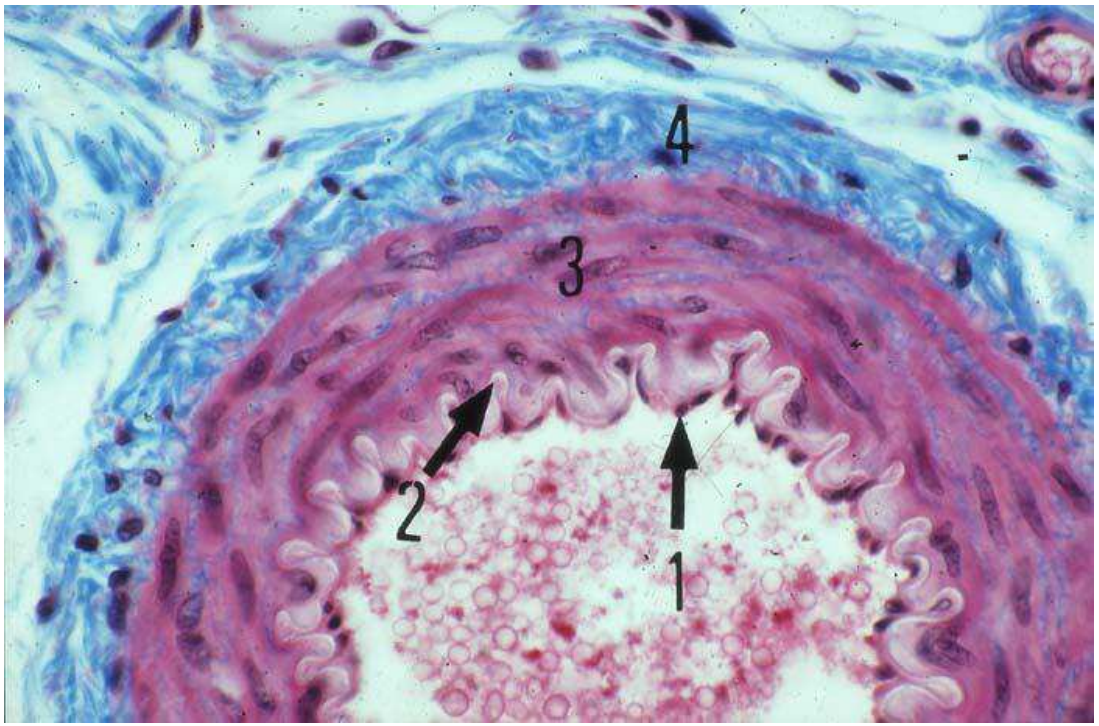
UPSP : Physiopathologie Animale et Pharmacologie Fonctionnelle

