

# **Dynamic Pharmacodynamics: Modeling and Optimization**

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# Strange Nomenclatures

## What is “dynamics”?

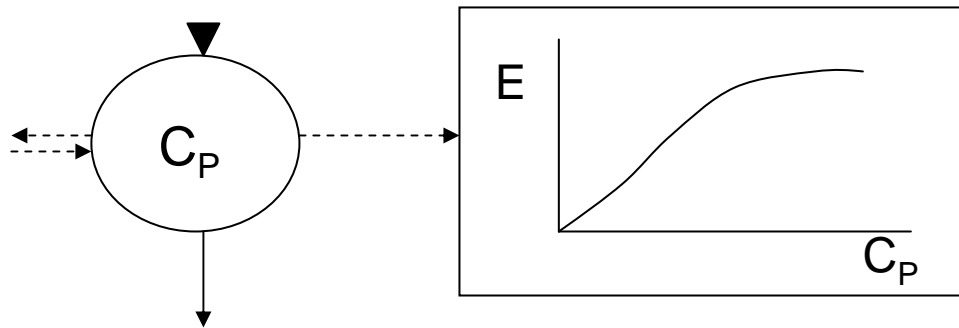
We usually associate this word with some kind of *change*, but actual word route is “dyne” which is a unit of force. In static situations, forces may be present (but balanced), yet there is no change.

*Thermodynamics* is usually associated with *equilibria*, although *nonequilibrium thermodynamics* has been applied to *steady states*. Some have proposed an alternate term, *thermostatics* for equilibrium situations, but this has not caught on.

*Molecular dynamics* actually tracks movement of molecules due to intermolecular forces and thermal excitation, which may occur even when system is macroscopically at equilibrium.

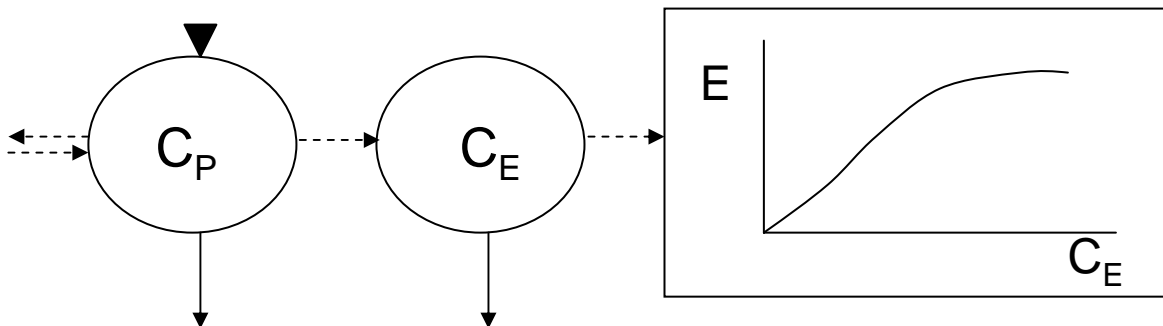
# Pharmacodynamics?

*Classical Pharmacodynamics*—Assumes instantaneous 1:1 relation between drug concentration in plasma and drug effect

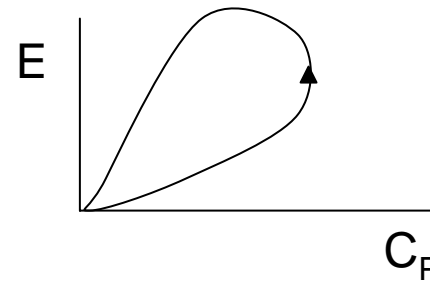
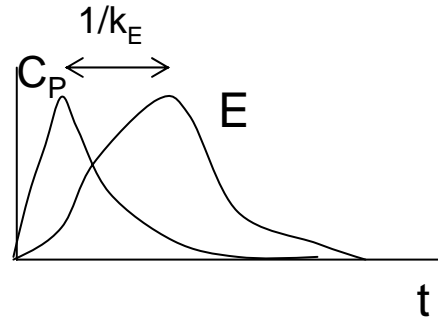
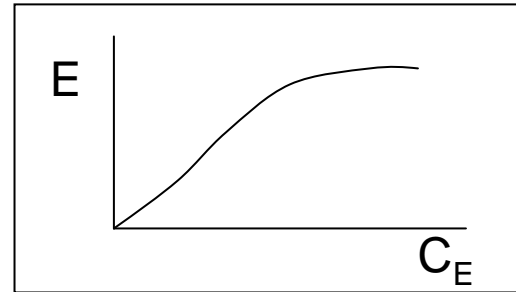
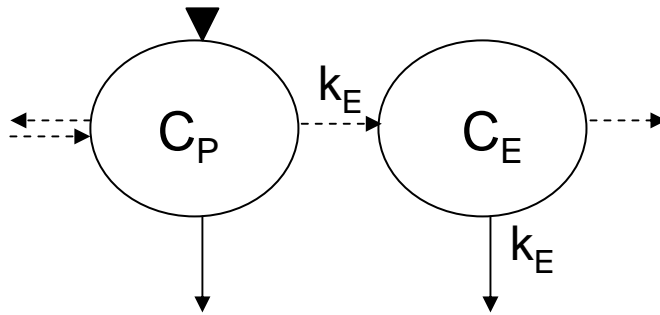


**No apparent dynamics here**

*Link Model*—Postulates delay between plasma concentration and concentration in “effect compartment, or “biophase”

