

# Physiological Modeling

## Parametric

- *Structural*
- *System Components*
- *Differential Equations*

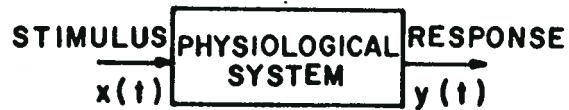
Rate Processes

## Nonparametric

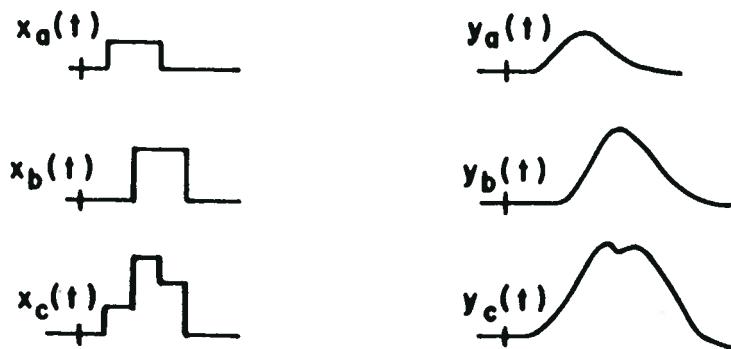
- *Functional*
- *System Kernels*
- *Integral Equations*

Input-Output Maps

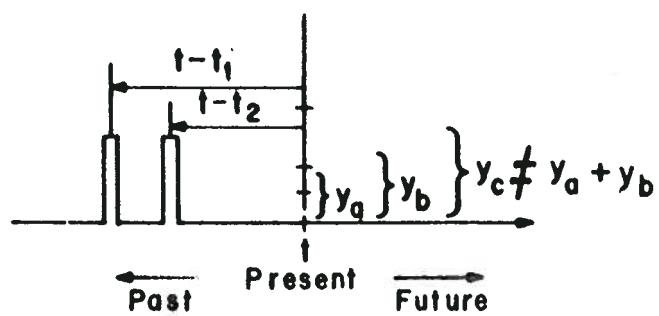
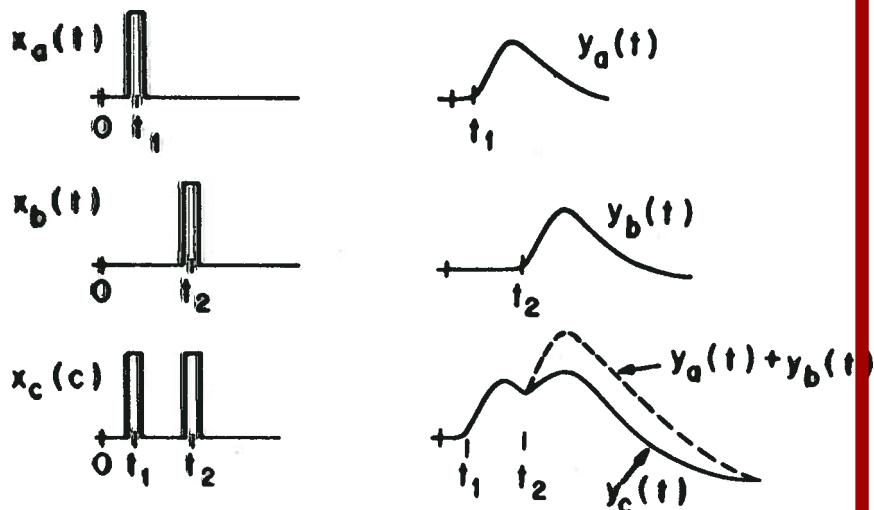
# Linear and Nonlinear Systems



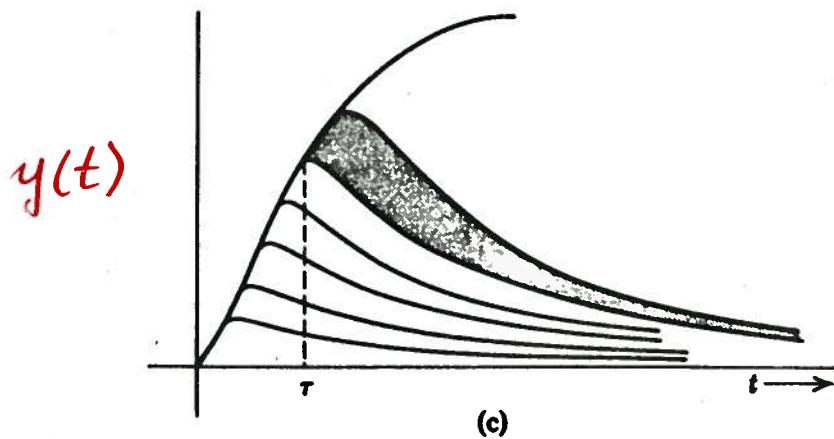
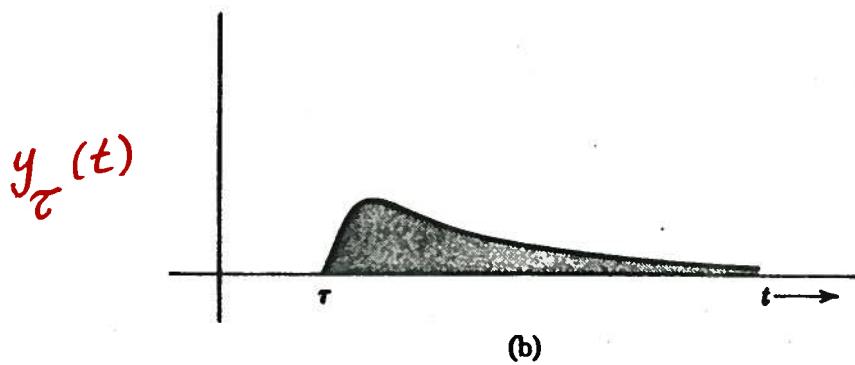
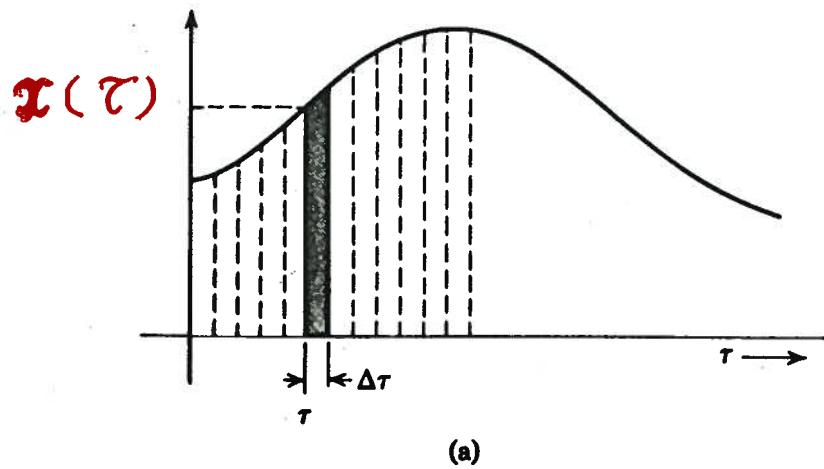
Linear



Non linear



# Response of a Linear System



If  $x(\tau)$  is represented as a sum of narrow pulses of width  $\Delta\tau$  and height  $x(\tau)$ . As  $\Delta\tau \rightarrow 0$  each narrow pulse becomes an impulse of strength  $x(\tau) \Delta\tau$ .

The response of the system to a unit impulse at  $\tau$  is  $h_L(t-\tau)$ . Hence, the response to an impulse of strength  $x(\tau) \Delta\tau$  is

$$y_\tau(t) = \lim_{\Delta\tau \rightarrow 0} x(\tau) \Delta\tau h_L(t-\tau)$$

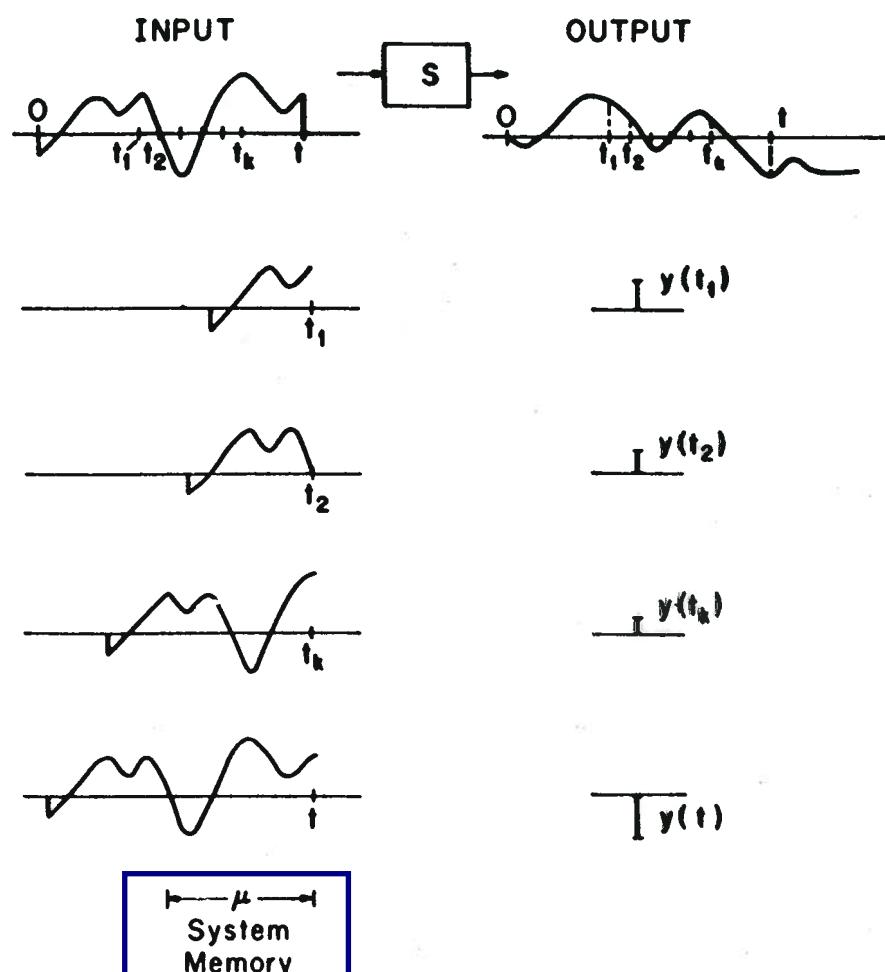
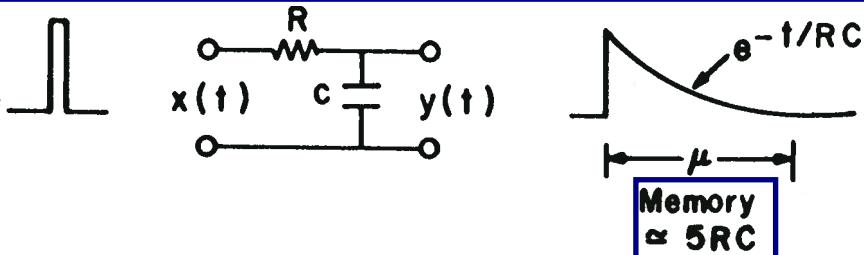
The response  $y(t)$  is the sum of such responses from  $\tau=0$  to  $\tau=t$

$$\begin{aligned} y(t) &= \lim_{\Delta\tau \rightarrow 0} \sum_{\tau=0}^t x(\tau) h_L(t-\tau) \Delta\tau \\ &= \int_0^t x(\tau) h_L(t-\tau) d\tau \end{aligned}$$

This is called the **Convolution Integral**

# Output Dependence on the Input Past

## System Memory



**Definition :** A functional is a function of a function (i.e. a function whose argument is a function) and whose value is a number. We may write it as

$$y = F [x(t)]$$

where  $F$  is the functional, the function  $x(t)$  is the argument, and  $y$  is the value of the functional.