Pharmacological background

Drug-receptor interactions

Example in cardio vascular desaeses

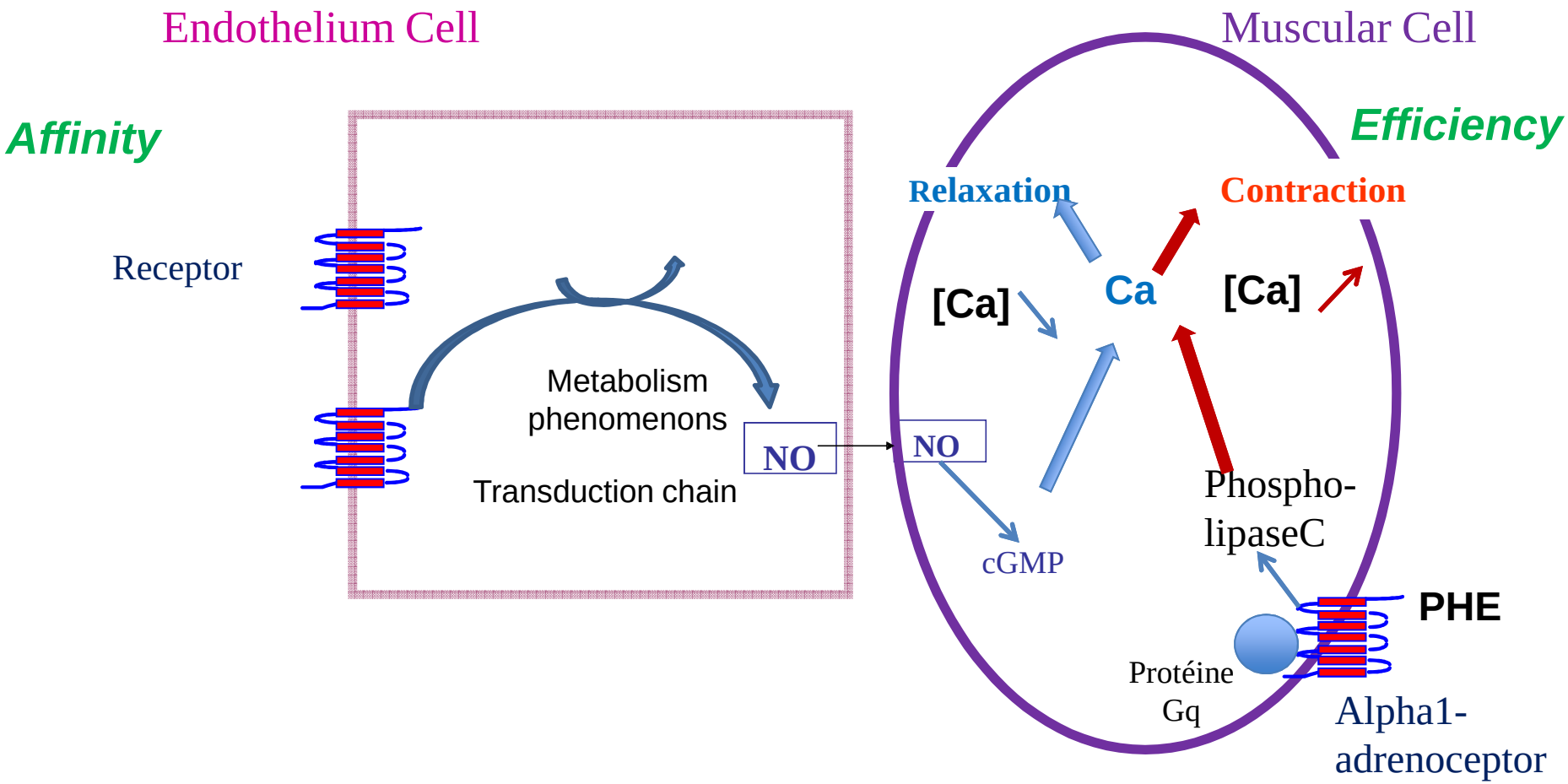
1 : Endothelium
2 : Media
3 : Muscular fiber
4 : Adventice