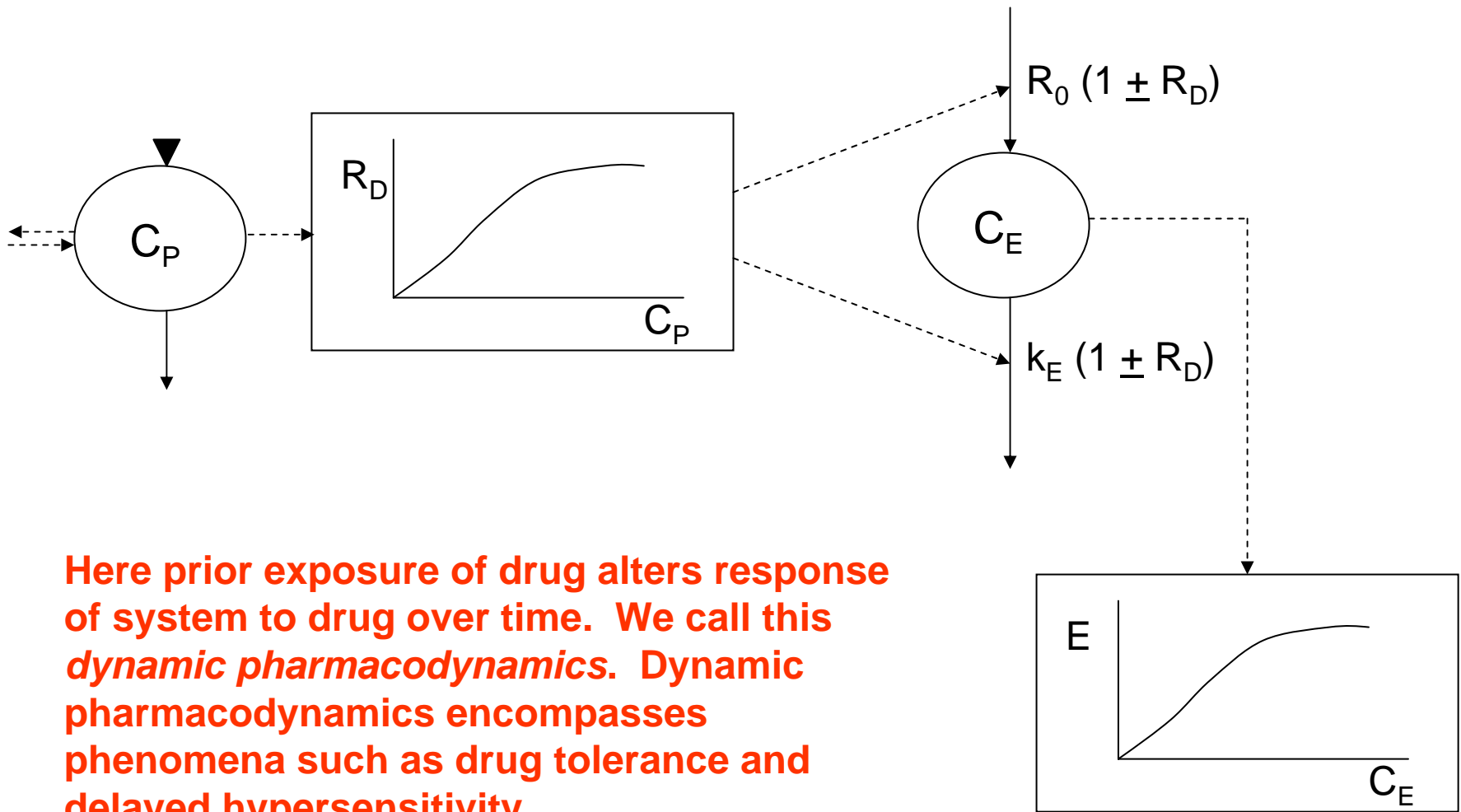


# Link Model, cont.



**A dynamic relation between plasma concentration and drug effect exists here, but drug itself is not the “cause” of dynamics.**

# Indirect Effect Models



Here prior exposure of drug alters response of system to drug over time. We call this *dynamic pharmacodynamics*. Dynamic pharmacodynamics encompasses phenomena such as drug tolerance and delayed hypersensitivity.

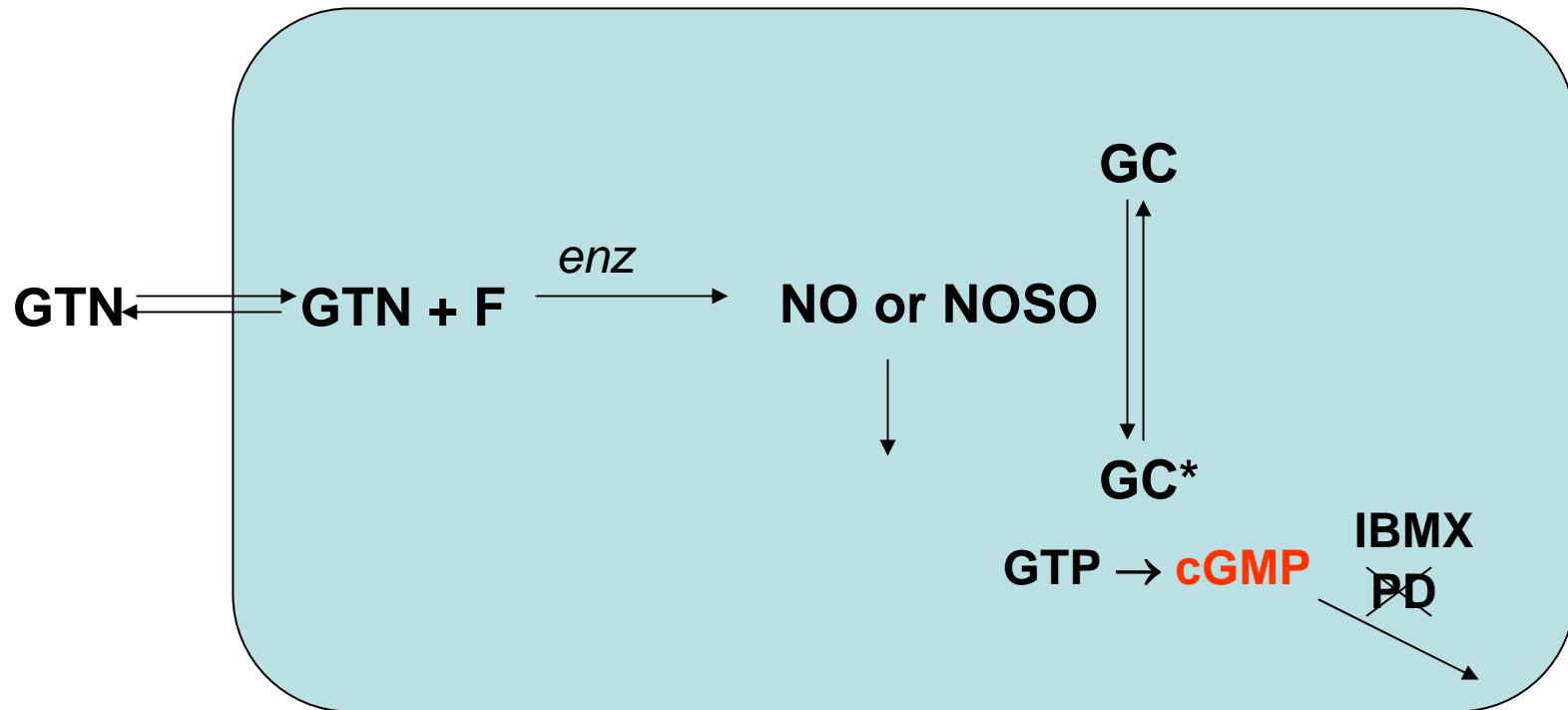
# Topics in Dynamic PD

- **Experiments and modeling of nitroglycerin tolerance in cultured cells**  
**(Jim Uchizono, UCSF, now UOP)**
- **A dynamic model for PD variability**  
**(J.E. Lee, UMn, now Vertex Pharmaceutical)**
- **“Optimal control” of drug administration under tolerance**  
**(S. Varigonda, UMn, now in controls industry)**

# Nitroglycerin Tolerance

- Nitroglycerin = glyceryl trinitride (GTN), a smooth muscle relaxant
- Tolerance discovered in late 19<sup>th</sup> century in context of munitions workers—Monday morning headaches
- GTN used for acute treatment of angina attacks—ampule delivery
- Tolerance “rediscovered” during development of transdermal patches for prophylactic treatment.