**Example :**

The convolution integral

$$y(t) = \int_0^t x(\tau) h_L(t-\tau) d\tau$$

is a functional representation of a linear system.

# Vito Volterra [1860 (Ancona) - 1940 (Roma)]



Vito Volterra was an **Italian mathematician and physicist**. He is known for his contributions to **mathematical biology** and **integral equations**. He joined the opposition to the Fascist regime (1922). Because of his political philosophy, he also refused to take a mandatory oath of loyalty (1931). He lived largely abroad, returning to Rome just before his death.

Royal Society (1910) - Royal Society of Edinburgh (1913)  
A moon crater is named after him

# FIRST-ORDER VOLTERRA SYSTEMS

$$\begin{aligned}y(t) &= V_1 [x(t)] \\&= \int_0^{\infty} k_1(\tau) x(t-\tau) d\tau\end{aligned}$$

where

$V_1 [x(t)]$   $\cong$  First-order Volterra functional.

$k_1(t)$   $\cong$  First-order Volterra kernel .

## Example:

### Linear time-invariant systems

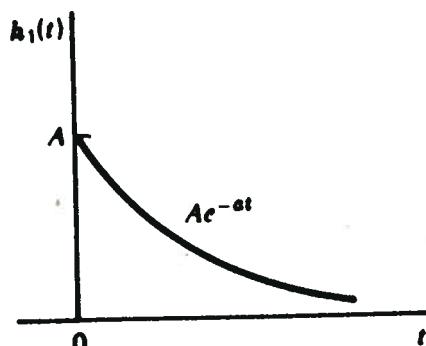
In this case  $k_L(t) = h_L(t)$

where  $h_L(t)$  is the impulse response of  
the system.

For example,  $h_L(t) = A e^{-at}$  for  
 $t \geq 0$  and  $a > 0$ .

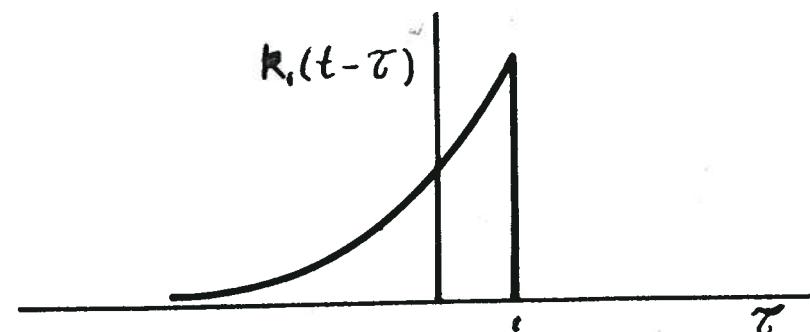
# Linear Time-Invariant System

$$k_1(t) = h_L(t)$$



$k_1(t)$

## Memory of System



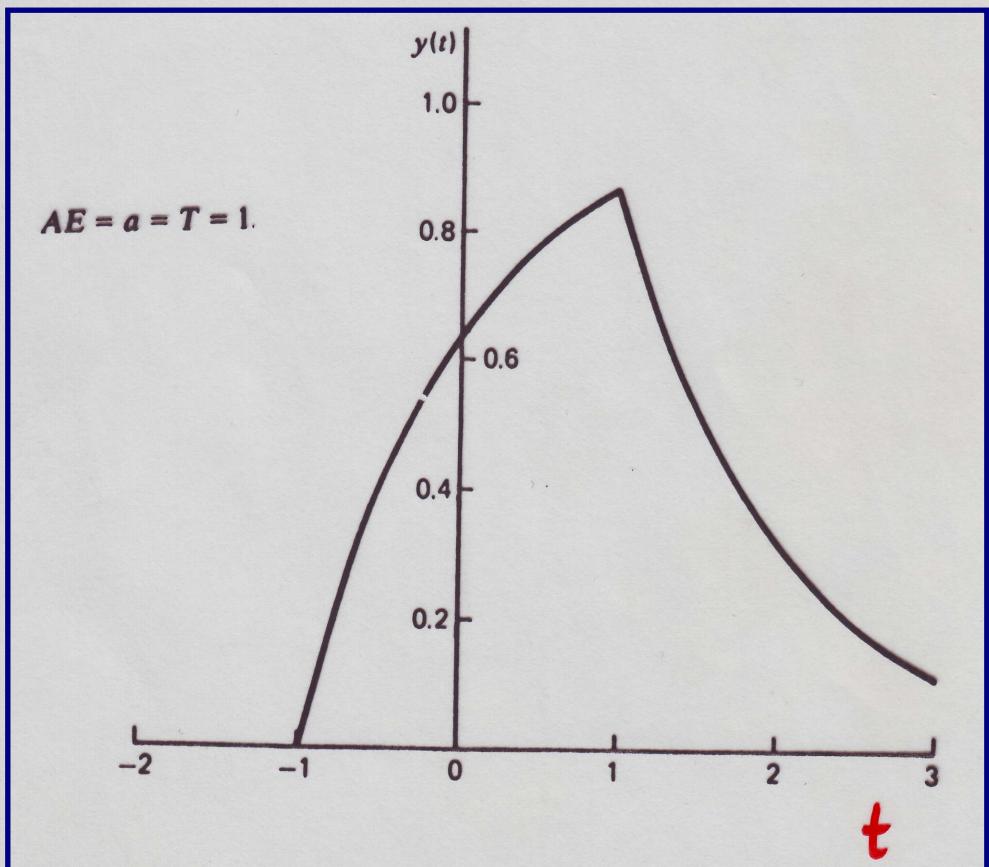
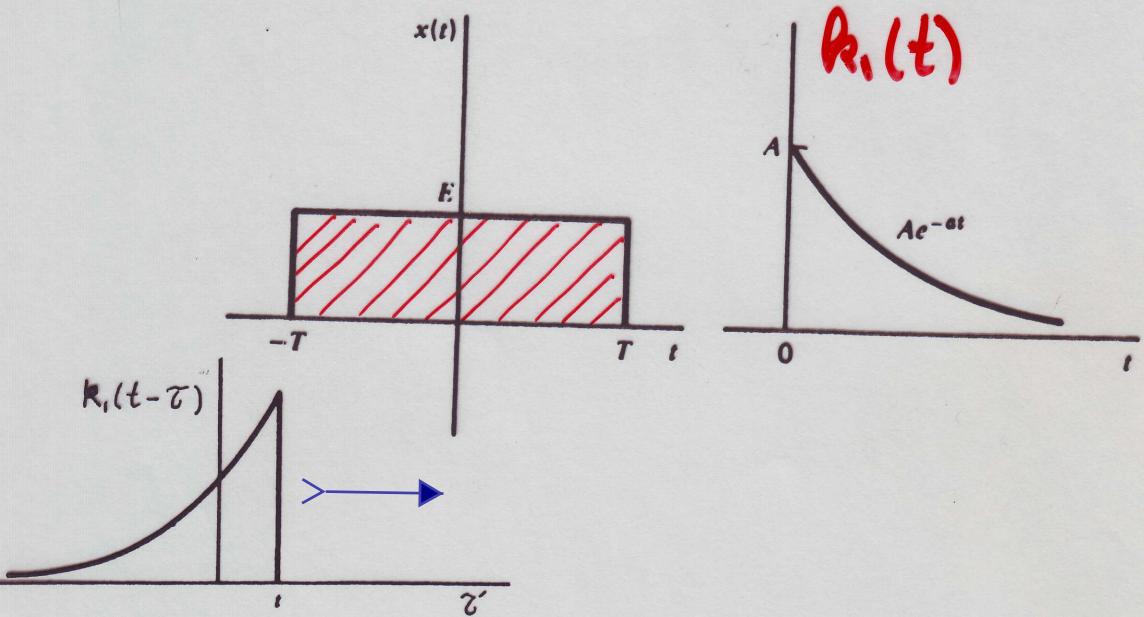
$k_1(t - \tau)$

$$y(t) = V_1 [x(t)] = \int_0^\infty x(\tau) k_1(t - \tau) d\tau$$

$$= \int_0^\infty k_1(\tau) x(t - \tau) d\tau$$

( The Convolution Integral )

For a rectangular input pulse  $x(t)$



## SECOND-ORDER VOLTERRA SYSTEMS

$$y(t) = V_2[x(t)]$$

$$= \int_0^\infty \int_0^\infty k_2(\tau_1, \tau_2) x(t - \tau_1) x(t - \tau_2) d\tau_1 d\tau_2$$

where

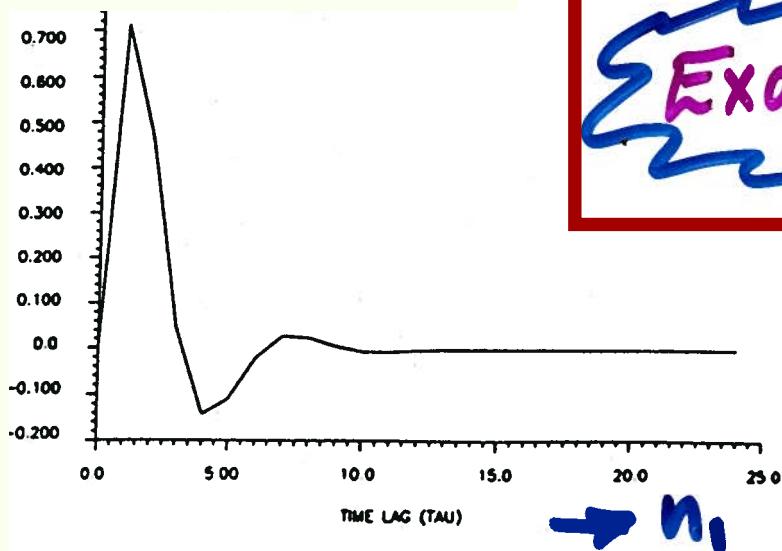
$V_2[x(t)] \triangleq$  Second-order Volterra functional.

$k_2(\tau_1, \tau_2) \triangleq$  Second-order Volterra Kernel.