Histological slice of blood vessel

Pharmacological background

Drug-receptor Interactions

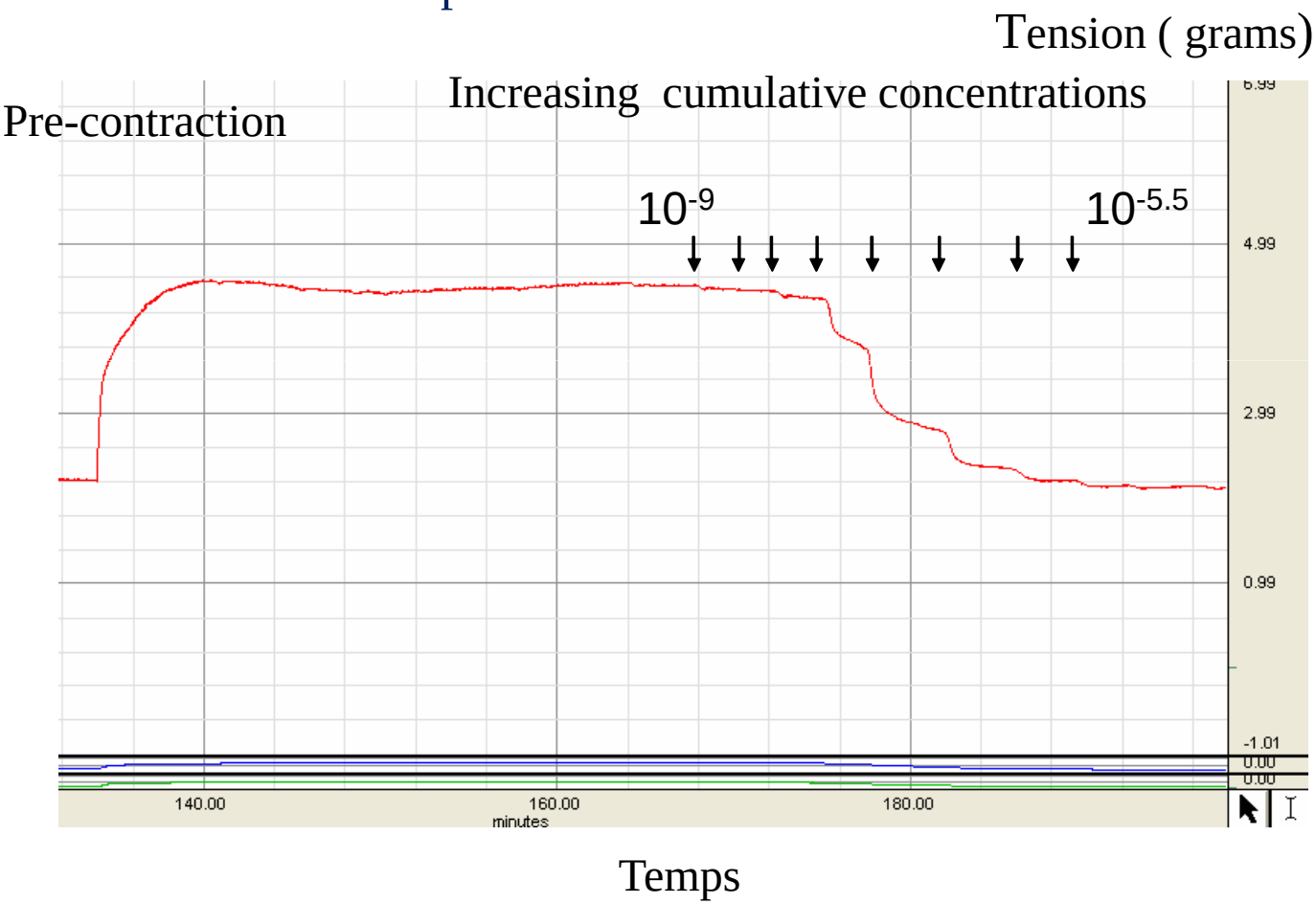


Affinity and efficiency are dependent of transduction chains (Chen *et al*, 2004)

Experimental approach

Cumulative Concentration Response Curves

Relaxation example



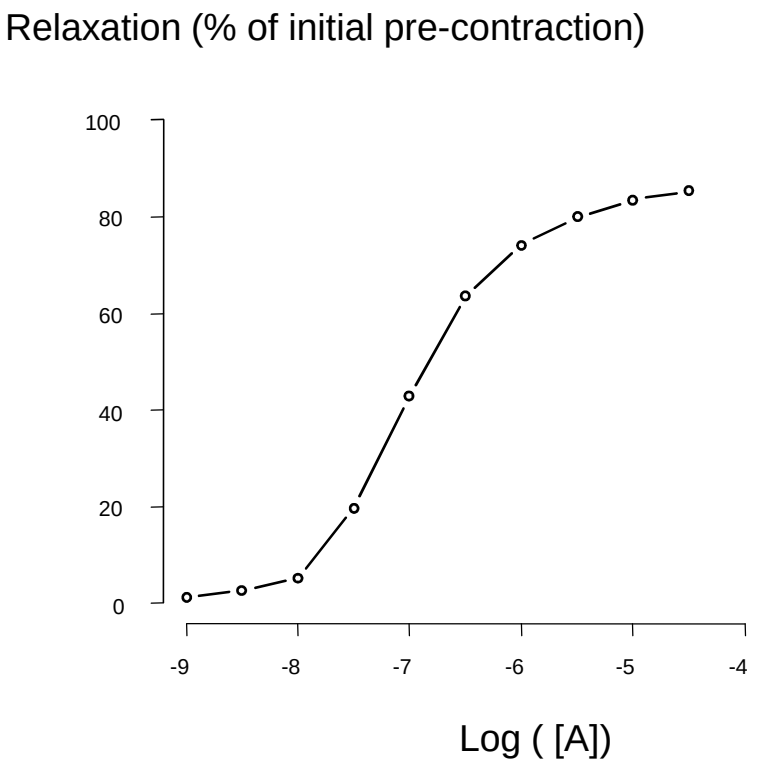
1 - artery ring suspended on stainless steel wires in an organ bath containing Krebs solution