# Cellular mechanism for GTN



NO = nitric oxide

NOSO = S-nitrosothiol

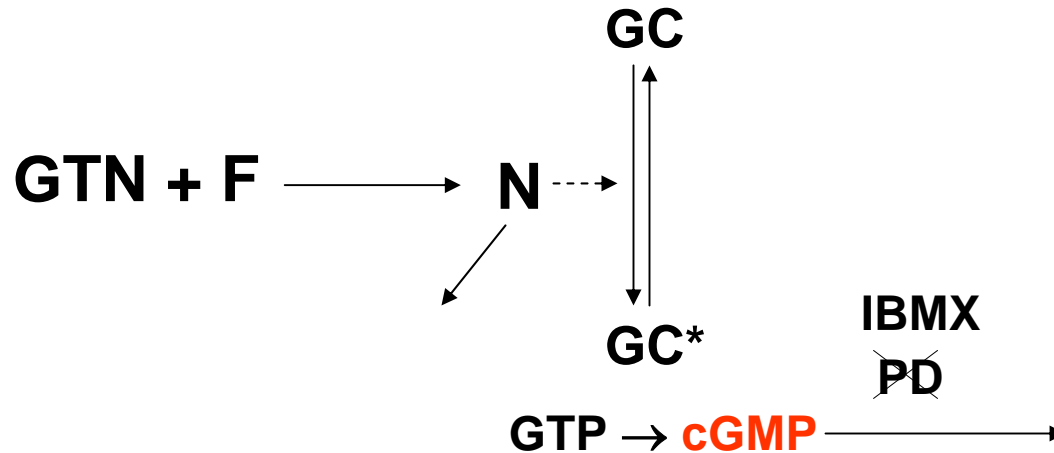
F = thiol reactant

PD = phosphodiesterase

IBMX = isobutylmethylxanthine

**Tolerance arises from depletion of F, enz**

# “Minimal model” of acute GTN response



$f$  = normalized concentration of F

$n$  = normalized concentration of N

$$\frac{df}{dt} = -k_1[\text{GTN}]f$$

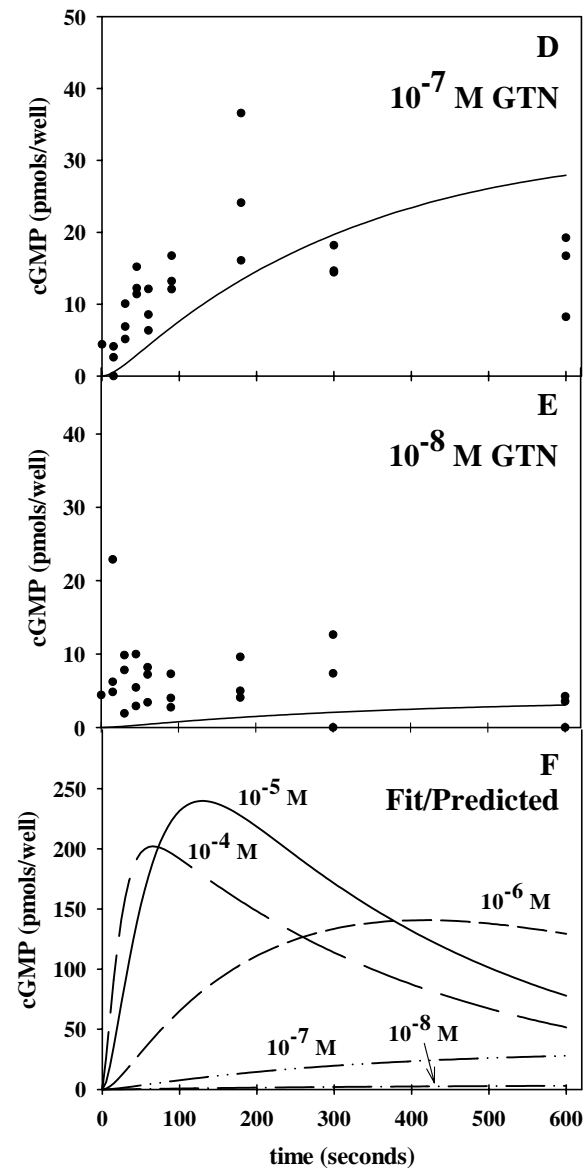
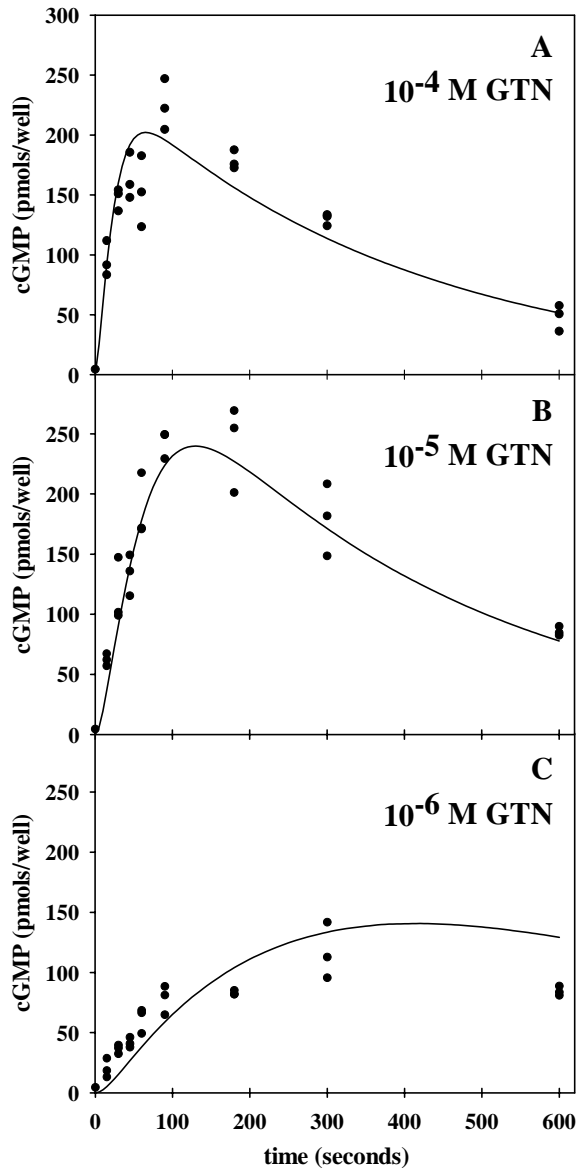
$$\frac{dn}{dt} = [\text{GTN}]f - k_2n$$

$$\frac{d[\text{cGMP}]}{dt} = \frac{\alpha_2 n}{\alpha_1 + n} - k_3[\text{cGMP}]$$

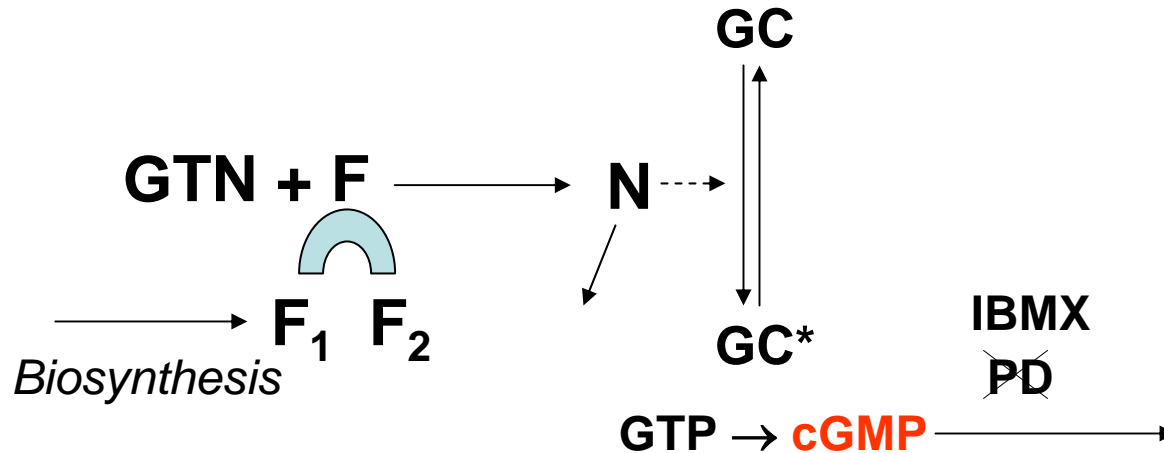
# Protocol – Acute Experiments

- **Porcine kidney (LLC-PK1) cells grown to confluence in 96-well plates**
- **Expose cells in plates to GTN at selected concentrations for selected (short) time periods, in presence of IBMX**
- **Aspirate GTN/IBMX and lyse cells**
- **Assay cGMP accumulation by RIA**