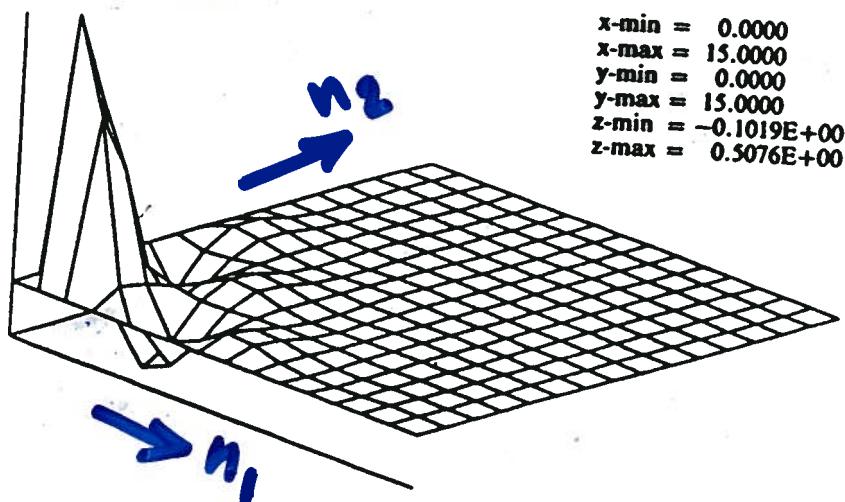
## General Second-Order Volterra Systems

$$\begin{aligned}y(t) &= V_0[x(t)] + V_1[x(t)] + V_2[x(t)] \\&= k_0 + \int_0^{\infty} k_1(\tau) x(t-\tau) d\tau \\&\quad + \iint_0^{\infty} k_2(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2\end{aligned}$$

## First Order Kernel



## Second Order Kernel



# Volterra Series



$$y(t) = k_0 + \int_0^\infty k_1(\tau) x(t-\tau) d\tau$$

$$+ \int_0^\infty \int_0^\infty k_2(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2$$

$$+ \int_0^\infty \int_0^\infty \int_0^\infty k_3(\tau_1, \tau_2, \tau_3) x(t-\tau_1) x(t-\tau_2) x(t-\tau_3) d\tau_1 d\tau_2 d\tau_3$$

+ ...

where  $k_i(\cdot)$  is the  $i^{\text{th}}$  Volterra Kernel.

# The impulse response of a nonlinear system

$$x(t) = \delta(t)$$

$$\begin{aligned}y(t) = & k_0 + k_1(t) + k_2(t,t) \\& + k_3(t,t,t) + \dots\end{aligned}$$

# GENERAL VOLTERRA SYSTEMS

$$y(t) = \sum_{n=0}^{\infty} V_n [x(t)]$$

$$= \sum_{n=0}^{\infty} \int_0^{\infty} \dots \int_0^{\infty} k_n(\tau_1, \dots, \tau_n) x(t-\tau_1) \dots x(t-\tau_n) d\tau_1 \dots d\tau_n$$

⇒ This is a generalization of the convolution integral representation of a linear system.

## Limitations of the Volterra Series :

1. Convergence : Same limitations as those encountered in Taylor series .
2. Measurement of Volterra Kernels .

**Norbert Wiener** : A famous child prodigy, he later became an early researcher in stochastic and noise processes, contributing work relevant to electronic engineering, electronic communication, and control systems.

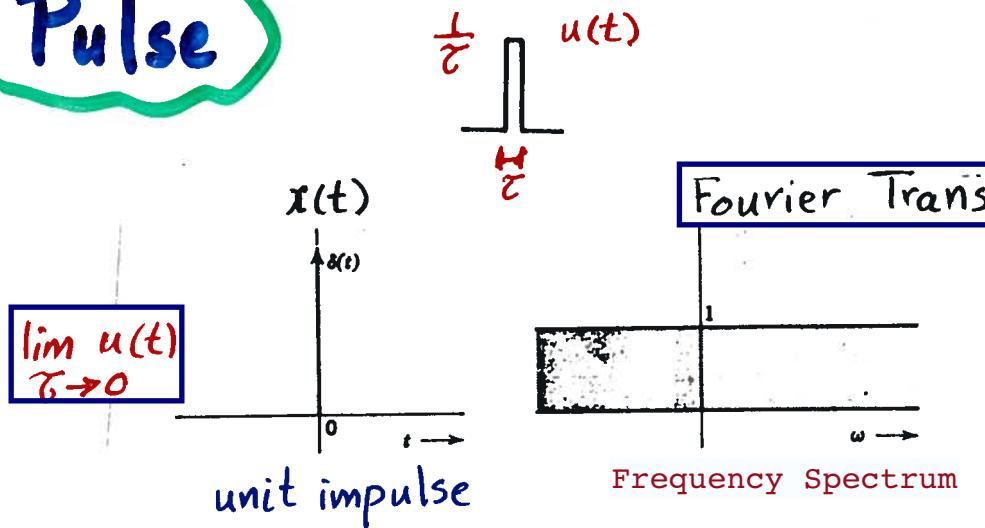
Wiener is considered the originator of **cybernetics**, a formalization of the notion of feedback, with implications for engineering, systems control, computer science, biology, neuroscience, philosophy, and the organization of society.

**Cybernetics: Or Control and Communication in the Animal and the Machine** was written by Norbert Wiener and published in 1948. It is the first public usage of the term "cybernetics" to refer to **self-regulating mechanisms**. The book laid the theoretical foundation for servomechanisms (whether electrical, mechanical or hydraulic), automatic navigation, analog computing, and reliable communications.

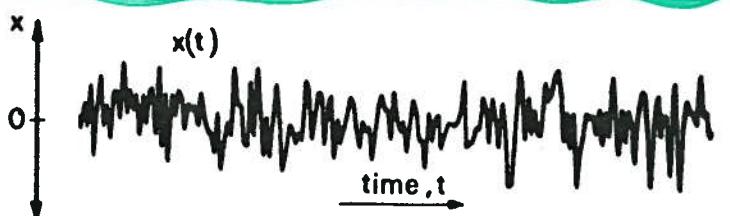
**Wiener Filter** : For signal processing. Its purpose is to reduce the amount of noise present in a signal by comparison with an estimation of the desired noiseless signal.

# INPUT STIMULI

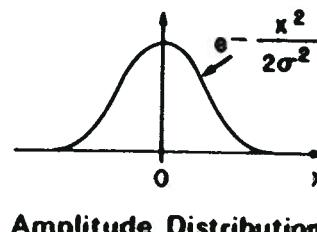
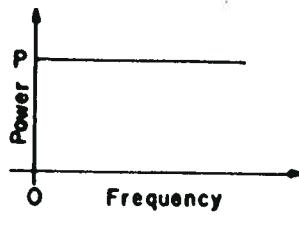
## Pulse



## Gaussian White Noise



‘zero mean’



Any two samples are statistically independent.



Stationary random process.

# THE WIENER SERIES

$$y(t) = \sum_{n=0}^{\infty} G_n [h_n; x(t)]$$

The Wiener G-Functionals are orthogonal to each other with respect to a Gaussian White Noise (GWN) input  $x(t)$ .

**Definition:** The  $n$ th order Wiener G-functional is the sum of  $n+1$  homogeneous Wiener functionals of decreasing order.

$$G_n [h_n; x(t)] = W_n [x(t)] + \sum_{i=0}^{n-1} W_{i(n)} [x(t)]$$

for  $n \geq 1$

$$\begin{aligned}
y(t) = & h_0 \\
& + \int_0^\infty h_1(\tau_1) x(t-\tau_1) d\tau_1 + h_{0(1)} \\
& + \int_0^\infty \int_0^\infty h_2(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2 \\
& + \int_0^\infty h_{1(2)}(\tau_1) x(t-\tau_1) d\tau_1 + h_{0(2)} \\
& + \int_0^\infty \int_0^\infty \int_0^\infty h_3(\tau_1, \tau_2, \tau_3) x(t-\tau_1) x(t-\tau_2) x(t-\tau_3) \\
& \quad d\tau_1 d\tau_2 d\tau_3 \\
& + \int_0^\infty \int_0^\infty h_{2(3)}(\tau_1, \tau_2) x(t-\tau_1) x(t-\tau_2) d\tau_1 d\tau_2 \\
& + \int_0^\infty h_{1(3)}(\tau_1) x(t-\tau_1) d\tau_1 \\
& + h_{0(3)} \\
& + \dots
\end{aligned}$$

$h_i(\cdot) \triangleq$   $i$ th order Wiener Kernel

$h_{j(i)}(\cdot) \triangleq$  derived  $j$ th order Wiener Kernel  
associated with  $i$ th order Wiener kernel

Orthogonality Condition on G-functionals

$\Rightarrow \mathcal{E} \{ G_i G_j \} = 0 \quad \text{for GWN}$

$$h_{0(1)} = 0$$

$$h_{1(2)}(\tau_1) = 0$$

$$h_{0(2)} = -P \int_0^\infty h_2(\tau_1, \tau_1) d\tau_1$$

where  $P \triangleq$  input power level

$$h_{2(3)}(\tau_1, \tau_2) = 0$$

$$h_{1(3)}(\tau_1) = -3P \int_0^\infty h_3(\tau_1, \tau_2, \tau_2) d\tau_2$$

$$h_{0(3)} = 0$$

	0 <sup>th</sup> -order kernels	1 <sup>st</sup> -order kernels	2 <sup>nd</sup> -order kernels	3 <sup>rd</sup> -order kernels	4 <sup>th</sup> -order kernels	5 <sup>th</sup> -order kernels
G-functional						

$G_0$        $h_0$

$G_1$        $h_1$

$G_2$        $h_{0(2)}$        $h_2$

$G_3$        $h_{1(3)}$        $h_3$

$G_4$        $h_{0(4)}$        $h_{2(4)}$        $h_4$

$G_5$        $h_{1(5)}$        $h_{3(5)}$        $h_5$

## The Relation Between Wiener & Volterra Kernels

$$y(t) = \sum_{n=0}^{\infty} V_n [x(t)] = \sum_{n=0}^{\infty} G_n [h_n; x(t)]$$

There is a unique analytical relation between the Wiener and Volterra kernels of a system, which represents the transformation of the functional expansion basis.

Example :

For a fifth-order system

$$\sum_{n=0}^5 V_n [x(t)] = \sum_{n=0}^5 G_n [h_n ; x(t)]$$

Collect and Equate Similar terms

1. Constants

$$k_0 = h_0 + 0 + h_0(2) + 0 + h_0(4)$$

2. First-order Kernels

$$k_1 = 0 + h_1 + 0 + h_1(3) + 0 + h_1(5)$$

3. Second-order Kernels

$$k_2 = 0 + 0 + h_2 + 0 + h_2(4) + 0$$

4. Third-order Kernels

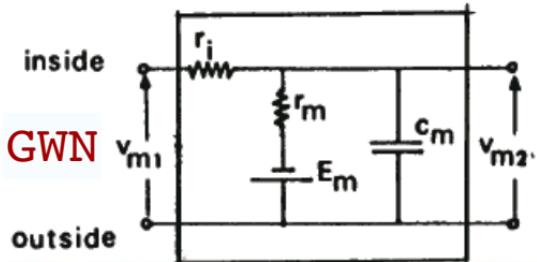
$$k_3 = 0 + 0 + 0 + h_3 + 0 + h_3(5)$$

5. Fourth-order Kernels

$$k_4 = 0 + 0 + 0 + 0 + h_4 + 0$$

6. Fifth-order Kernels

$$k_5 = 0 + 0 + 0 + 0 + 0 + h_5$$



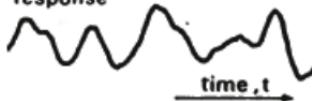
Linear System

Response to GWN

stimulus

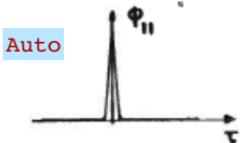


response

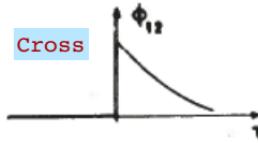


Correlation Functions

Auto

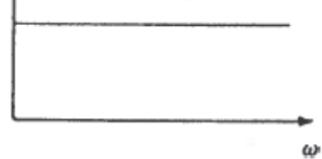


Cross

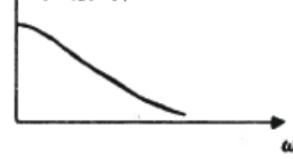


Fourier Transforms

$\Phi_{11}(\omega)$



$|\Phi_{12}(\omega)|$



## Auto correlation Function

$$\Phi_{xx}(\tau) = \lim_{R \rightarrow \infty} \frac{1}{2R} \int_{-R}^R x(t) x(t-\tau) dt$$
$$= E \{ x(t) x(t-\tau) \}$$

where

$E \{ \cdot \}$  denotes Expected value.

