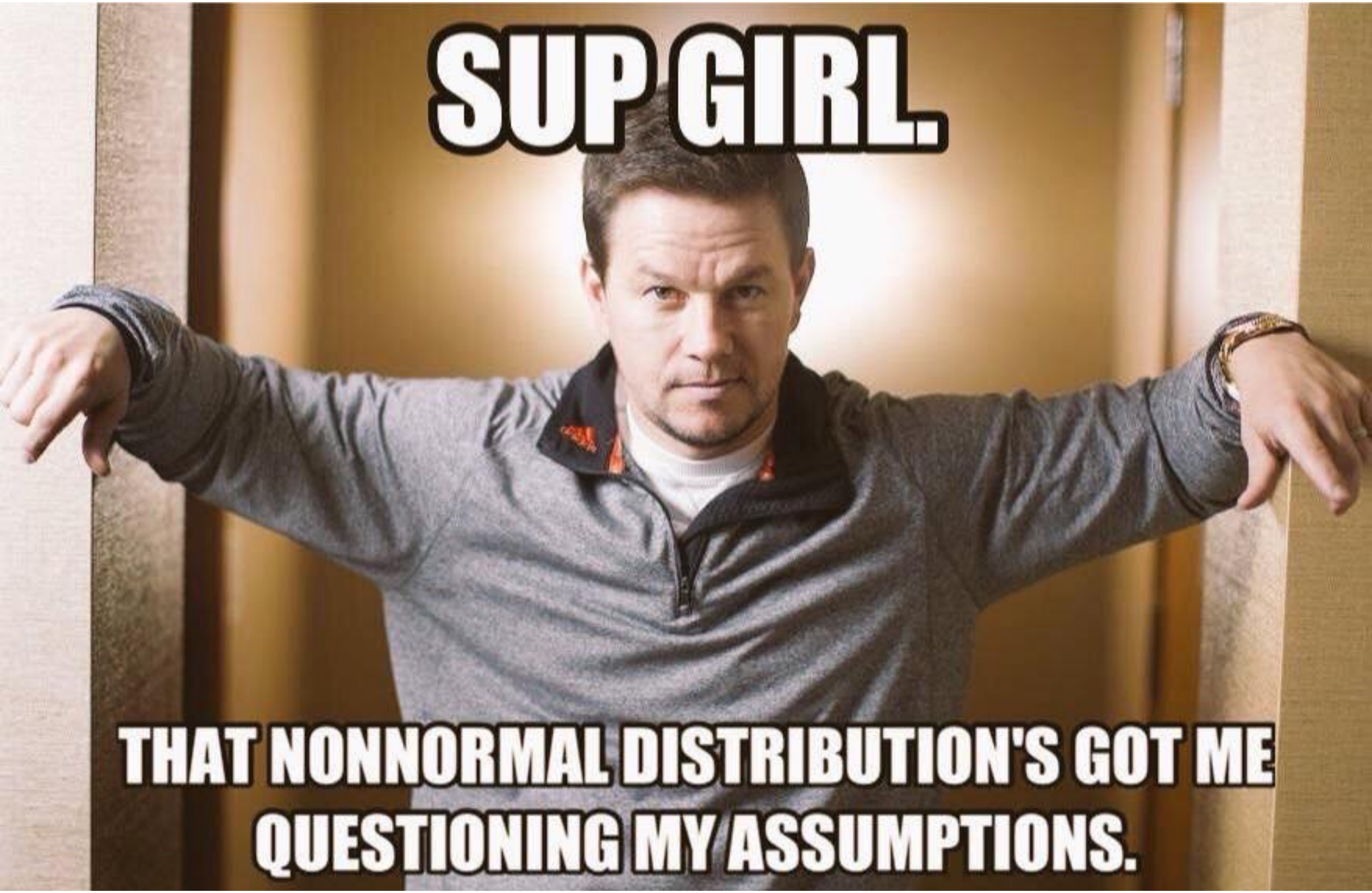

SUP GIRL.
THAT NONNORMAL DISTRIBUTION'S GOT ME
QUESTIONING MY ASSUMPTIONS.