# Results + Model Best Fits



# “Minimal model” of long term GTN response



$$\frac{df}{dt} = -k_1[GTN]f$$

$$\frac{dn}{dt} = [GTN]f - k_2n$$

$$\frac{d[cGMP]}{dt} = \frac{\alpha_2 n}{\alpha_1 + n} - k_1[cGMP]$$

$$\frac{df_1}{dt} = r - (r + k_1[GTN])f$$

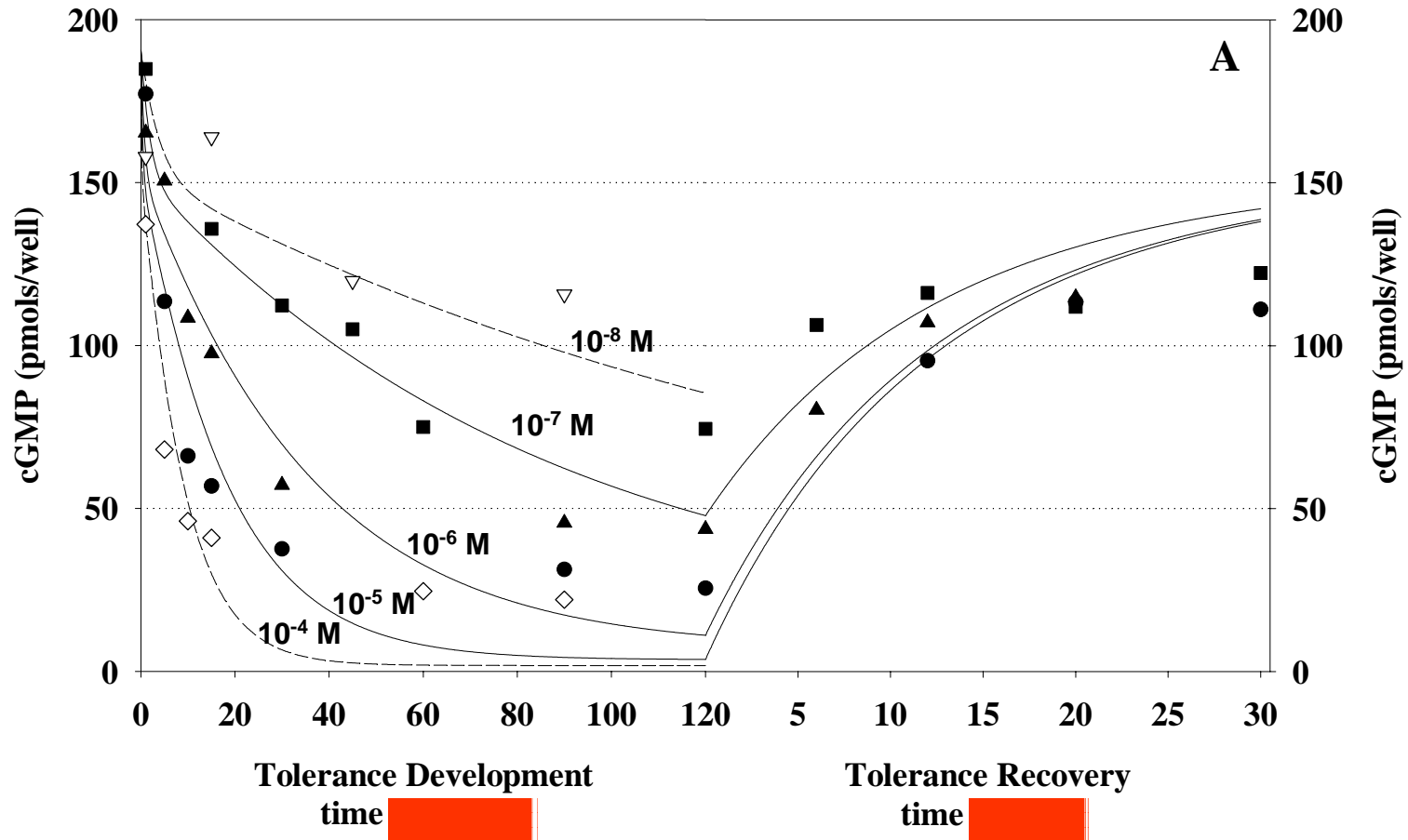
$$\frac{df_2}{dt} = -k_1[GTN]f_2$$

$$f = f_1 + f_2$$

# **Protocol – Tolerance development and recovery experiments**

- **Porcine kidney (LLC-PK1) cells grown to confluence in 96-well plates**
- **Expose cells in plates to GTN at selected concentrations for selected (long) time periods. No IBMX at this point.**
- **For recovery experiments, wash cells and re-expose to GTN-free medium.**
- **Wash cells**
- **Expose cells to  $10^{-5}$ M GTN in presence of IBMX for 3 min**
- **Assay cGMP accumulation by RIA**

# Results, Model Fits



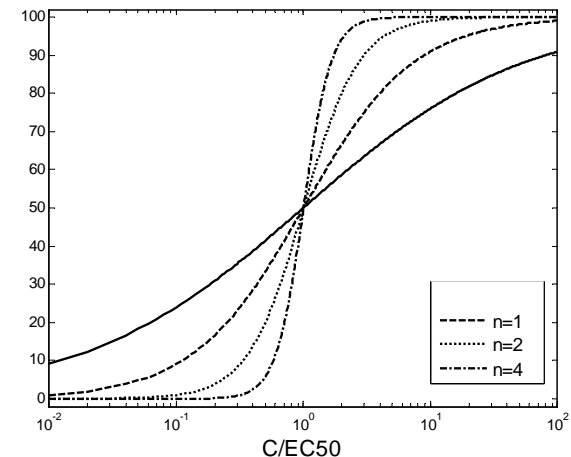
# Summary: GTN Tolerance

- Short term exposure data is well fit by minimal model at GTN concentrations that will be used in long term probe experiments.
- Long term experiments reasonably well fit assuming two pools of “factor” F that reacts with GTN. One pool is assumed to be continuously replaced by biosynthesis while other pool is not replaced.

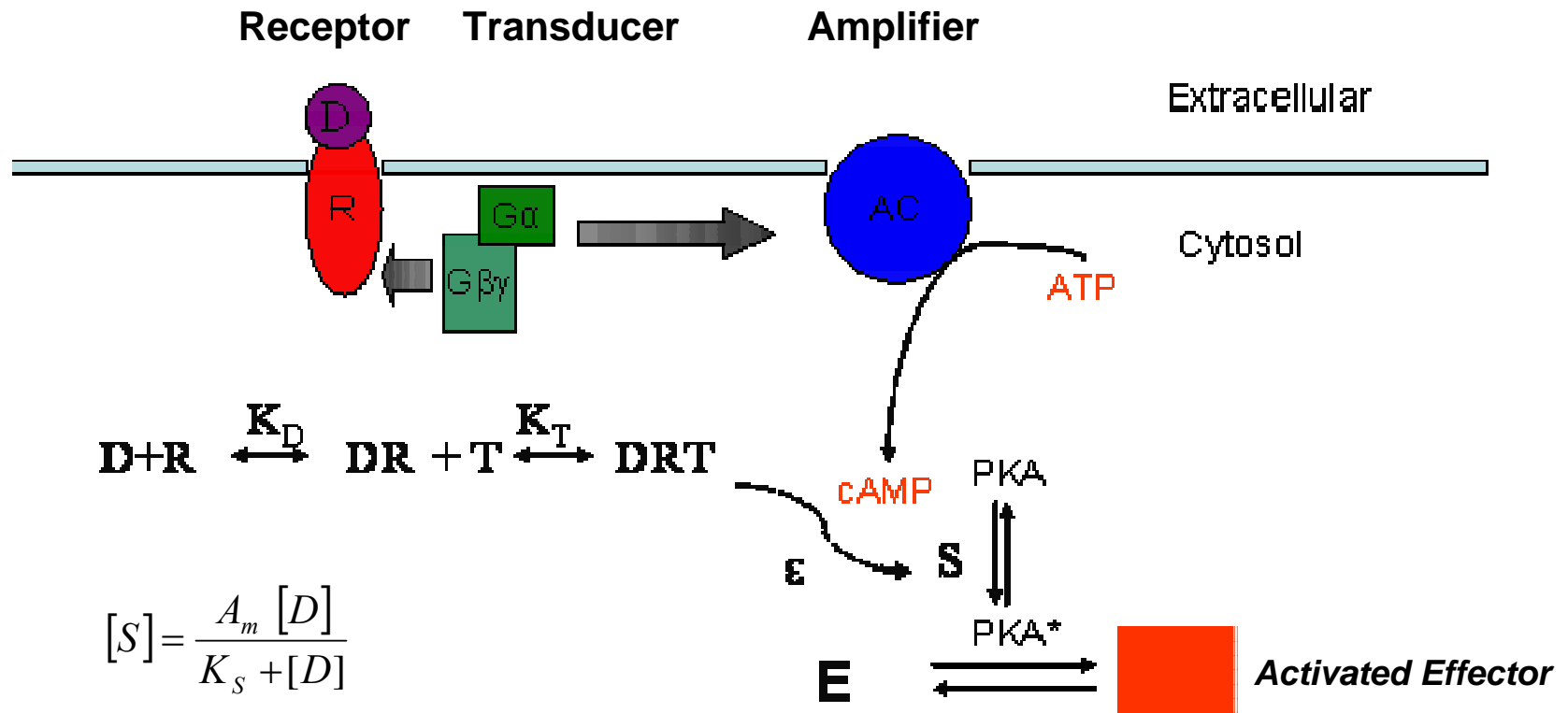
# A Dynamic “Cellular” Model for PD Variability (Jee Eun Lee)