Practically  $\phi_{xx}$  is estimated as

$$\hat{\phi}_{xx}(\tau) = \frac{1}{R-\tau} \int_0^R x(t) x(t-\tau) dt$$

\* For white noise

$$\phi_{xx}(\tau) = E \{ x(t) x(t-\tau) \}$$

$$= P S(\tau)$$

↗  
Power Level

## Cross correlation Function

$$\Phi_{yx}(\tau) = \lim_{R \rightarrow \infty} \frac{1}{2R} \int_{-R}^R y(t) x(t-\tau) dt$$

$$\hat{\Phi}_{yx}(\tau) = \frac{1}{R-\tau} \int_0^R y(t) x(t-\tau) dt$$

$$\begin{aligned}\Phi_{yx}(\tau) &= E \{ y(t) x(t-\tau) \} \\ &= E \{ y(t+\tau) x(t) \}\end{aligned}$$

$$* \Phi_{yx}(\tau) = \Phi_{xy}(-\tau)$$

For a Linear System:  $x(t)$   $\xrightarrow[\text{GWN}]{h_L(\cdot)}$   $y(t)$

$$\Phi_{yx}(\tau) = \mathcal{E} \{ x(t) y(t+\tau) \}$$

$$= \mathcal{E} \{ x(t) \int_0^{\infty} h_L(\sigma) x(t+\tau-\sigma) d\sigma \}$$

$$= \int_0^{\infty} h_L(\sigma) \underbrace{\mathcal{E} \{ x(t) x(t+\tau-\sigma) \}}_{\Phi_{xx}(\sigma-\tau)} d\sigma$$

$$\Phi_{xx}(\sigma-\tau)$$

$$= P \delta(\sigma-\tau)$$

for Gaussian White Noise

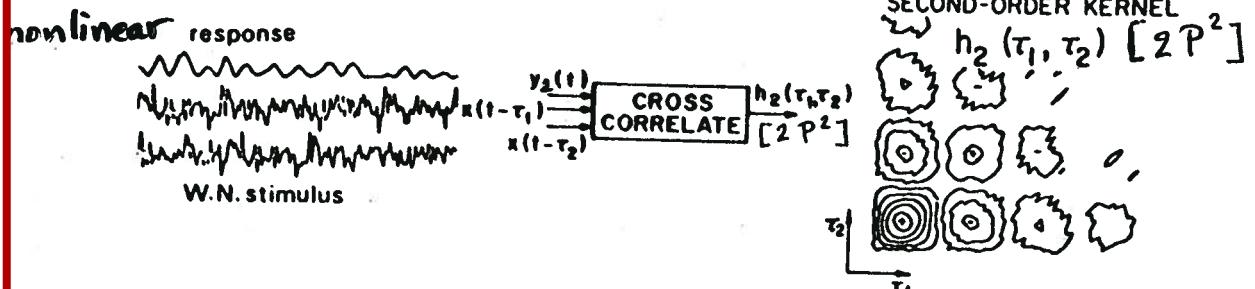
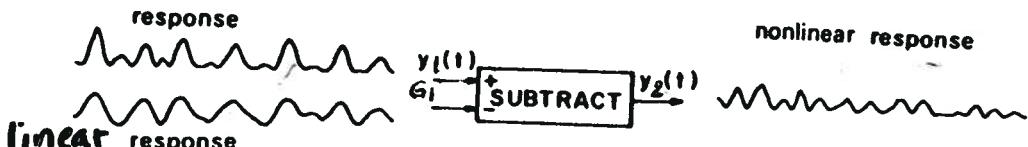
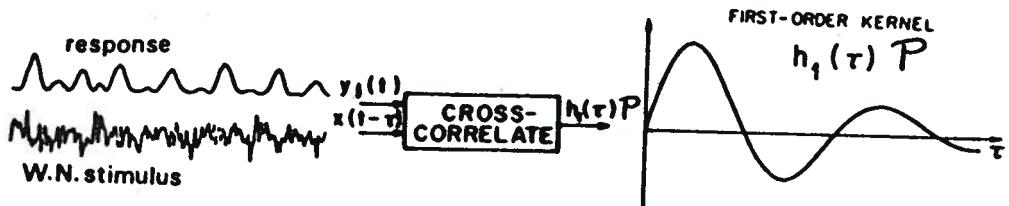
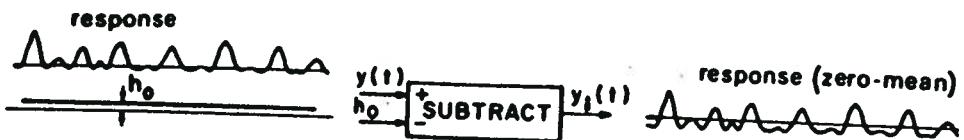
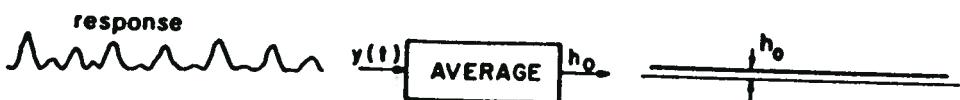
$$\Phi_{yx}(\tau) = P \int_0^{\infty} h_L(\sigma) \delta(\sigma-\tau) d\sigma$$

$$= P h_L(\tau)$$

# The Lee-Schetzen Approach for Estimation of Wiener Kernels Using a GWN Input

Estimation of  $h_n(\tau_1, \dots, \tau_n)$  is through  
input-output crosscorrelation for  $n \geq 1$

# The Lee-Schetzen Approach



**Limitations :** (a) The requirement of a band-limited GWN stimulus that covers the entire system bandwidth.

(b) Long data-records are required to obtain estimates of satisfactory accuracy. Estimates converge to the true values at a rate proportional to  $\sqrt{\text{record length}}$ .

# A Block- Structured Wiener Model

## The Wiener-Bose Model

Consider a first-order Wiener System

$$y(t) = G_1 [h_1; x(t)]$$

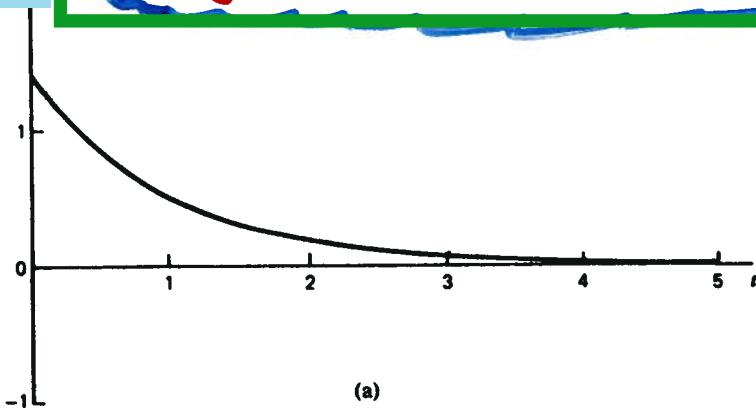
Expand  $h_1(\tau)$  in terms of the orthogonal Laguerre functions  $l_0(\tau), l_1(\tau), \dots, l_n(\tau), \dots$