Nonlinear Equations (Ch. 5)

- You can skip sections 5.3, 5.4 (regula-falsi and fixed-point iteration)
- So far we have focused on linear equations. This is because we can solve these equations in a finite number of steps!

$$\mathbf{Ax} = \mathbf{b} \text{ is solved in } (N^3) \text{ steps!}$$

Nonlinear Equations (Ch. 5)

- Example : suppose we are trying to fit some reaction rate data as a function of T.
- If we have a <u>single irreversible</u> reaction:

$$k = a\, e^{-E_a/k_B T}$$

a: pre-exponential factor

E_a: activation energy

k_B: Boltzmann's constant

Nonlinear Equations (Ch. 5)

- If we have a series of measured reaction rates $k_i(T_i)$ we can solve for a and E_a using <u>linear</u> regression.
- Transform equation: $\underset{b}{\ln k} = \underset{x_1}{\ln a} - \underset{x_2}{E_a/k_B}\,(1/T)$
- So find the **x** that minimizes norm$(\mathbf{Ax}-\mathbf{b})^2$, where $\mathbf{b} = (\ln k_1; \ln k_2; \ldots; \ln k_n)$

  and $\mathbf{A} = (1, 1/T_1; 1, 1/T_2; \ldots; 1, 1/T_n)$.

Nonlinear Equations (Ch. 5)

- So we know how to solve that. Suppose now we have a more complex problem in which a substance can follow 2 reaction pathways.
- In this case:

$$k = a_1 e^{-E_{a1}/kT} + a_2 e^{-E_{a2}/kT}$$

- You can't linearize this!
- We can still set it up as a least squares problem…

Nonlinear Equations

- So we still find the x that minimizes

  $\text{norm}(k_i - k(T_i))^2 = S(\mathbf{x})$,

  where $\mathbf{x} = (a_1; E_{a1}; a_2; E_{a2})$.
- We can determine the minimum by requiring

  $dS(\mathbf{x})/d\mathbf{x} = 0$: 4 equations with 4 unknowns.

- But this is a <u>nonlinear problem</u>.

Nonlinear Equations

- Nonlinear problems are <u>nasty</u> because:
  1. It may not have a unique solution!

     You may have multiple roots, local minima, etc.

     For linear problems (non-singular) you are

     <u>guaranteed</u> a unique solution!
  2. For linear systems, you can solve it in a finite number of steps ($O(n^3)$).

     For nonlinear problems there is <u>no</u> guarantee – sometimes algorithms will fail to converge on <u>any</u> solution!

Nonlinear Equations

- Let's focus on the problem $f(x) = 0$

  (we'll generalize this to the system $\mathbf{f}(\mathbf{x}) = \mathbf{0}$ later)
- Let x^* satisfy $f(x^*) = 0$
- We will say that x' "solves" $f(x)=0$ if:

  $$|f(x')| \sim 0 \quad \text{or} \quad |x' - x^*| \sim 0$$

  (~ 0 means less than some set tolerance)
- We need this dual definition because $f(x)$ may have a steep slope near x^*.

Method of Bisection

- The approaches to solving $f(x) = 0$ are iterative – we obtain a series (sequence) of approximations to the solution:

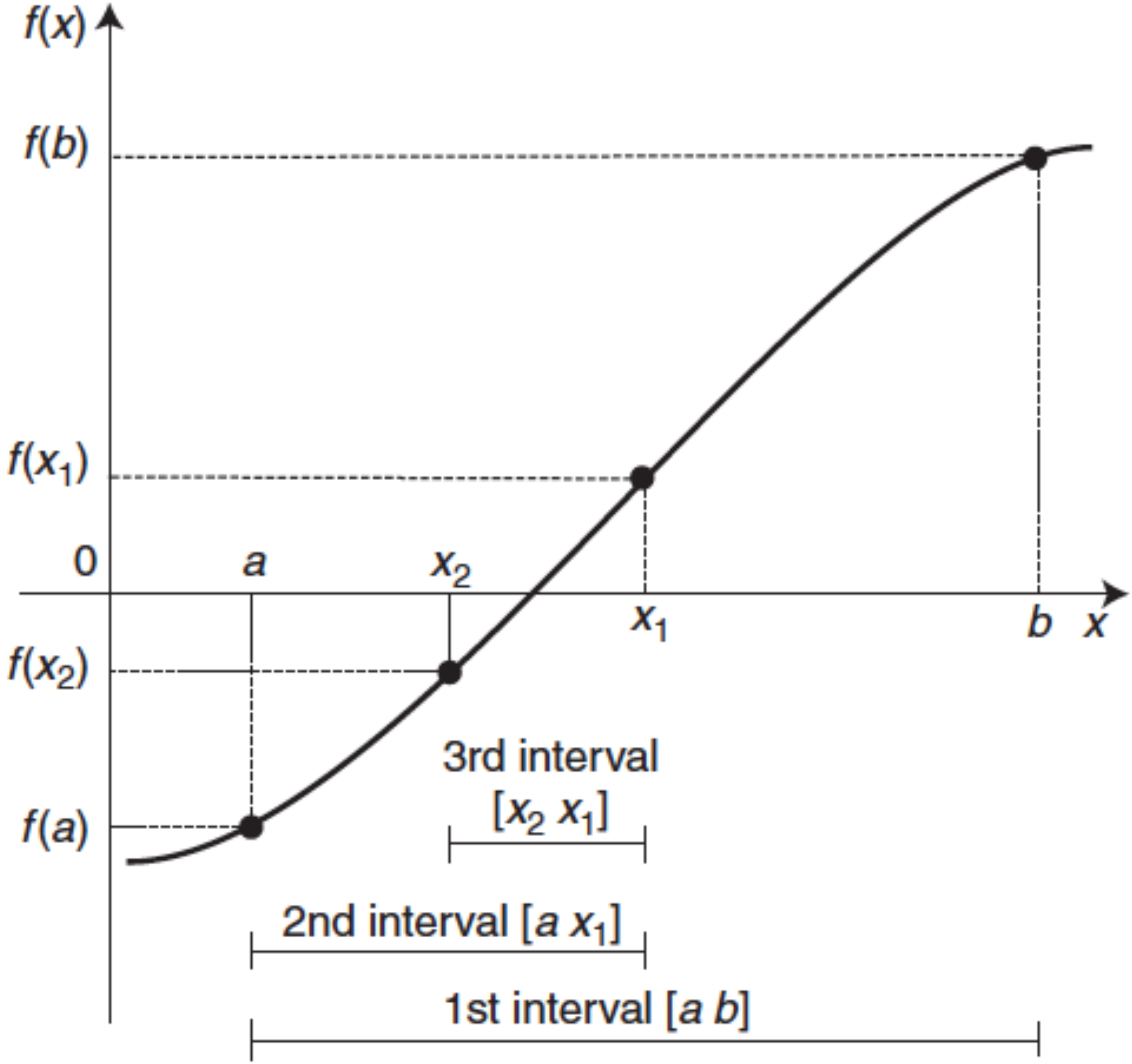
$$x_1, x_2, x_3, \ldots, x_n$$

  which hopefully converges on x^* !
- How do we do this?
- The simplest approach is the method of bisection.