- Both PK and PD variability contribute to response variations across populations, and may be associated with disease states or biological rhythms.
- For certain drugs, PD variability is dominant
- PD variability is seen in potency ( $EC_{50}$ ), efficacy ( $E_{max}$ ), and sensitivity (n).

Emax (Hill) Model: 
$$E = \frac{E_{max} C^n}{EC_{50}^n + C}$$



# Signal Transduction with Tolerance: G-Protein Coupled Receptors (GPCR's)



Potency and Efficacy Depend on Receptor, Transducer, and Amplifier Levels

# Zero Order Ultrasensitivity (A. Goldbeter and D. Koshland)



## Saturable (Michaeli-Menten) Conversions

$$R_{\textit{kin}^*} = V_{M,\textit{kin}^*} \frac{[E]}{K_{M,\textit{kin}^*} + [E]} \quad ; \quad R_{\textit{phos}} = V_{M,\textit{phos}} \frac{[E^*]}{K_{M,\textit{phos}} + [E^*]}$$

## (Quasi)Steady State

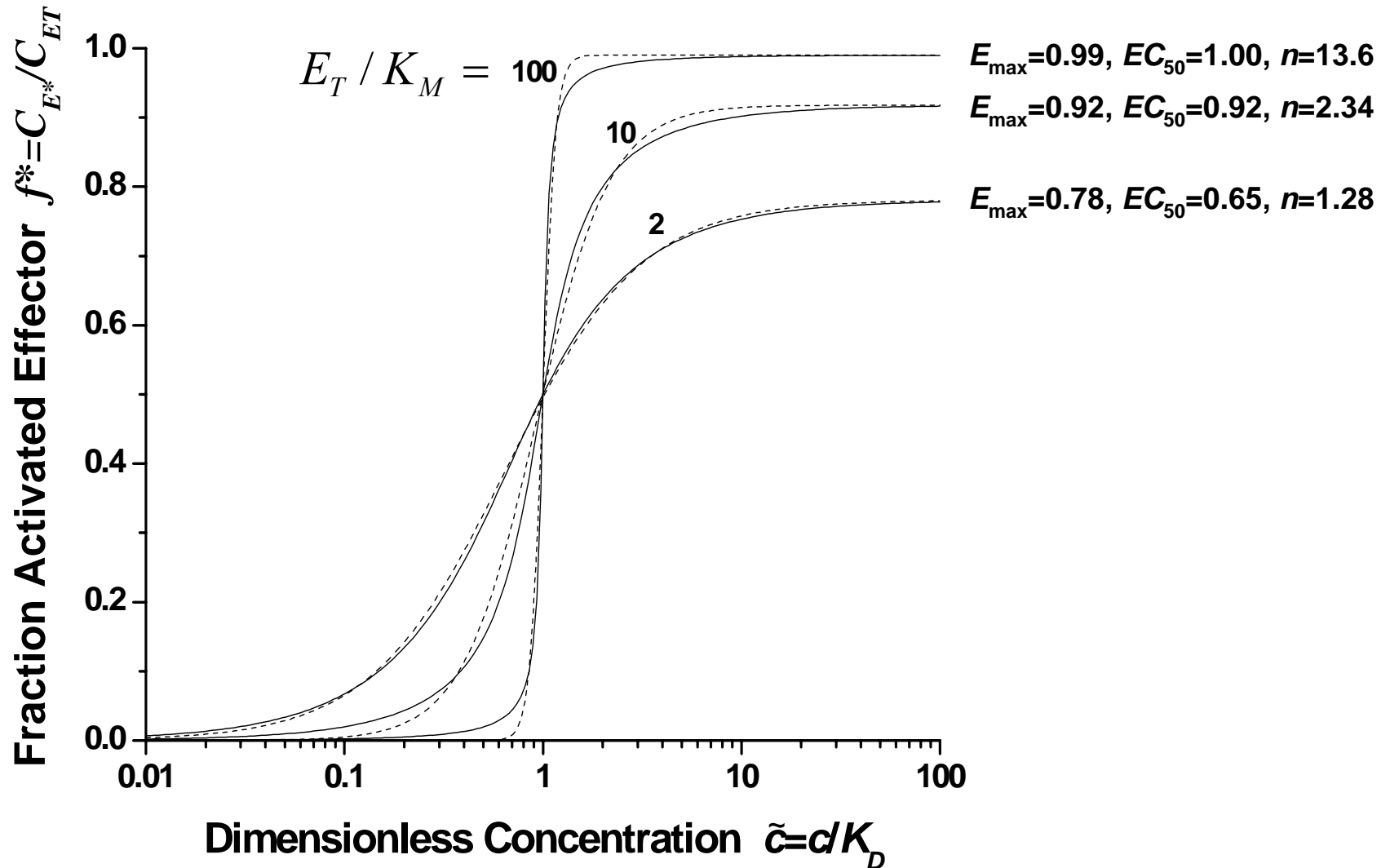
$$R_{\textit{kin}^*} = R_{\textit{phos}} \quad \longrightarrow \quad \frac{[E^*](K_{M,\textit{kin}^*} + [E])}{[E](K_{M,\textit{phos}} + [E^*])} = \frac{V_{M,\textit{kin}^*}}{V_{M,\textit{phos}}}$$

When  $E_T \gg K_{M,\textit{kin}^*}, K_{M,\textit{phos}}$ , near switchlike behavior ensues

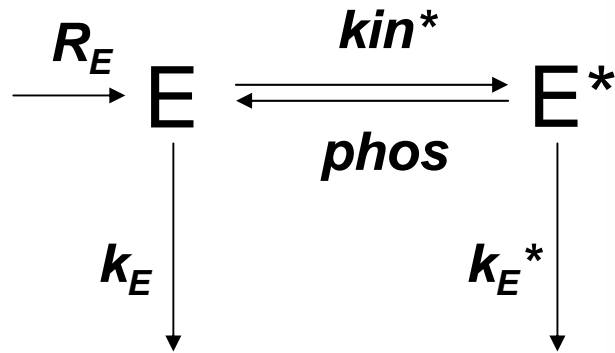
$V_{M,\textit{kin}^*} < V_{M,\textit{phos}} \Rightarrow [E^*] \ll [E]$ ; mostly inactive effector

$V_{M,\textit{kin}^*} > V_{M,\textit{phos}} \Rightarrow [E^*] \gg [E]$ ; mostly active effector