$$h_1(\tau) = \sum_{n=0}^{\infty} c_n l_n(\tau)$$

Wiener Kernel  
Expansion using  
Orthogonal Set of  
Basis Functions

# Laguerre Functions

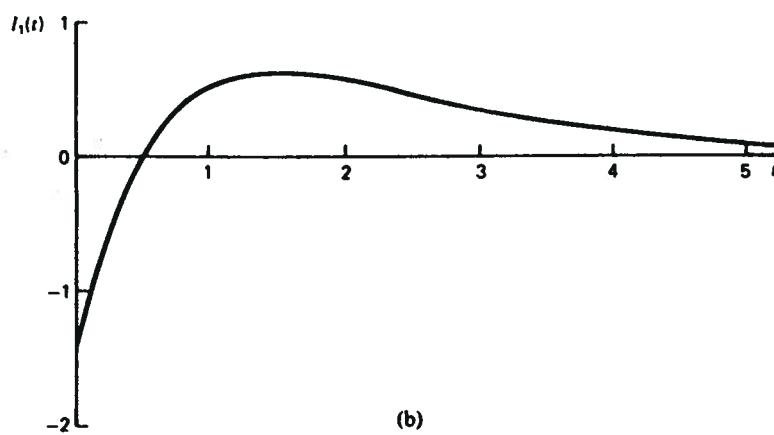
$l_0(t)$



Number  
of zero  
crossings

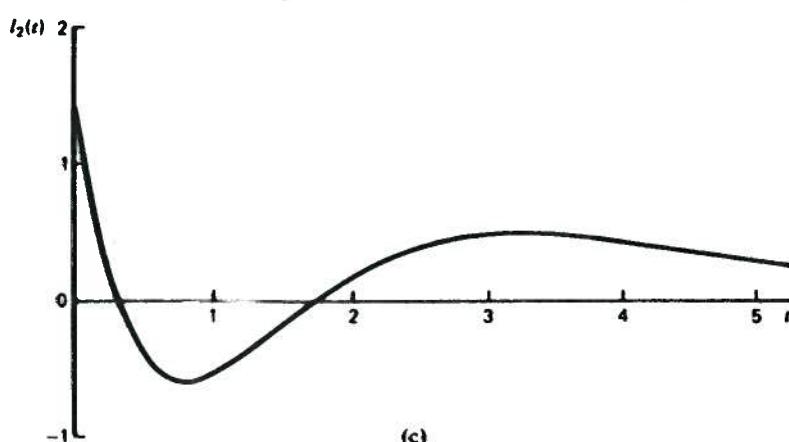
0

$l_1(t)$



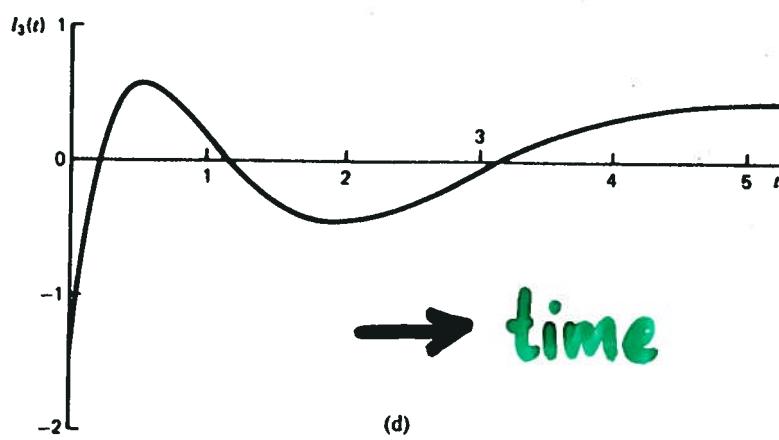
1

$l_2(t)$



2

$l_3(t)$



→ time

# A Block- Structured Wiener Model

## The Wiener-Bose Model

Consider a first-order Wiener System

$$y(t) = G_1 [h_1; x(t)]$$

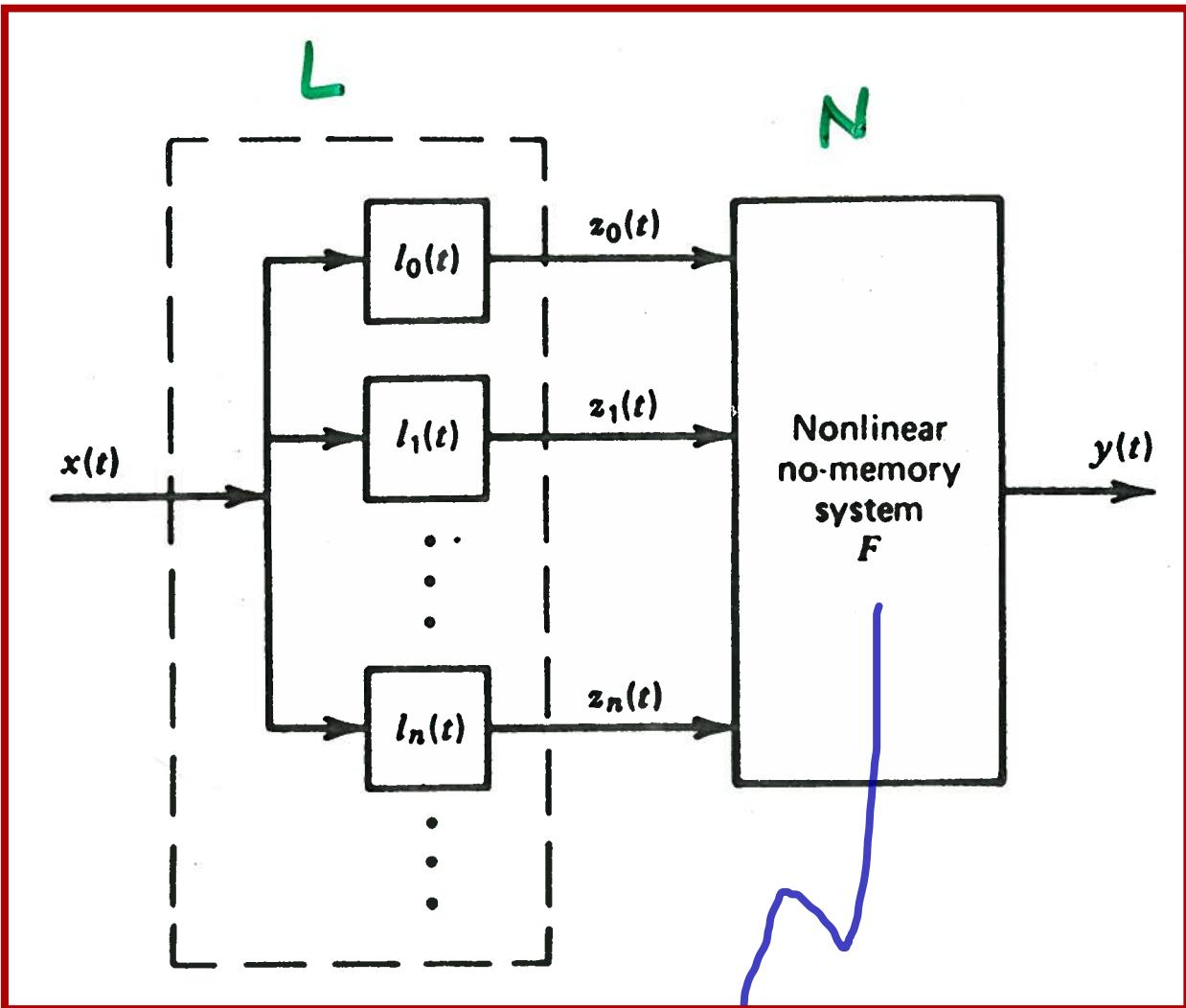
Expand  $h_1(\tau)$  in terms of the orthogonal Laguerre functions  $l_0(\tau), l_1(\tau), \dots, l_n(\tau), \dots$

$$h_1(\tau) = \sum_{n=0}^{\infty} c_n l_n(\tau)$$

$$\begin{aligned} G_1 [h_1; x(t)] &= G_1 \left[ \sum_{n=0}^{\infty} c_n l_n; x(t) \right] \\ &= \sum_{n=0}^{\infty} c_n G_1 [l_n; x(t)] \\ &= \sum_{n=0}^{\infty} c_n \int_0^{\infty} l_n(\tau) x(t-\tau) d\tau \\ y(t) &= \sum_{n=0}^{\infty} c_n z_n(t) \end{aligned}$$

In general,  $y(t) = F(z_0(t), z_1(t), \dots, z_n(t), \dots)$   
and  $\lambda$  is expanded in terms of  $\{e_i\}_{i=0}^{\infty}$ .

# The Wiener-Bose Model



♫ LN Cascade

♫  $y(t) = F(z_0(t), z_1(t), \dots, z_n(t), \dots)$

Let  $F(z_0(t), z_1(t), \dots)$  be analytic so that it can be expanded in a multidimensional power series

$$\begin{aligned}
 y(t) = & h_0 + \sum_{j=0}^{\infty} c_1(j) z_j(t) \\
 & + \sum_{j_1} \sum_{j_2} c_2(j_1, j_2) z_{j_1}(t) z_{j_2}(t) \\
 & + \sum_{j_1} \sum_{j_2} \sum_{j_3} c_3(j_1, j_2, j_3) z_{j_1}(t) z_{j_2}(t) z_{j_3}(t) \\
 & + \dots
 \end{aligned}$$

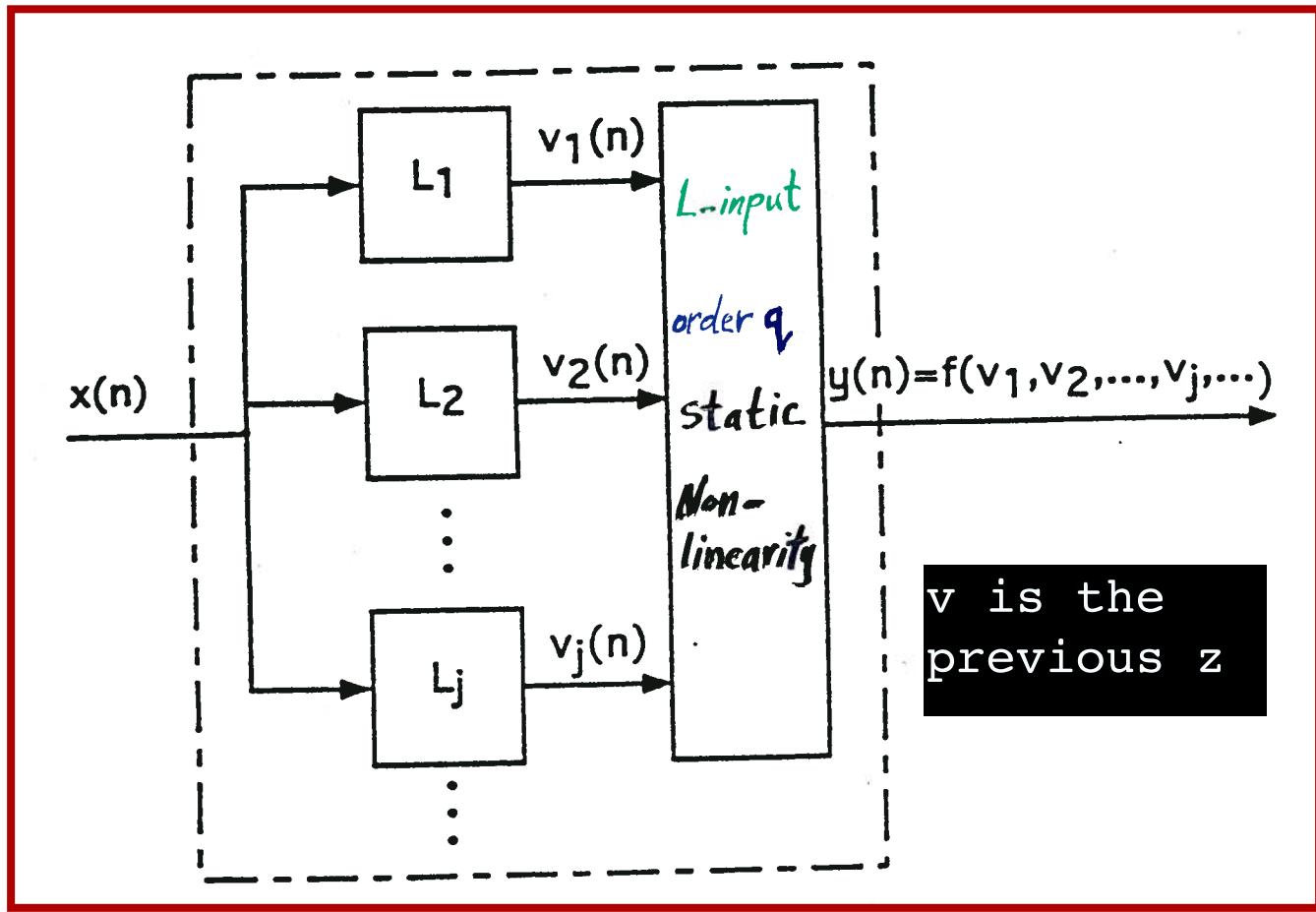
where

$$z_j = \int_0^{\mu} l_j(\tau) x(t-\tau) d\tau$$

$\mu \triangleq$  System memory

The Wiener and Volterra Kernels are described by summations involving coefficients  $c_n(\cdot)$  and Laguerre fns  $l_n(t)$ .

# The Discrete-Time Wiener-Bose Model



$L_j \triangleq$  Linear Filter whose impulse response  
 $b_j(m)$  is the  $(j-1)^{th}$  Laguerre function.

$h_m(n_1, \dots, n_m) \triangleq$  m<sup>th</sup>-order Wiener Kernel

$$h_m(n_1, \dots, n_m) = \sum_{j_1} \dots \sum_{j_m} c_m(j_1, \dots, j_m) b_{j_1}(n_1) \dots b_{j_m}(n_m)$$

The model parameters :

$q$ ,  $L$ ,  $\{c_r (1, \dots, r) ; 0 \leq r \leq q\}$

order of system      number of Laguerre functions      Coefficients of power series of  $f$

$$y(n) = c_0 + \sum_j c_1(j) v_j(n)$$

$$+ \sum_{j_1} \sum_{j_2} c_2(j_1, j_2) v_{j_1}(n) v_{j_2}(n)$$

+ ...

$$= f(v_1, v_2, \dots, v_j, \dots)$$

$$v_j(n) = \sum_m b_j(m) x(n-m)$$

- Apply  $x(n) = GWN$   
and measure  $y(n)$
- $C_m(j_1, \dots, j_m)$  can be estimated by least squares fitting using the known signals  $y(n)$  and  $\{v_j(n)\}$

How to compute  $v(n)$

$$v_j(n) = \sum_m b_j(m) x(n-m)$$

For Laguerre basis functions, then

$$v_j(n) = \sqrt{\alpha} [v_j(n-1) + v_{j-1}(n)] - v_{j-1}(n-1)$$

$$v_i(n) = \sqrt{\alpha} v_i(n-1) + \sqrt{1-\alpha} x(n)$$

choice of  $\alpha$  is based on the system memory and  $L$ .