Method of Bisection

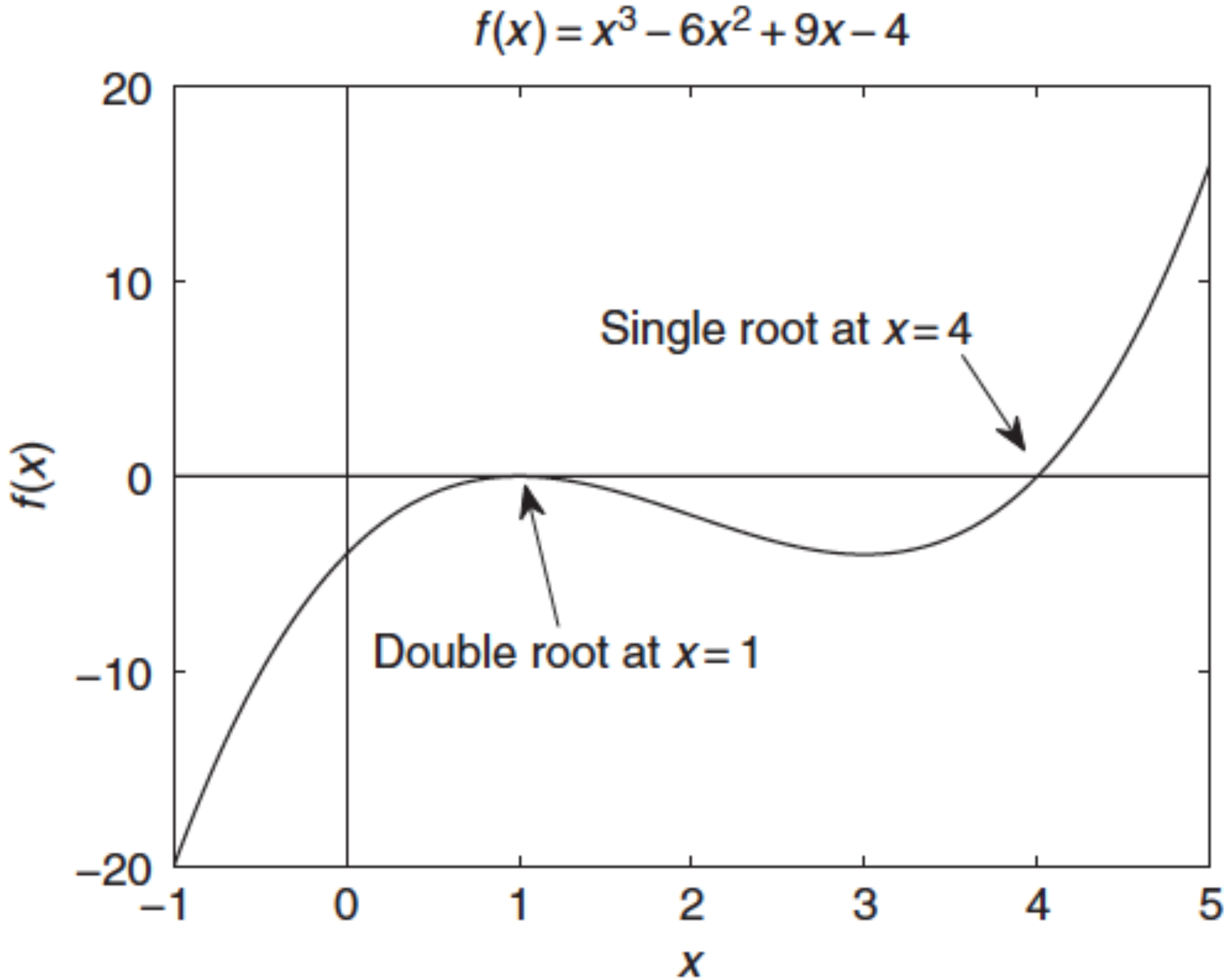
- Suppose $f(x)$ is <u>continuous</u> over the interval $x \sim [a,b]$ <u>and</u> that $f(a)f(b) < 0$.
- Then we <u>know</u> that there is <u>at least</u> one root in this interval!
- We can get within some interval of x^* in a finite number of steps!
- We divide the interval in half and test to see which is satisfied:

  $f(a)f(m) < 0$ <u>or</u> $f(m)f(b) < 0$, where $m=(a+b)/2$
- We just keep the half with the root!



f(x)
f(b)
f(x1)
0
a
x2
x1
b
x
f(x2)
f(a)
3rd interval
[x2 x1]
2nd interval [a x1]
1st interval [a b]

Method of Bisection



Method of Bisection

- How fast does this converge?
- Each iteration divides the interval in half, the midpoint is an estimate of x*, thus

$$|m - x^*|$$

is cut in half (approximately) at each iteration.

- The error is less than 10^{-7} of the original interval after about 24 iterations.

Method of Bisection

- Let's take e_i as the error at the ith iteration (e.g., $m - x^*$).
- Then for bisection, $|e_{i+1}|/|e_i| \sim ½$ on average.
- In general, a method is said to converge at a rate r if:

$$\text{limit}(i \to \text{inf})\ |e_{i+1}|/|e_i|^r = c$$

- In general, $|e_i| << 1$ so we want r to be large (>1) and c to be small.

Nonlinear Equations

- If c is too large the method won't converge!
- If r=1 the method is linear
- If r=2 the method is quadratic
- If r>1 the method is superlinear

- For bisection, r=1 (linear convergence).

Q1: Is the following model “linear”? Meaning, can it be formulated as a linear regression?

$$y = a \cdot e^{-kt}$$

A. Yes
B. No

Q2: How many <u>model parameters</u> does this model have?

$$y = a \cdot e^{-kt}$$

A. 1
B. 2
C. 3
D. 4

Q3: How about the following model. Is it “linear”? Can it be formulated as a linear regression?

$$y = a_1 \cdot e^{-k_1 t} + a_2 \cdot e^{-k_2 t}$$

A. Yes
B. No

Q4: Okay, so we must use nonlinear regression to fit this model to a data set. So how many model parameters does it have?

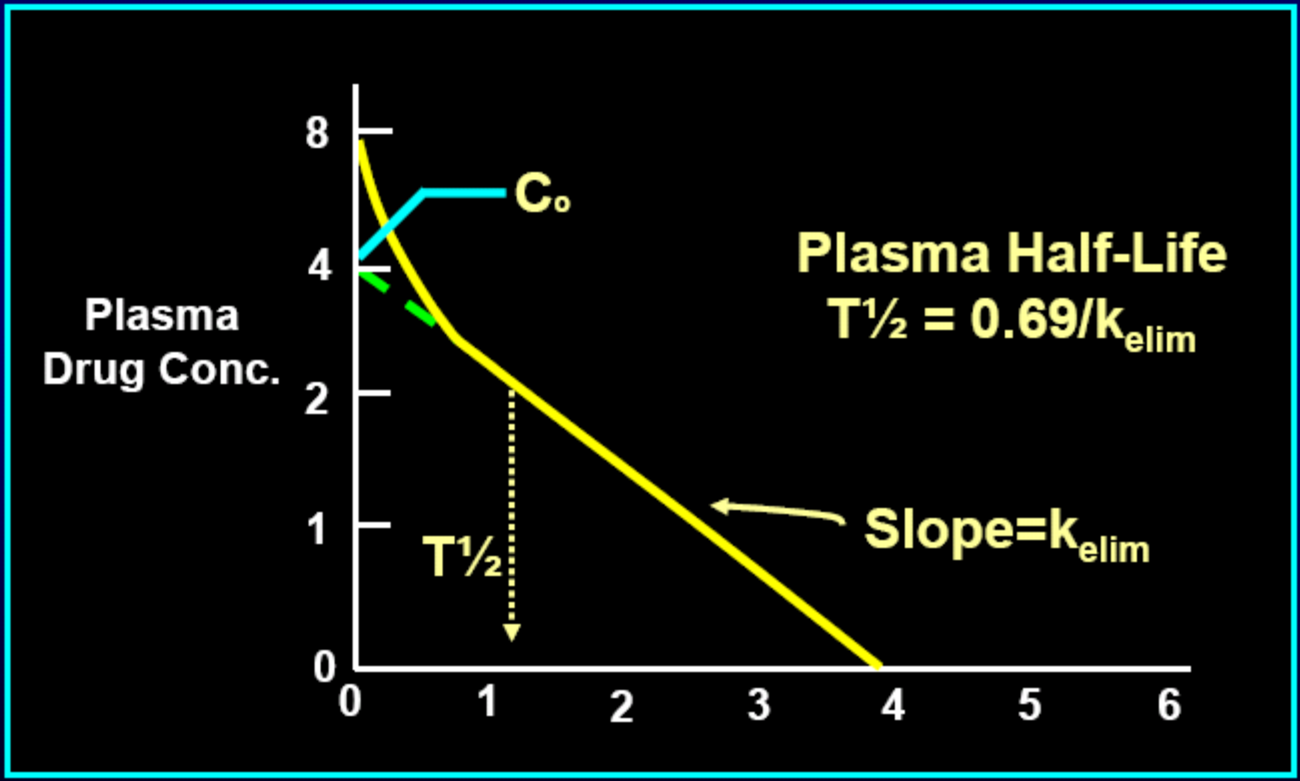
$$y = a_1 \cdot e^{-k_1 t} + a_2 \cdot e^{-k_2 t}$$