# Zero-Order Ultrasensitivity

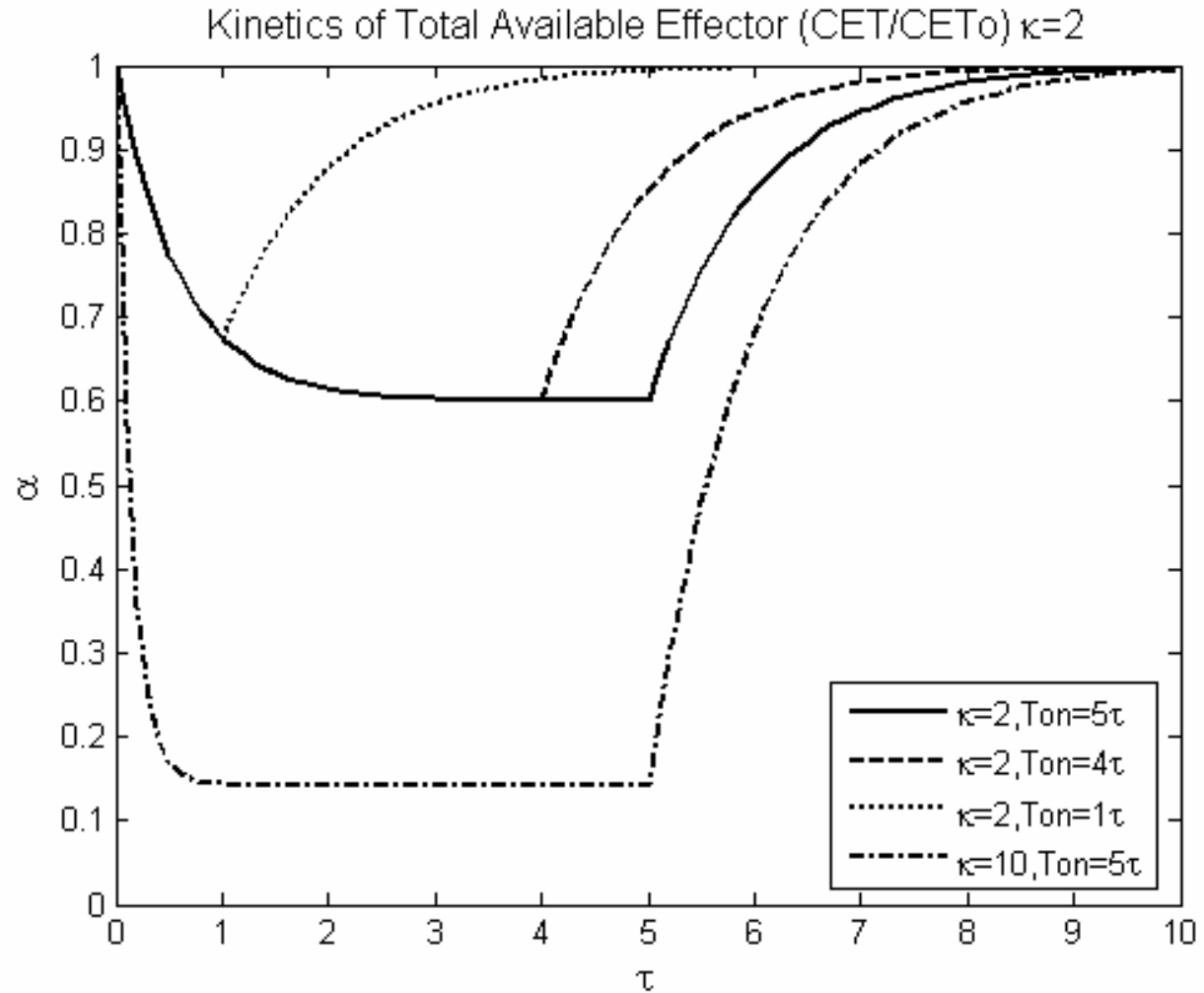


# Tolerance Kinetics

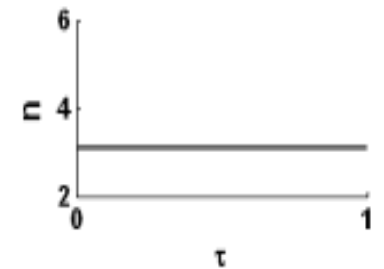
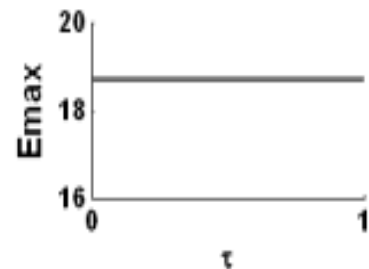
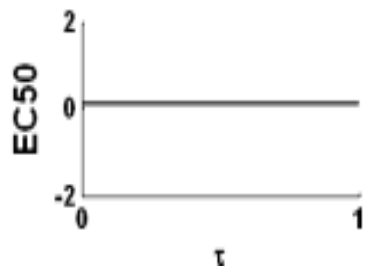
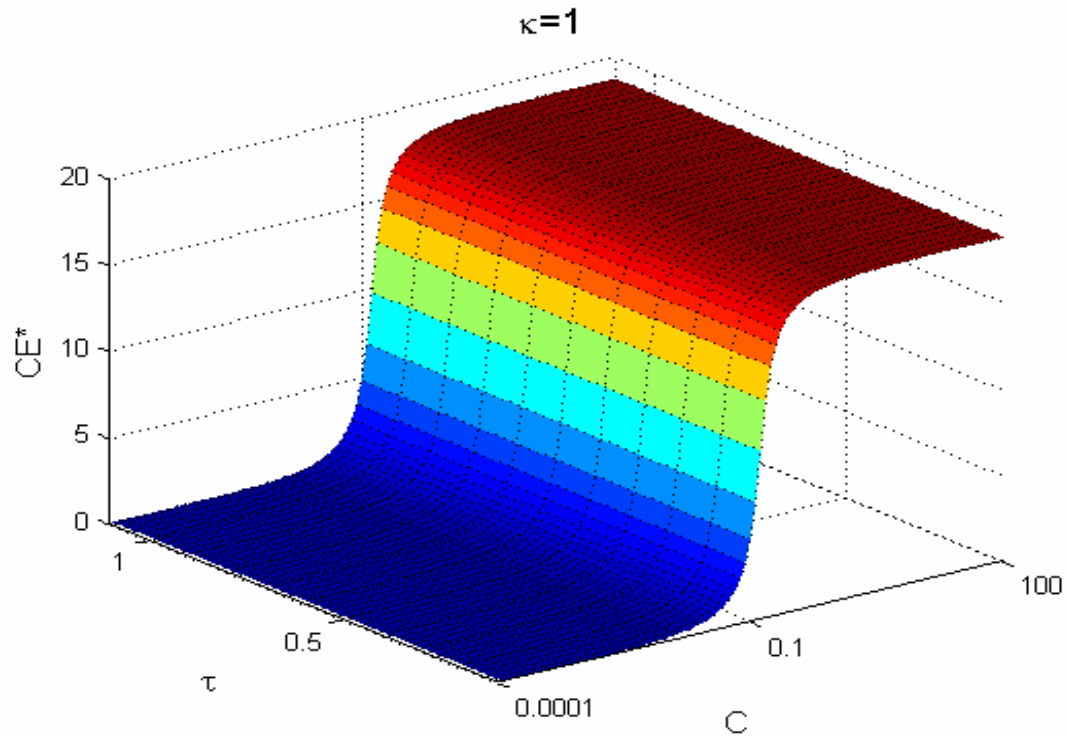