♪ The discrete-time Laguerre function is

$$l_j(m) = \alpha^{\frac{m-j}{2}} (1-\alpha)^{\frac{j}{2}} \sum_{k=0}^j (-1)^k \binom{m}{k} \binom{j}{k} \cdot [\alpha^{(j-k)} (1-\alpha)^k]$$

for  $m \geq 0$ ,  $j=0, 1, \dots, L-1$ ,

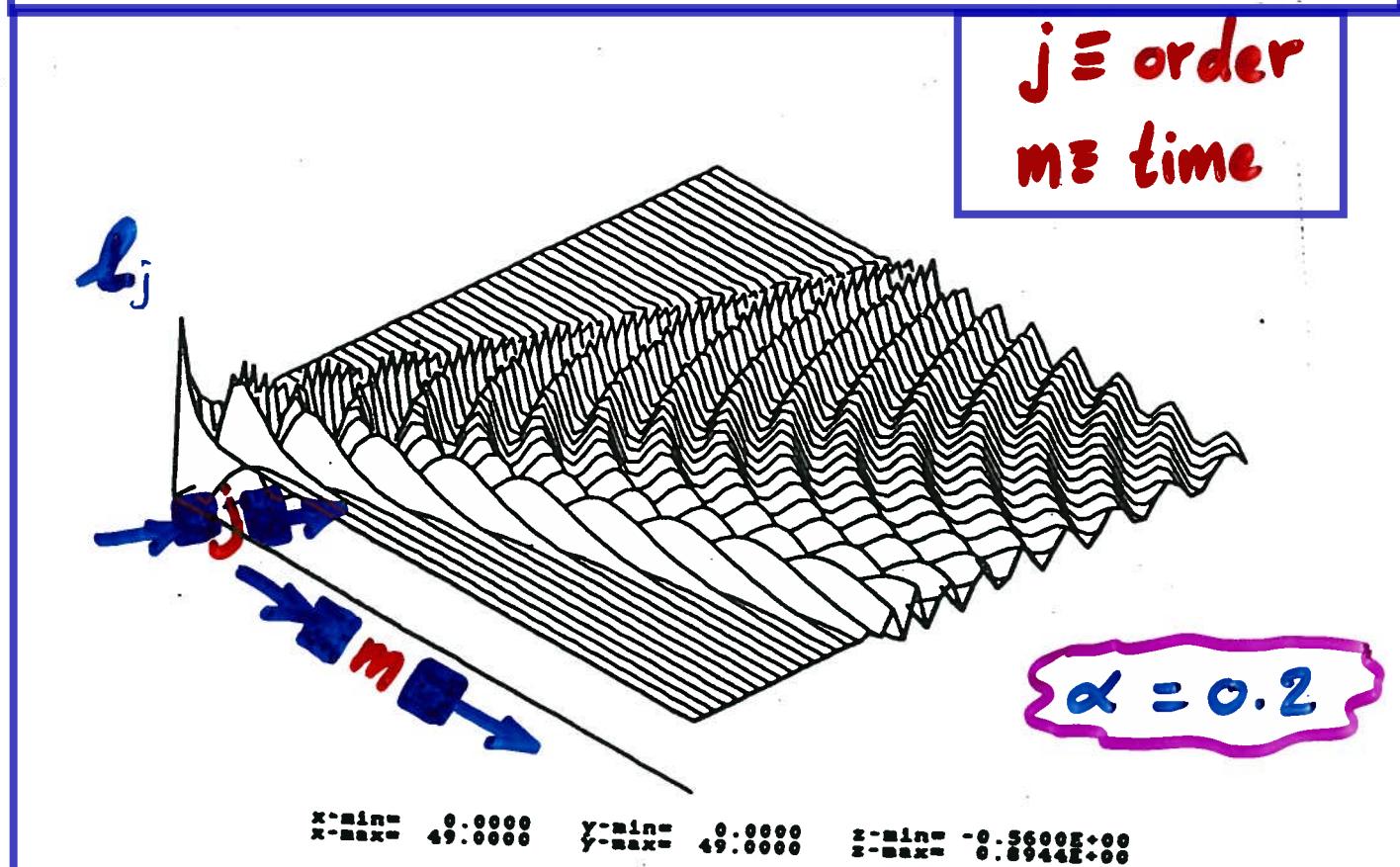
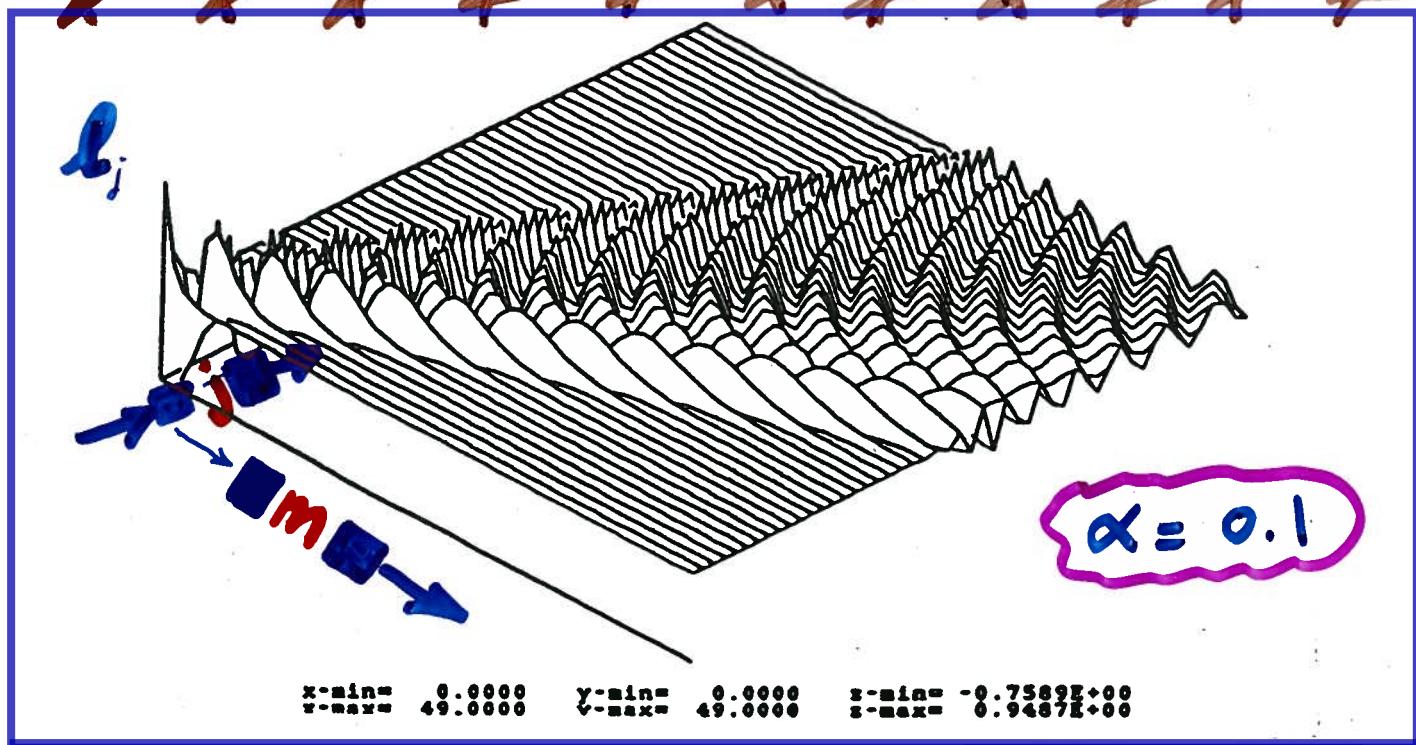
$$0 < \alpha < 1$$