A. 1
B. 2
C. 3
D. 4
E. 5

A. The Single Compartment Model of drug distribution assumes that the drug distributes evenly throughout a single homogeneous space in the body. While this is obviously an over-simplification, it often allows us to predict the general pharmacokinetic properties of the drug sufficiently well for clinical use.

B. The Apparent Volume of Distribution (V_d) of this single compartment can be estimated by dividing the intravenously administered dose by the initial blood concentration (C_o):

$$V_d = \text{IV Dose} / C_o$$



Simple Compartmental Model (lumped)

Absorption → **Body** → Elimination

R or k_0 $\qquad$ k_1

1st order absorption: $\dfrac{dA}{dt} = -k_0 A$ $\qquad$ $\dfrac{dE}{dt} = k_1 B$ $\qquad$ $\dfrac{dB}{dt} = k_0 A - k_1 B$

Solution: $A(t) = A_0 \exp(-k_0 t)$

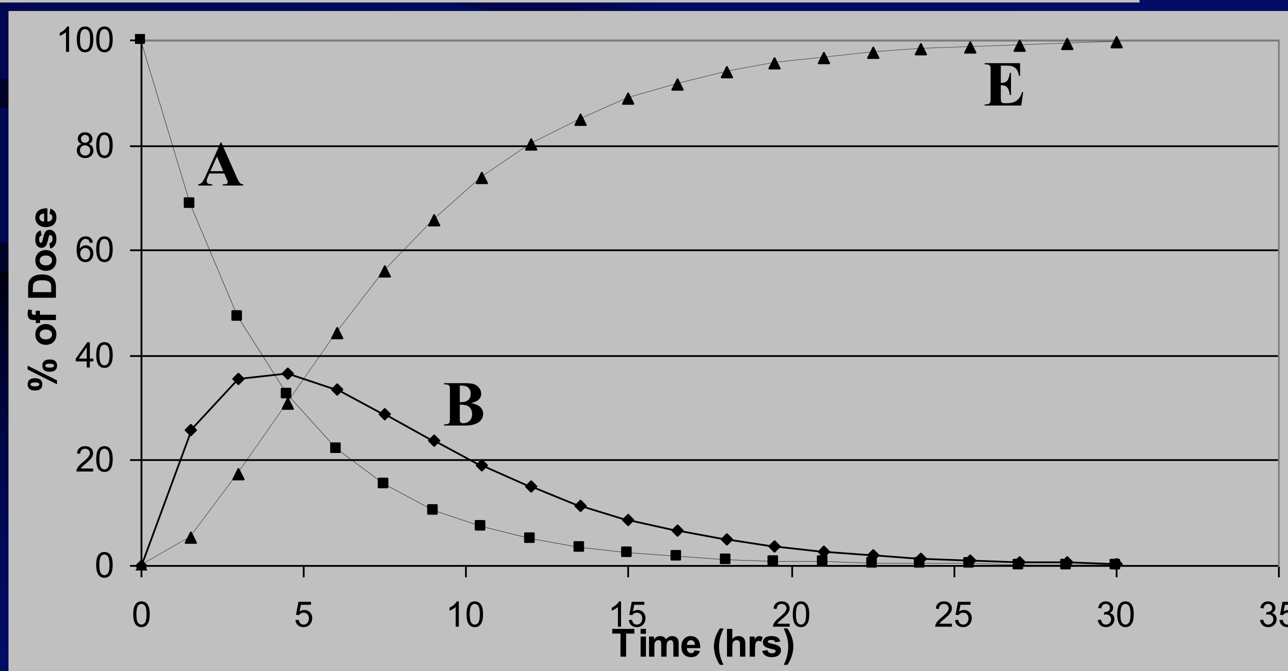
$$B(t) = \frac{k_0 A_0}{k_1 - k_0} = [\exp(-k_0 t) - \exp(k_1 t)]$$

$$E(t) = A_0 - A(t) - B(t) = A_0 \left\{ 1 - \left(\frac{1}{k_1 - k_0} \right) [k_1 \exp(-k_0 t) - k_0 \exp(-k_1 t] \right\}$$

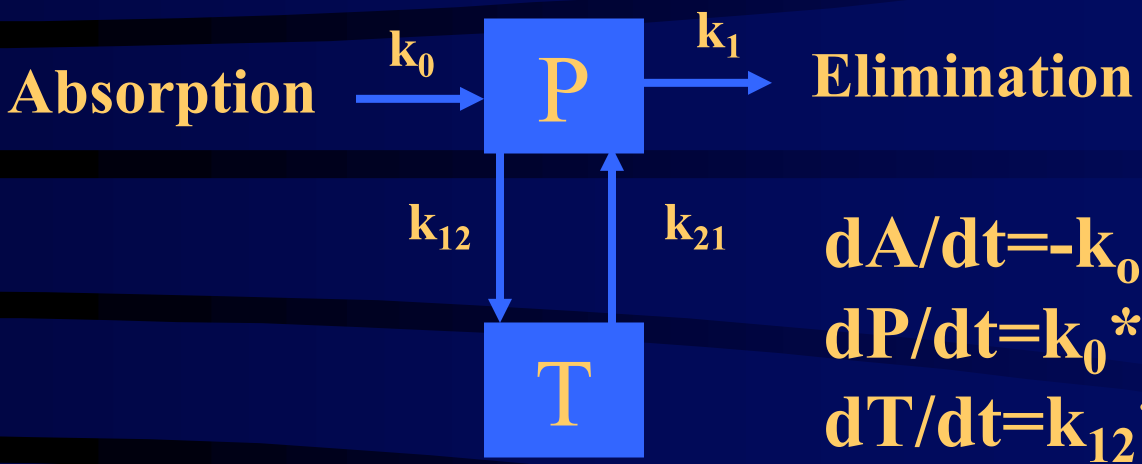
IC's: $A(o)=A_0$

$B(0)=0$

$E(o)=0$



Simple Compartmental Model (lumped)



$$dA/dt=-k_o*A$$
$$dP/dt=k_0*A-k_1*P-k_{12}*P+k_{21}*T$$
$$dT/dt=k_{12}*P-k_{21}T$$
$$dE/dt=k_1P$$