$$\kappa = k_{E}^* / k_E$$

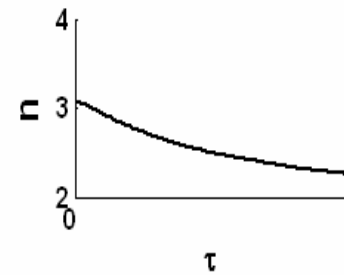
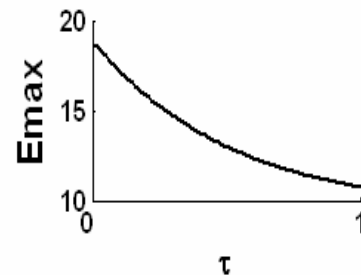
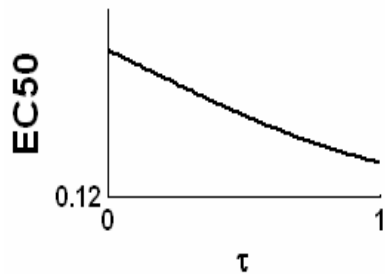
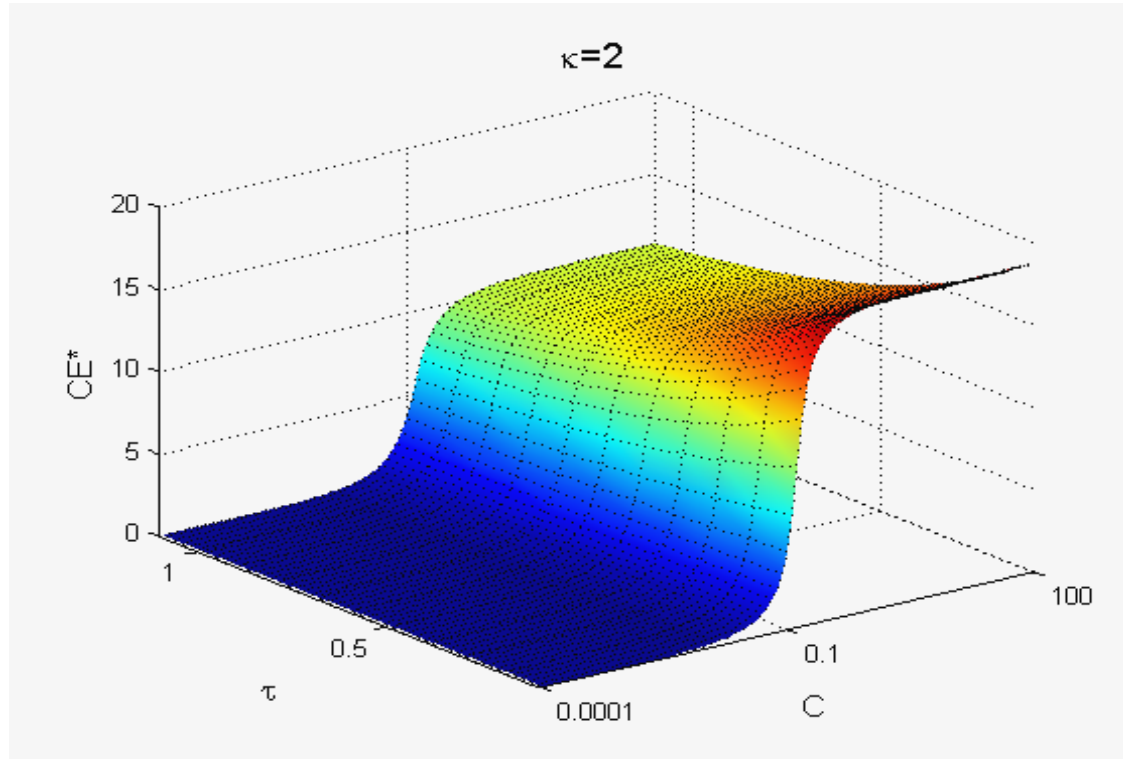
$$\tau = k_E t$$



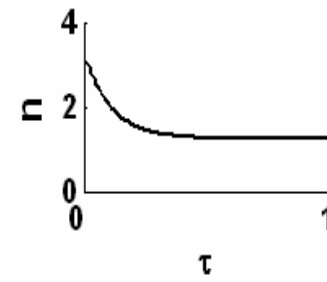
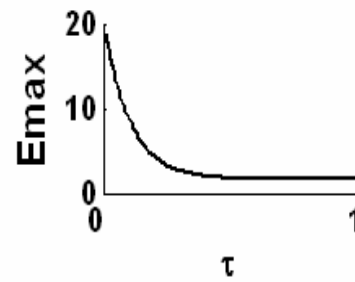
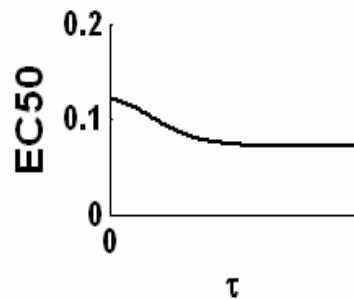
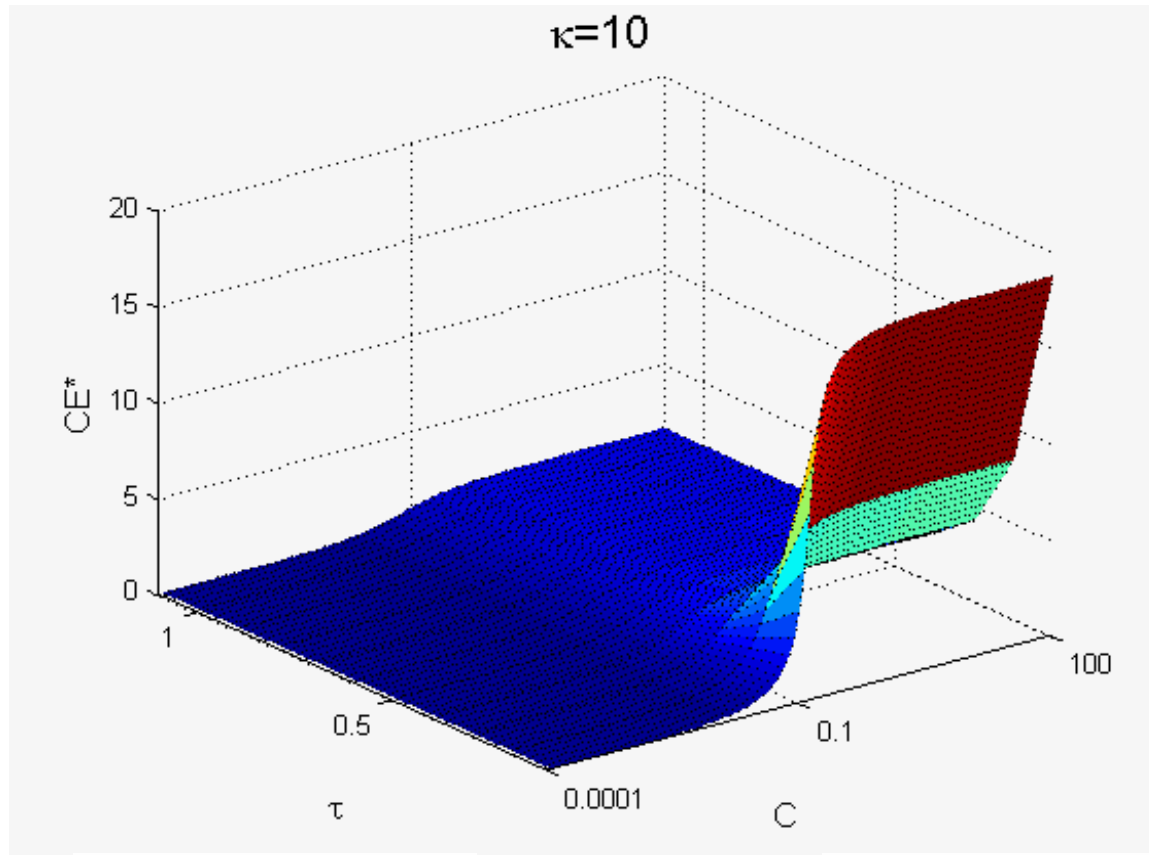
# No Tolerance ( $\kappa = 1$ )