2 – the effect produced by each concentration (delta tension) is recorded

3 – Data sets : $([A]_i, Effect_i)$ $i=1\ldots M$

Experimental approach

Cumulative Concentration Response Curves



Usually,

CCRC Data are fitting using the Hill equation by non linear mixed effects models

$$E = \frac{E_m}{1 + 10^{n(pA - pD_2)}} \qquad pA = -\log_{10}([A])$$

- E_m : maximum effect ~ **Efficiency**
- n : sigmoidicity parameter
- EC_{50} concentration producing ½ E_m
- $pD_2 = -\log_{10}(EC_{50})$ ~**Potency**

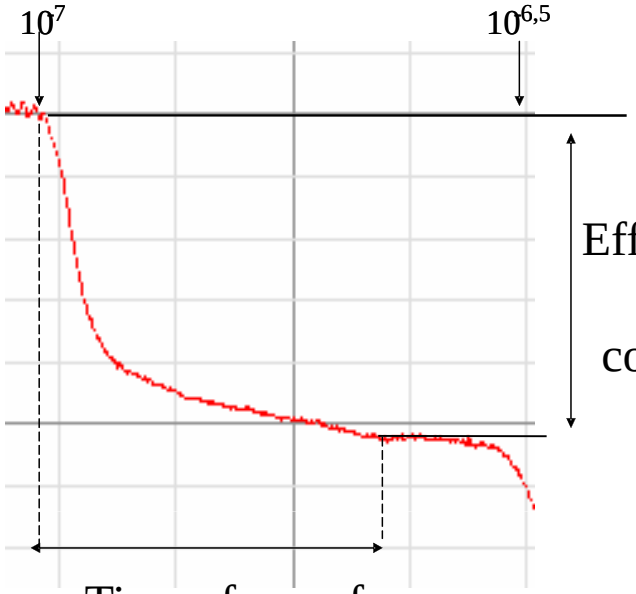
But,

Biological effects are time dependent (Danhof *et al*, 2008)

and

Hill's equation lacks to fit some experimental situations (Giraldo *et al*, *2002*)

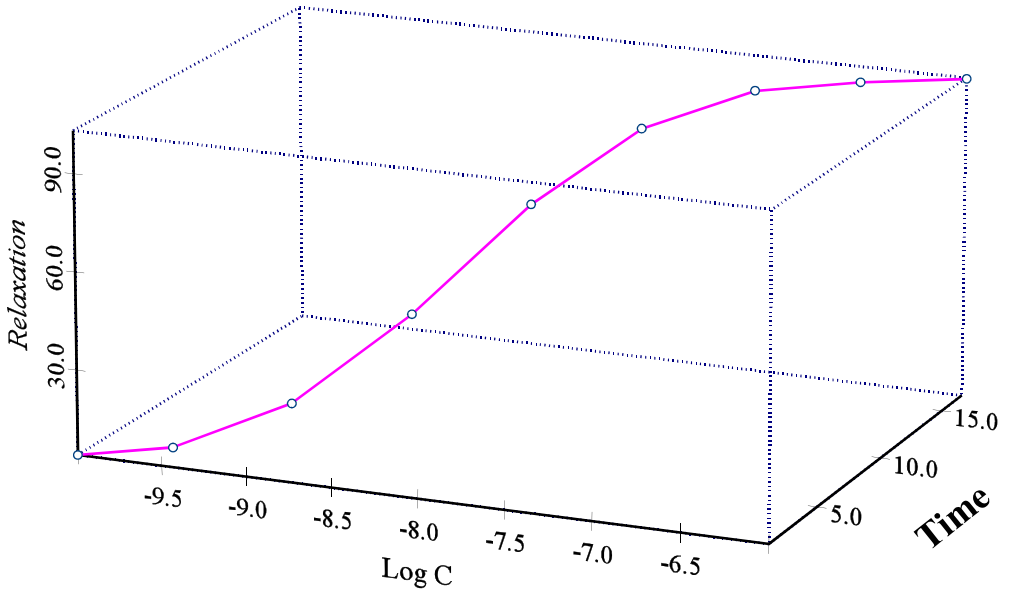
Model of kinetic of effects



Recording data

Time and effect measured for each concentration are added to respect the cumulative design