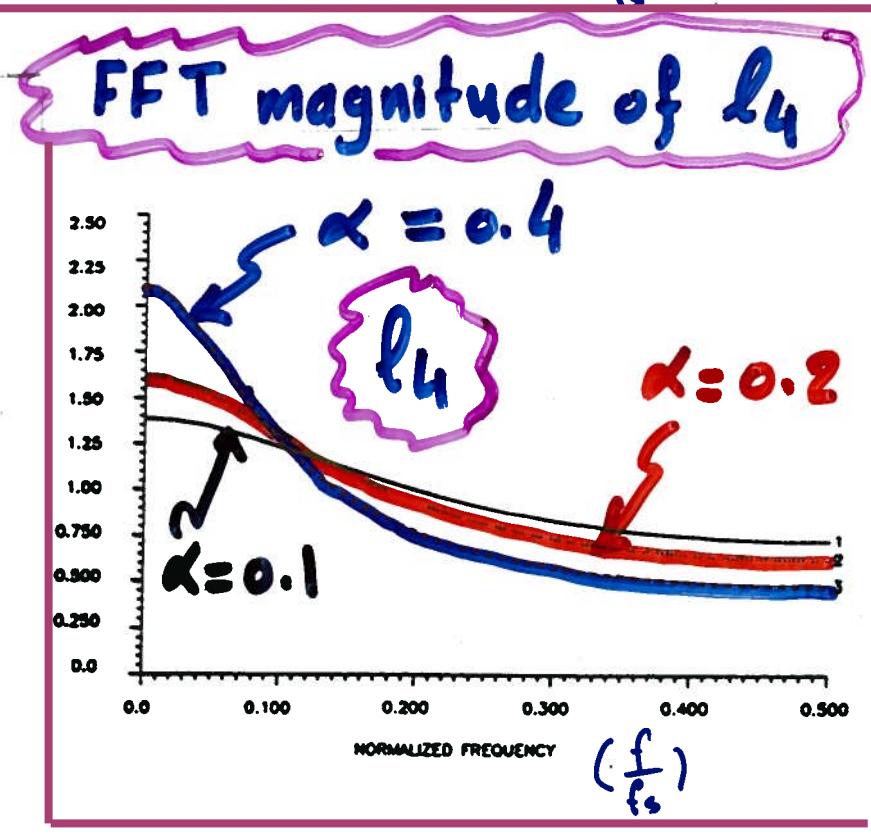
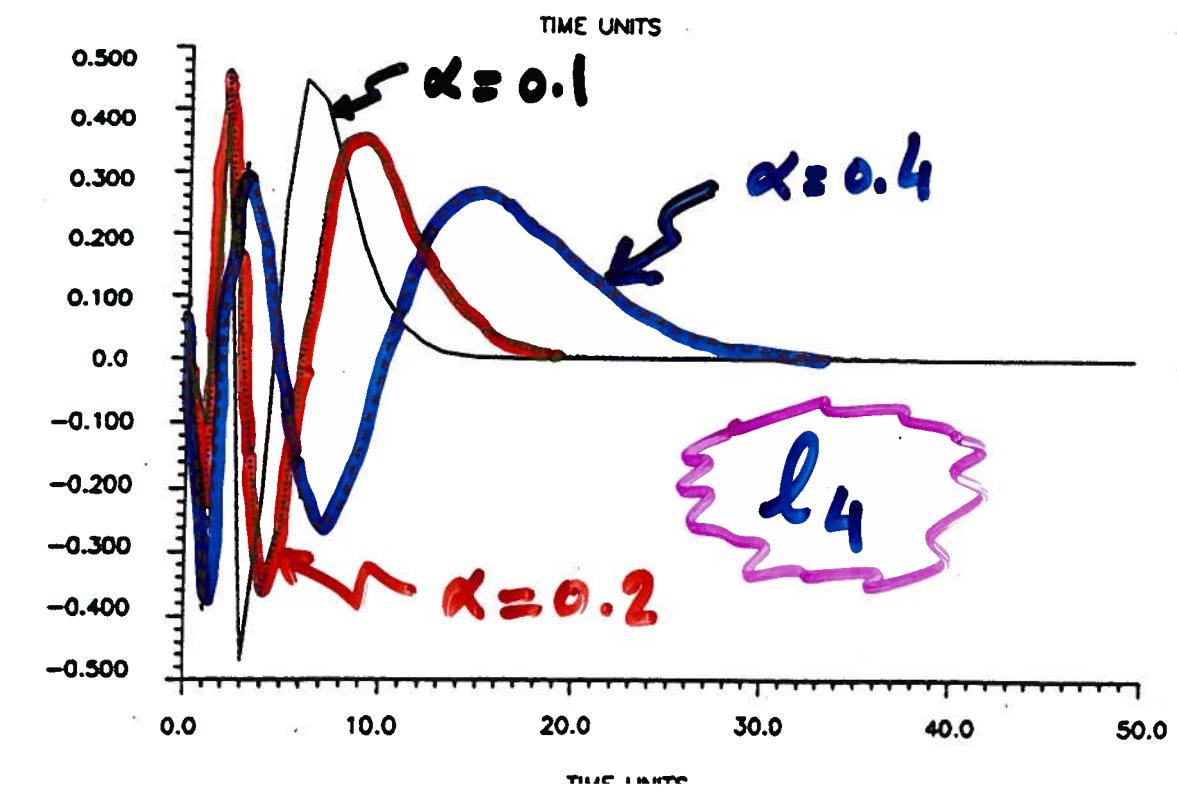
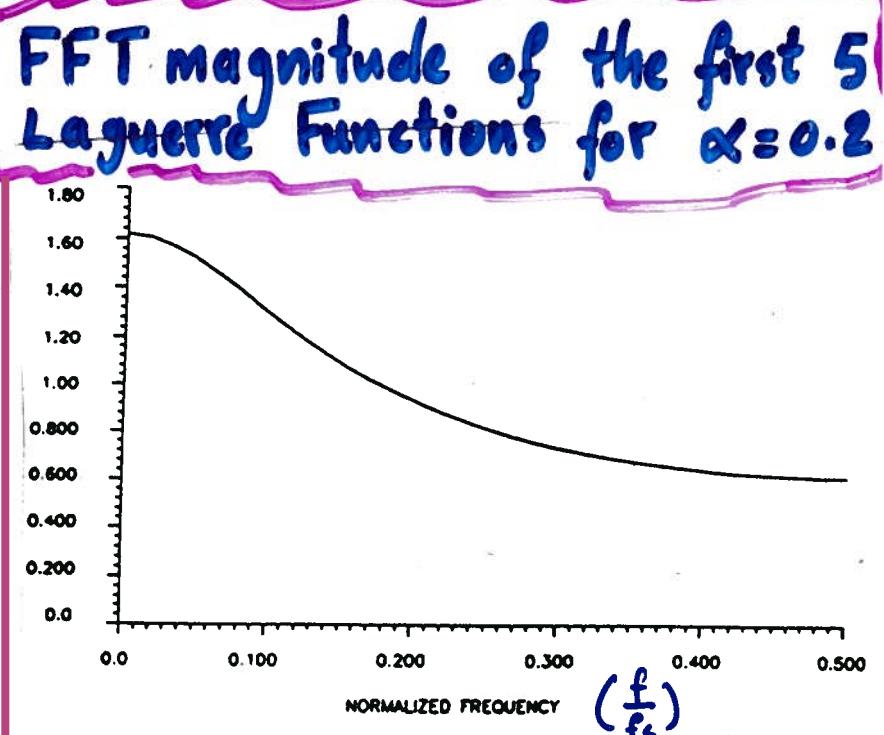
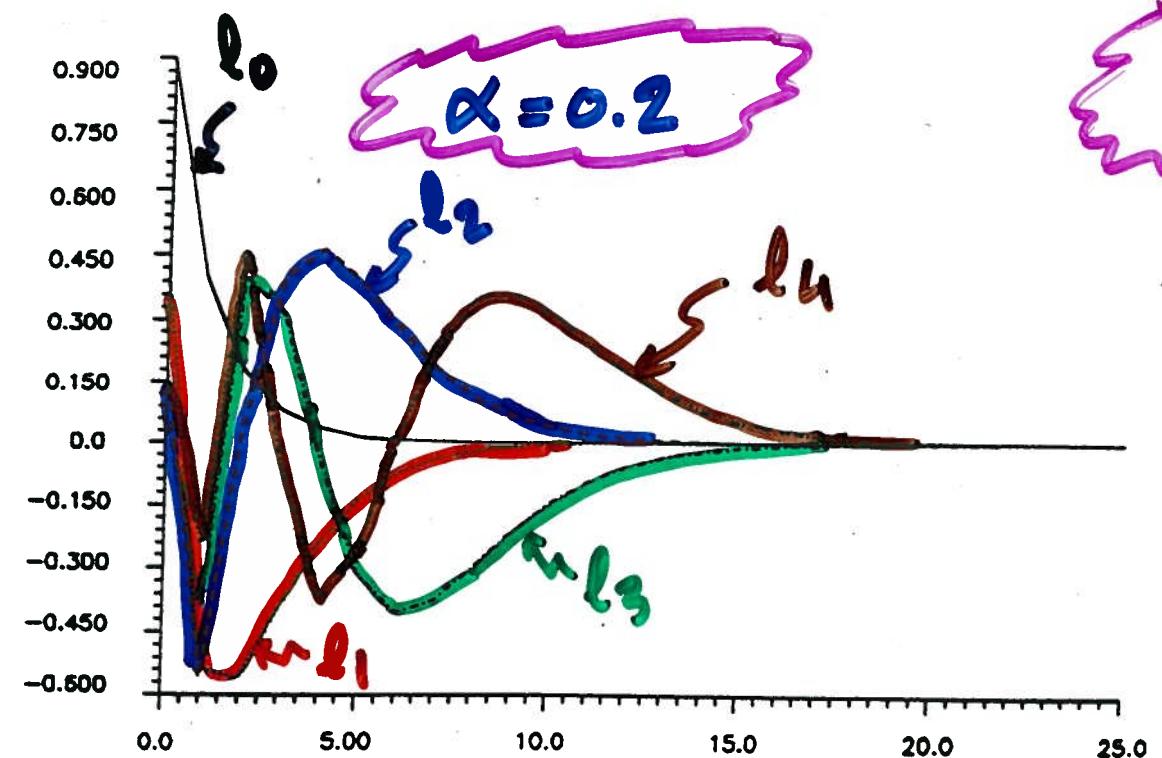
discrete-time Laguerre parameter

♪  $\binom{j}{k} = \frac{j!}{(j-k)! k!}$  for  $k \leq j$

$b_j(m) = l_{j-1}(m)$  ;  $j = 1, \dots, L$

The first 50 Laguerre Functions , plotted as  
a square matrix over 50 time units (0-49 lag)





## Choice of L

- The number of Laguerre functions  $L$  must be much smaller than the memory-bandwidth product  $M$  of the system.

$$L \ll M$$

- e.g.,  $M = 100 \Rightarrow L = 10$

# Practical Hints for LET

- ① Inject  $x(t) = AWN$  and estimate response  $y(t)$ .
- ②  $\text{FFT} \{y(t)\} \Rightarrow \text{System Bandwidth}$
- ③ Estimate first order kernel  $k_1(\tau)$  by:
  - a) Cross correlation of  $x(t)$  &  $y(t)$ .
  - or b)  $\mathcal{F}^{-1} \left\{ \frac{\mathcal{F}[y(t)]}{\mathcal{F}[x(t)]} \right\}$

$\mathcal{F} \triangleq \text{FFT}$
- ④ Duration of  $k_1(\tau) \Rightarrow \text{System Memory}$
- ⑤ Estimate number of Laguerre Functions  $L \ll \text{Memory-Bandwidth product}$
- ⑥ Estimate  $\alpha$  to cover system memory.

# LYSIS

LYSIS (the Greek word for “solution”) is an interactive software of a set of modular programs (each performing a specific task) that provide an integrated computing environment for data analysis and system modeling. Unique capabilities of LYSIS include input-output nonlinear system modeling and the novel methodology of “Principal Dynamic Modes” (PDMs). This package has evolved over time to incorporate emerging methodologies developed by the Biomedical Simulations Resource (BMSR) at USC, under the supervision of Prof. V.Z. Marmarelis.

**LYSIS 7.2 – Matlab version** is the current version and is focused on the unique capabilities of input-output nonlinear system modeling using the Volterra-Wiener approach and its efficient variants that have been developed and tested by the BMSR over the years, utilizing Laguerre expansions of the kernels and the novel concept/tool of Principal Dynamic Modes (PDMs). The source code of modular Matlab programs are made available that can be incorporated in the Matlab computational environment of the user.

<https://bmsr.usc.edu/software/lysis/>

The development of LYSIS is supported by the Biomedical Simulations Resource (BMSR) in the Department of Biomedical Engineering at the University of Southern California, under support from the National Institute for Biomedical Imaging and Bioengineering (P41-EB001978) and the National Center for Research Resources (P41-RR01861) of the National Institutes of Health. LYSIS is made available to the biomedical community at large free of charge in order to promote research in this area and enhance the computational capabilities of biomedical investigators nationwide. The BMSR holds the copyright of LYSIS and its use must be acknowledged by individual investigators in their research publications.

## LYSIS

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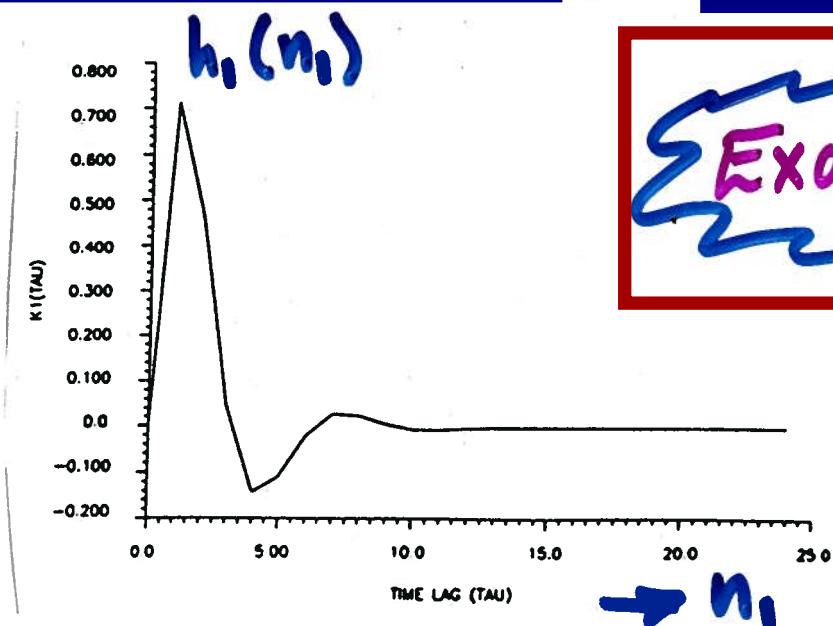
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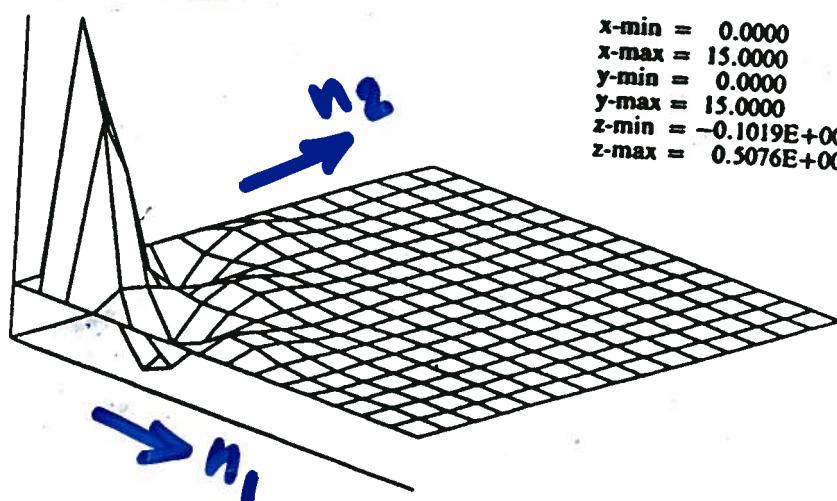
# Exact Kernels