# Weak Tolerance ( $\kappa = 2$ )



# Strong Tolerance ( $\kappa = 10$ )

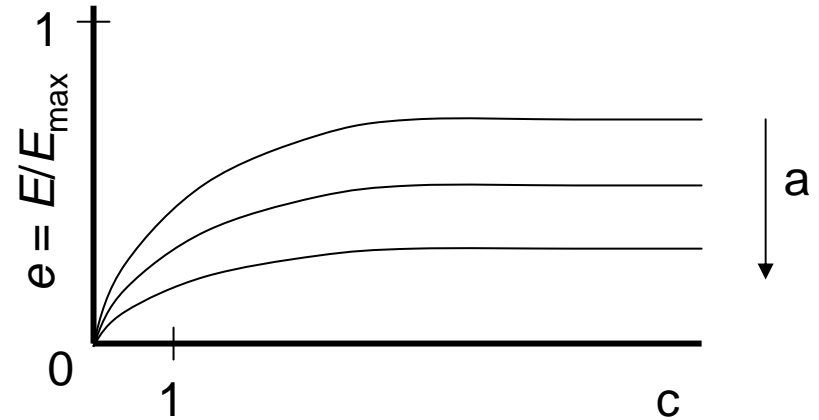
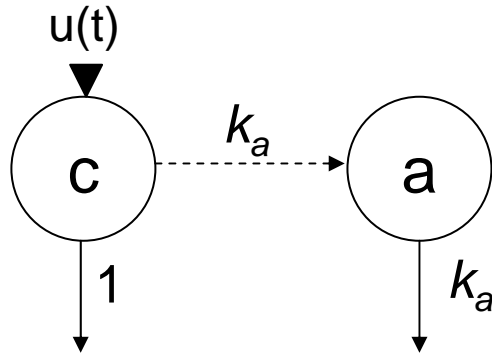


# Summary: Signal Transduction/Tolerance Model

- Model considers transduction events leading to activation of an effector by a kinase, which is opposed by deactivation by a phosphatase. Tolerance is manifestation of preferential degradation of activated effector.
- Potency and efficacy are affected by receptor, transducer, and amplifier levels in cell membrane. Sensitivity (Hill coefficient) is primarily affected by total level of effector relative to binding (Michaelis) constants of kinase and phosphatase.
- Tolerance leads to changes in efficacy, potency, and sensitivity.

# Optimal Infusion Schedule for Drugs with Tolerance

- Modified Porchet-Sheiner model (nicotine):



$$\frac{dc}{dt} = -c + u(t)$$

$$\frac{da}{dt} = k_a(c - a)$$

$$e = \frac{c}{(1+c)(1+a/a_{50})}$$

- Objective: Find  $u(t)$  that *maximizes* fraction of time over which drug effect exceeds a threshold value, i.e.

$$e(t) > e_{\min}$$

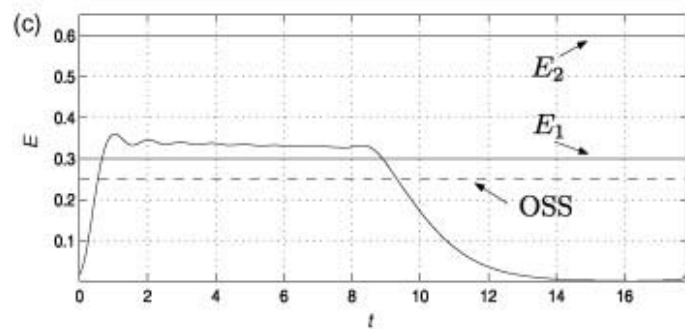
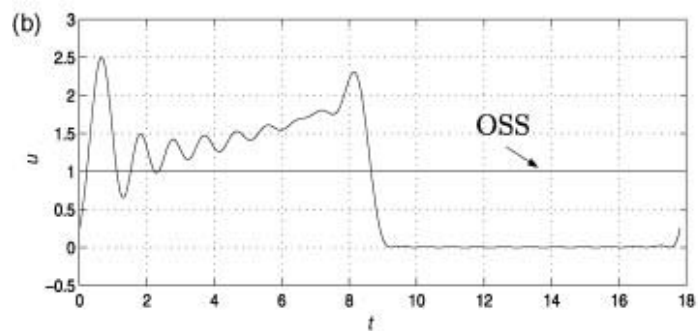
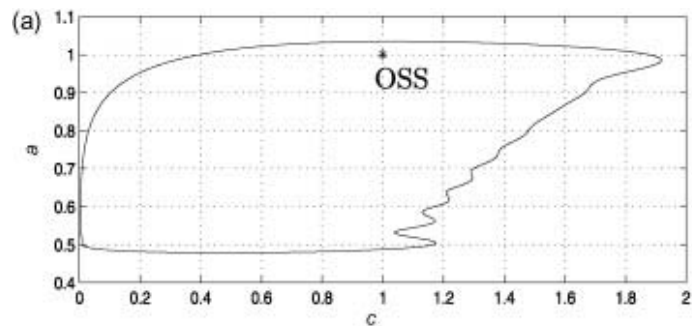
- Steady state solution:  $\bar{a} = \bar{c} = \bar{u}$

If  $\max \frac{\bar{u}}{(1+\bar{u})(1+\bar{u}/a_{50})} \geq e_{\min}$ , then constant infusion is optimal

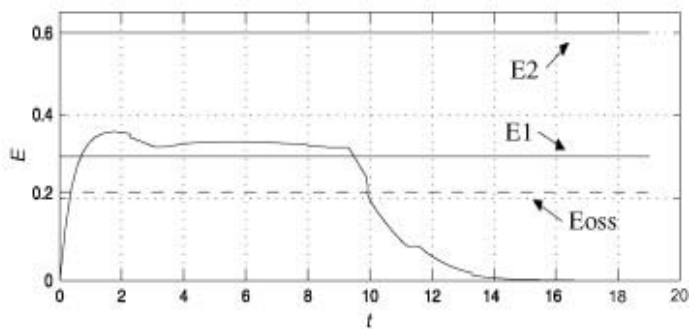
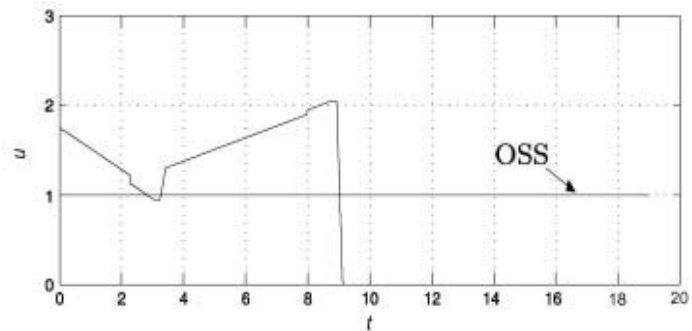
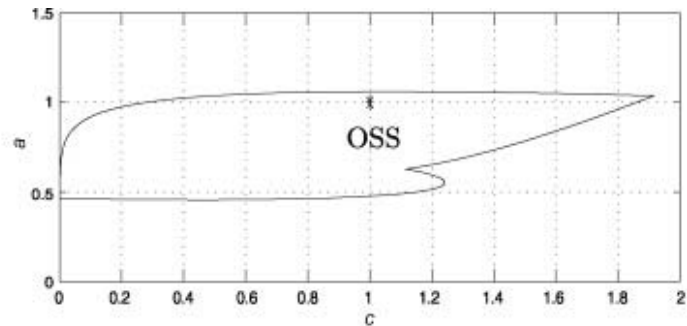
Otherwise, periodic solution is needed

- Search for optimal periodic solutions  $u(t)$ : Use Fourier series or piecewise linear functions constrained to be periodic.

## Fourier Series



## Piecewise Linear



# Summary: Optimal Infusion under Tolerance

- Under tolerance condition, average time with drug effect exceeding a minimal threshold level is obtained either with constant infusion, or with periodic infusion waveform.
- Periodic infusion waveform starts with bolus to boost effect over threshold, followed by steadily increasing infusion rate. When infusion can no longer keep effect above threshold, drug should be shut off to permit regeneration of efficacy.

# Acknowledgments

- Henning Schröder, Lewis Sheiner (GTN work)
- Prodromos Daoutidis (Optimal Infusions)