$(\log_{10}([A]_i), t_i, E_i)$



Model of kinetic of effects

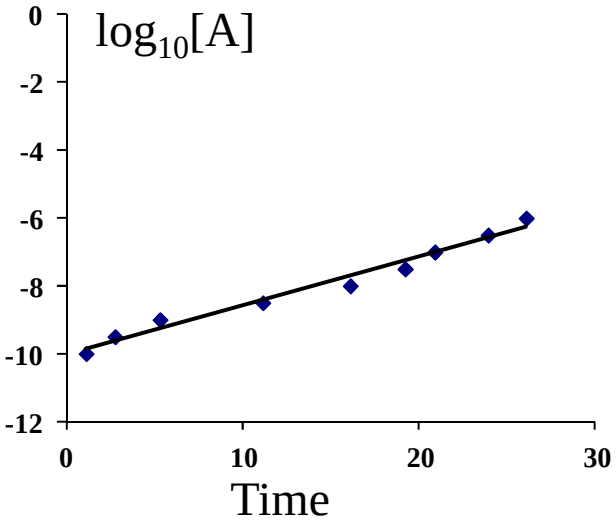
A+R↔ AR ↔…..Ca → Effect

Partial kinetic in biochemical reactions : Let r be the partial order for a constituant P of a given biochemical reaction

$$V_P = \frac{d([P])}{dt} = k * [P]^r$$

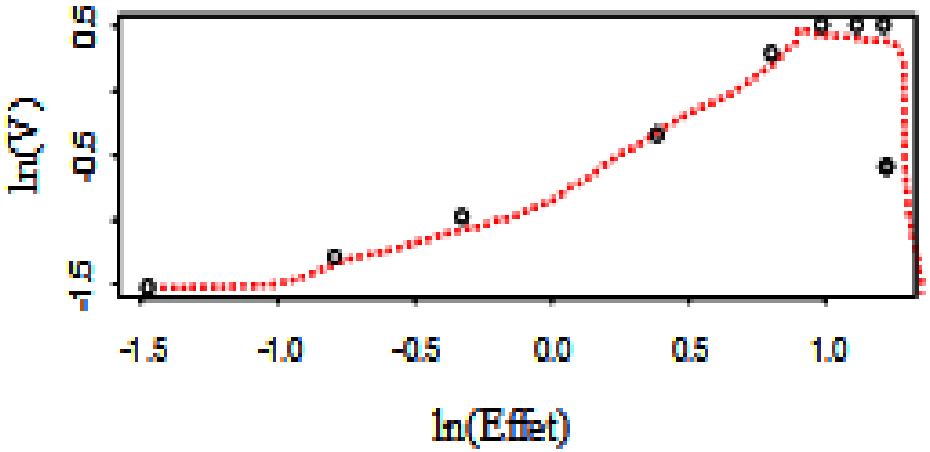
$$\ln(V_P) = \ln(k) + r * \ln([P])$$

Partial kinetic of the agonist A :



kinetic of first order

Partial kinetic of final effector :



Kinetic of complex order

Model of kinetic of effects

Partial kinetic of the agonist A : kinetic of first order

$$\frac{d([A])}{dt} = \beta\ [A] \qquad (1)$$

with:

$$pA_t = -\log_{10}([A]_t)$$

$$pA_0 = -\log_{10}([A]_0)$$

By integration of equation (1) gives :

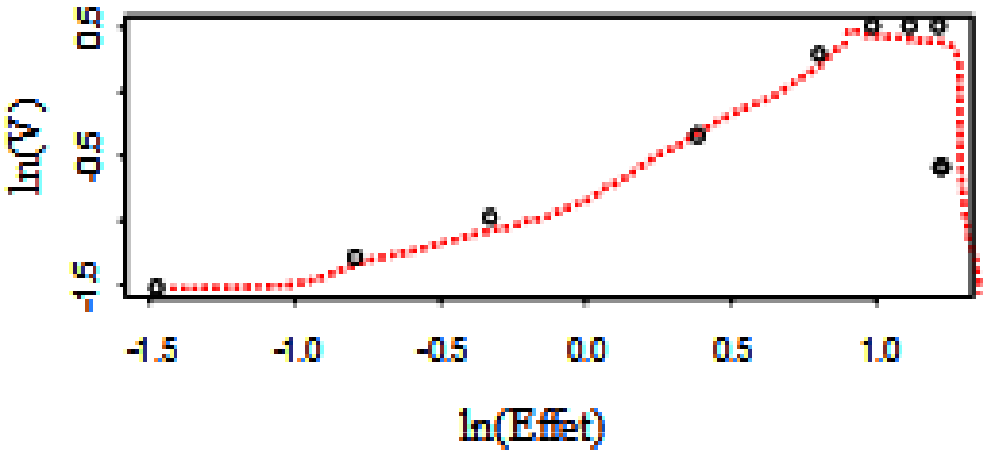
$$pA_t = pA_0 - \frac{1}{\ln(10)}\beta t$$