$$q_1 = 2$$

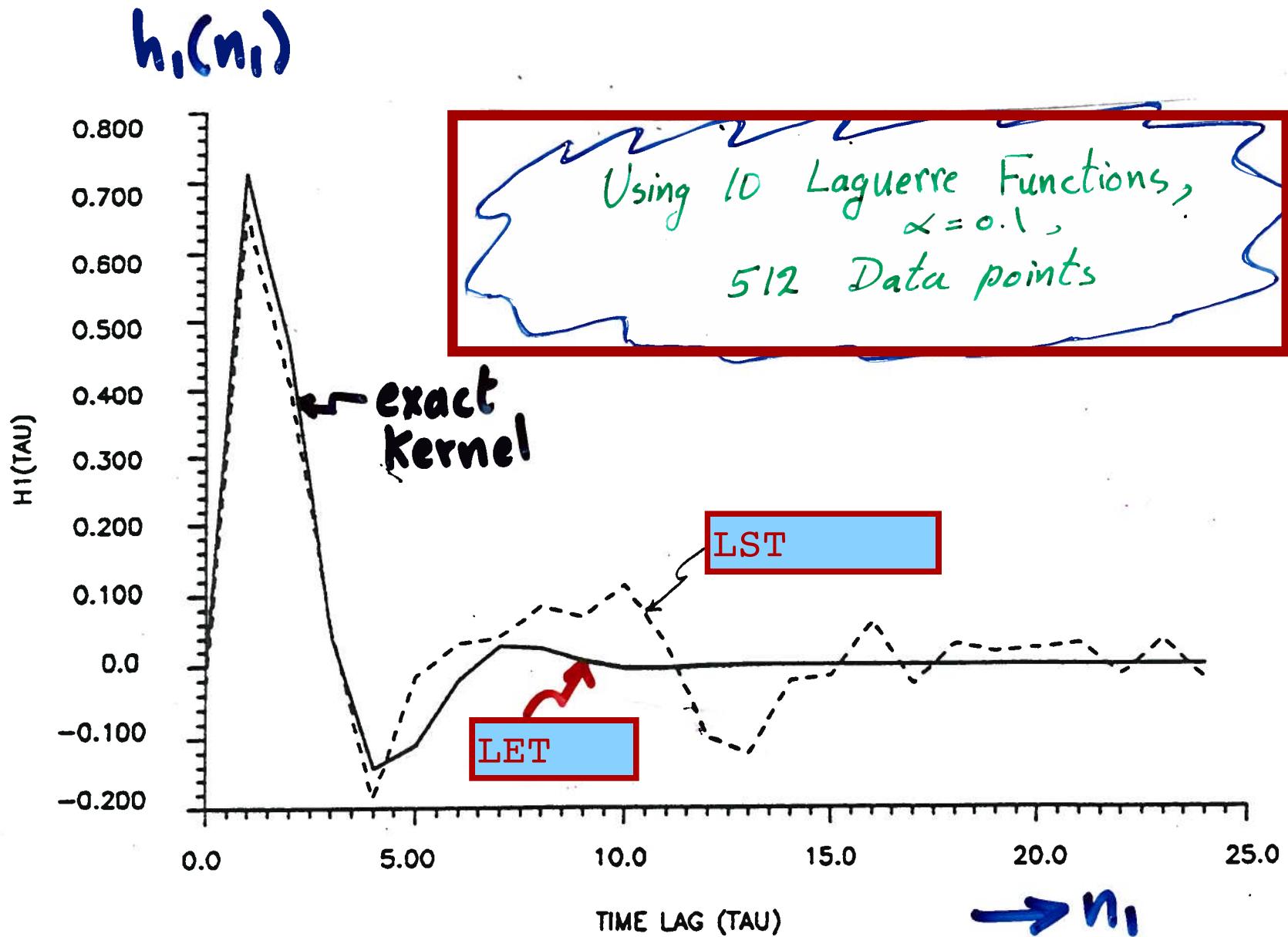


Example

$h_2(n_1, n_2)$



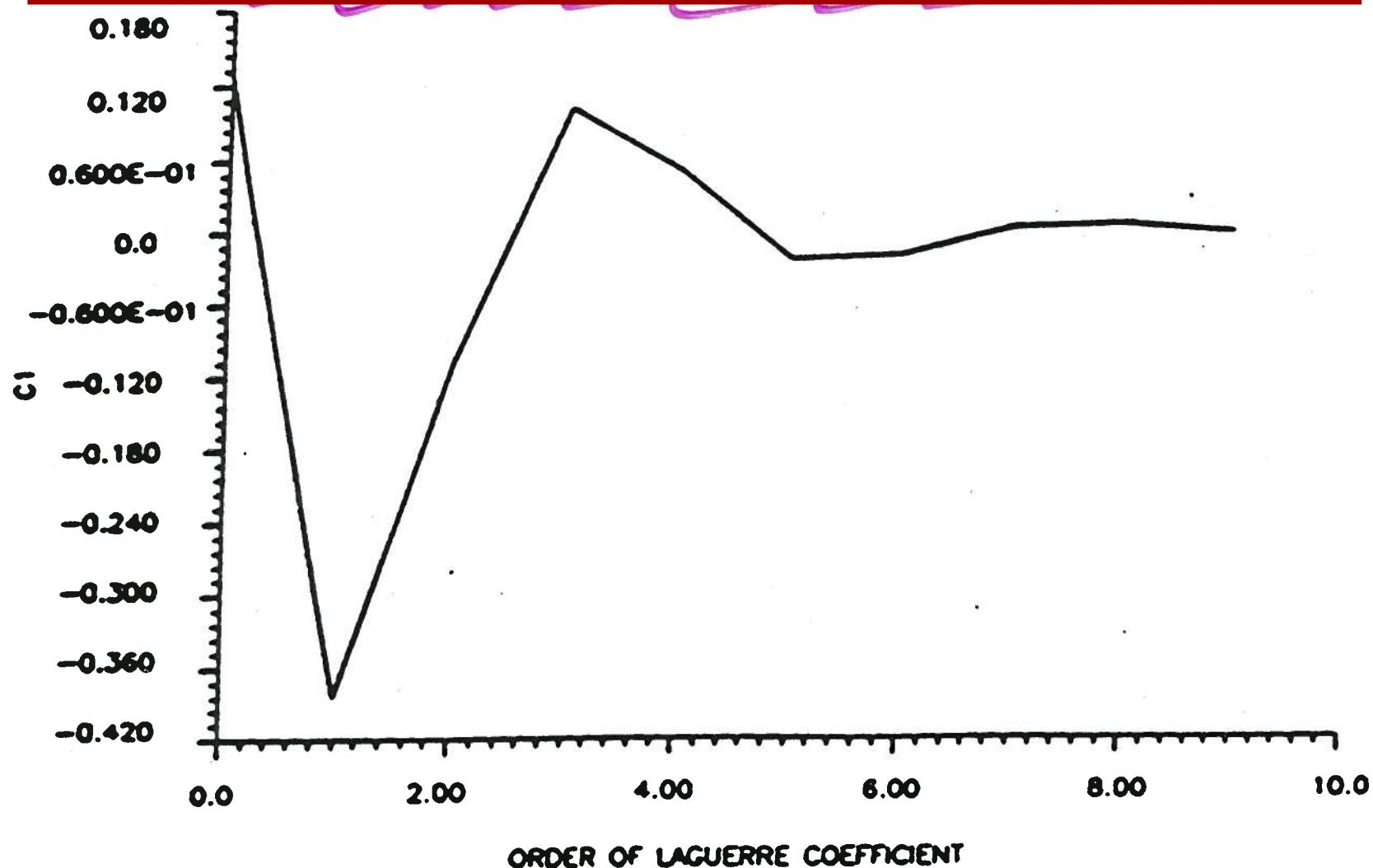
The model output is produced by convolution of GWN with the system kernels



$LST \triangleq$  Lee-Schatzen Technique

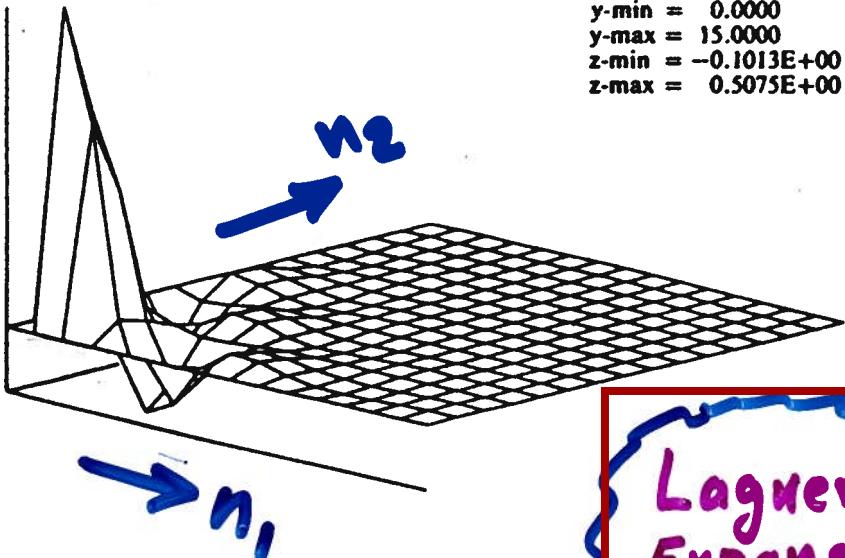
$LET \triangleq$  Laguerre Expansion Technique

# Estimates of the 10 Laguerre Expansion Coefficients for the first-order Kernel



The required  $L$  can be determined by estimating the first-order kernel for a large  $L$ , then inspect coefft estimates to select minimum number for significant values.

$h_2(n_1, n_2)$



x-min = 0.0000  
x-max = 15.0000  
y-min = 0.0000  
y-max = 15.0000  
z-min = -0.1013E+00  
z-max = 0.5075E+00

$h_2(n_1, n_2)$



x-min = 0.0000  
x-max = 15.0000  
y-min = 0.0000  
y-max = 15.0000  
z-min = -0.1464E+00  
z-max = 0.5421E+00

Laguerre  
Expansion  
Technique

LET

LST

Lee-Schetzen  
Technique