$[A]_0$ lowest concentration of action

β Constant rate of agonist use

Model of kinetic of effects

Partial kinetic of final effector : kinetic does not follow to a simple order



By analogy with phenomenona resulting of catabolism and anabolism

(Lindsey , 2004)

Pharmacological effect = results of sensitization and desensitization phenomenona

(Keitz *et al*, 1990)

$$\frac{d(E_t)}{dt} = \gamma\ E_t\left(1-\left(\frac{E_t}{E_m}\right)^{\lambda}\right)$$

$$E_t = E_m \frac{1}{\left(1+\left(\left(\frac{E_m}{E_0}\right)^{\lambda}-1\right)e^{-\gamma\lambda t}\right)^{1/\lambda}}$$

γ, λ : sensitization and desensitization parameters respectively ($\gamma > 0$, $\lambda > 0$)

E_m : Maximum effect , E_0 initial effect

Model of kinetic of effects

Estimation

Complete Model

Level 1

$$\begin{cases} pA_{it} = pA_{i0} - \dfrac{1}{\ln(10)}\,\beta_i t + \varepsilon 1_{it} \\ E_{it} = E_{mi}\,\dfrac{1}{\left(1+\left(\left(\dfrac{E_{mi}}{E_{0i}}\right)^{\lambda_i} - 1\right)e^{-\gamma_i\lambda_i t}\right)^{-1/\lambda_i}} + \varepsilon 2_{it} \end{cases}$$

Level 2

$$\begin{cases} pA_{0i} = pA_0 + \pi_i \\ \beta_i = \beta + b_i \\ E_{mi} = E_m + \xi_i \\ \gamma_i = \gamma + g_i \\ \lambda_i = \lambda + l_i \end{cases}$$

ε_{1it} iid $N(0,\sigma_1^2)$; ε_{2it} iid $N(0,\sigma_2^2)$
$(\pi_i, b_i, \xi_i, g_i, l_i) \sim N(O,\Sigma)$

E_m : efficiency

γ, λ : sensitization and desensitization parameters

$[A]_0$: minimum concentration producing an effect

β : constant rate of use of A

Model of kinetic of effects

Bayesian Estimator

a priori distributions

Level 1 :

$$\begin{cases} \left(pA_i | pA_{oi}, \beta_i, \varepsilon 1\right) \sim \mathcal{N}\left(h(pA_{oi}, \beta_i), \sigma_1^{\,2} I_{n_i}\right) \\ \left(E_i | E_{mi}, \gamma_i, \lambda_i, \varepsilon 2\right) \sim \mathcal{N}\left(f\left(E_{mi}, \gamma_i, \lambda_i\right), \sigma_2^{\,2} I_{n_i}\right) \end{cases}$$

Level 2 : $\phi_i = \phi + \varphi_i$

$$\phi = \left(pA_0, \beta, E_m, \gamma, \lambda\right)^t$$

$$\begin{cases} \phi \sim \mathcal{N}\left(\phi_0; S_0\right); \varphi_i \sim \mathcal{N}\left(0; \Sigma\right) \\ \Sigma \sim \text{ inverse Wishart } \left(\eta_0, S_0^{-1}\right) \\ \sigma_1^{\,2} \sim \text{inverse gamma}\left(\frac{\nu_0}{2}, \frac{\nu_0 \sigma_{10}^{\,2}}{2}\right) \\ \sigma_2^{\,2} \sim \text{inverse gamma}\left(\frac{\nu_0}{2}, \frac{\nu_0 \sigma_{20}^{\,2}}{2}\right) \end{cases}$$

(De La Cruz-Mesia et al, 2006)

Metropolis Hasting Algorithm in R using MCMCpack and mtvnorm packages

Model of kinetic of effects

Bayesian Estimator

Complete conditionnal distribution of ϕ

$$\{\phi \mid pA, E, \sigma_1, \sigma_2, \Sigma, pA_0, \beta, E_m, \gamma, \lambda\} \sim N(\phi_s; S_s)$$

$$\phi_s = S_s\left(S_0^{-1}\phi_0 + m\Sigma^{-1}\bar{\phi}\right)$$

$$S_s = \left(S_0^{-1} + m\Sigma^{-1}\right)^{-1} \qquad m = \dim(\phi_0)$$

Complete conditionnal distribution of Σ

$$\{\Sigma|\mathrm{pA},\mathrm{E},\varphi_1,\ldots,\varphi_5\} \sim \text{inverse-Wishart}\left(\eta_0 + m\left[S_0 + \sum_{i=1}^{5}(\varphi_i - \varphi)(\varphi_i - \varphi)^t\right]\right)$$

Conditionnal distribution of σ^2

$$\sigma_1^2 \sim \text{inverse-gamma}\left(\frac{\left(\nu_0 + \sum_{i=1}^{M} n_i\right)}{2}; \frac{\nu_0 \sigma 1_0^2 + SSR1}{2}\right) \quad \sigma_2^2 \sim \text{inverse-gamma}\left(\frac{\left(\nu_0 + \sum_{i=1}^{M} n_i\right)}{2}; \frac{\nu_0 \sigma_{20}^2 + SSR2}{2}\right)$$

$$SSR1 = \sum_{i=1}^{m}\left(pA_i - h_i(pA_{0i}, \beta_i)\right)^t\left(pA_i - h_i(pA_{0i}, \beta_i)\right) \qquad SSR2 = \sum_{i=1}^{M}\left(E_i - f_i(E_{mi}, \gamma_i, \lambda_i)\right)^t\left(E_i - f_i(E_{mi}, \gamma_i, \lambda_i)\right)$$

Example 1 : Intact aorta ring versus denuded aorta ring

Phenylephrine

Aorta ring intact	Estimate	Standard Error	95 % bayesian confidence interval	
pAo	7.823	0.0518	7.924528	7.721472
Beta	0.222	0.003	0.21612	0.22788
Em	2.168	0.251	1.67604	2.65996
Gamma	2.22	0.136	1.95344	2.48656
Lambda	0.158	0.033	0.09332	0.22268

Denuded aorta ring	Estimate	Standard Error	95 % bayesian confidence interval	
pAo	9.396	0.126	9.64296	9.14904
Beta	0.156	0.1	-0.04	0.352
Em	3.625	0.239	3.15656	4.09344
Gamma	0.94	0.136	0.67344	1.20656
Lambda	0.225	0.034	0.15836	0.29164

Endothelium spontaneous activity limits the contraction of muscular cell

Example 1 : Acetylcholine versus Bradykinin on Horse Digital Vein

Acetylcholine	Estimate	Standard Error	95 % bayesian confidence interval	
pAo	8.995	0.031	8.934	9.056
Béta	0.209	0.001	0.207	0.211
Em	85.207	4.934	75.536	94.878
Gamma	1.001	0.277	0.458	1.544
Lambda	0.84	0.193	0.462	1.218

Bradykinin	Estimate	Standard Error	95 % bayesian confidence interval	
pAo	9.626	0.05	9.528	9.724
Béta	0.191	0.002	0.187	0.195
Em	69.987	3.682	62.77	77.204
Gamma	2.479	0.174	2.138	2.82
Lambda	0.18	0.018	0.145	0.215

Laminitis equin

Alls parameters significantly different

Bradikinin has
- a higher potency
- a lower efficacy

than Acetylcholine

Bradikinin activates several transdcution chains at a time

Discussion

Interest:

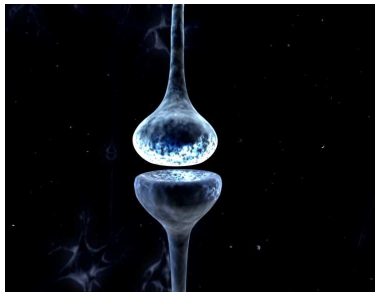
Kinetic of effects model provide more informations about the complex Agonist – Receptor actions

Limit :

Density of receptors in the tissue considered is not included in that model

Project:

Record more data sets
Estimation by SAEM



Thank you
for
your attention