Stochastic neuronal models

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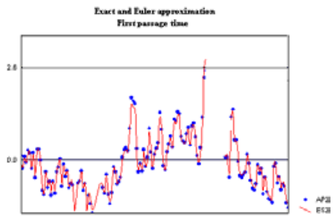

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Summary

- Basic Introduction to Neurosciences
  - Structure and function of the nervous system
  - Elements of Neuroanatomy
  - Neuronal signals
- Mathematical models for single units
  - Aims of models
    - First models
    - Hodgkin and Huxley type models
    - Stochastic models
    - Diffusion type models
- Mathematical methods and related problems
- Usefullness of single neuron activity models
- Models for assemblies of neurons
  - Aims of the models
    - Models of jump diffusion type
  - Mathematical methods and related problems
  - Alternative approaches and new researches topics

Diffusion type models

- Describe underthreshold membrane potential time evolution
  - Wiener process (Perfect Integrator)

$$\frac{\partial f}{\partial t}+\mu\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}\frac{\partial^2 f}{\partial x^2}=0 \quad \Leftrightarrow \quad dV_t=\mu dt+\sigma dW_t$$

  - Ornstein- Uhlenbeck process (Leaky Integrate and Fire)

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}\frac{\partial^2 f}{\partial x^2}=0 \quad \Leftrightarrow \quad dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma dW_t$$

  - Feller process (Leaky Integrate and Fire with inferior reversal potential)

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}(x-V_I)\frac{\partial^2 f}{\partial x^2}=0 \quad \Leftrightarrow \quad dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma\sqrt{X_t-V_I}dW_t$$

  - Reversal potentials Leaky Integrate and Fire

$$\frac{\partial f}{\partial t}+(-\frac{x}{\theta}+\mu)\frac{\partial f}{\partial x}+\frac{\sigma^2}{2}(x-V_I)(x-V_E)\frac{\partial^2 f}{\partial x^2}=0 \quad \Leftrightarrow \quad dV_t=(-\frac{V_t}{\theta}+\mu)dt+\sigma\sqrt{V_t-V_I}\sqrt{V_t-V_E}dW_t$$

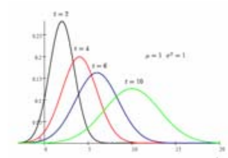
Analytical results: underthreshold behaviour 1/3

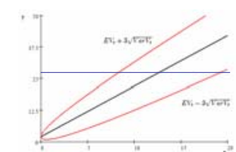
- **Transition probability density**: it is solution of the Kolmogorov diffusion equation.
  - **Perfect integrator model**

$$f(x,t|x_0,0)\ \frac{1}{\sqrt{2\pi\sigma^2 t}}\exp\left\{-\frac{(x-x_0-\mu t)^2}{2\sigma^2 t}\right\}$$

$$EV_t = x_0+\mu t$$
$$VarV_t = \sigma^2 t$$

$$P(V_t<x|V_{t_0}=x_0)=\int_{-\infty}^{x} f(y,t|x_0)\,dy=\begin{cases}0 & \mu>0\\ 1 & \mu<0\\ \frac{1}{2} & \mu=0\end{cases}$$





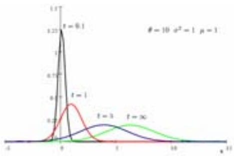
As time increases:

1. a large range of values can be attained,
2. the distribution moves toward right if $\mu>0$ (the opposite if $\mu<0$)
3. No stationary distribution is attained

Analytical results: underthreshold behaviour 2/3

- Ornstein-Uhlenbeck process (only process simultaneously Markov, Gaussian and admitting stationary distribution)

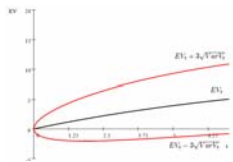
$$f(x,t\,|x_0,t_0) = \frac{1}{\sqrt{\pi\sigma^2\theta\left(1-e^{-2(t-t_0)/\theta}\right)}}\exp\left\{-\frac{\left(x-\mu\theta-(\mu\theta-x_0)\,e^{-(t-t_0)/\theta}\right)^2}{\sigma^2\theta\left(1-e^{-2(t-t_0)/\theta}\right)}\right\}$$



$$\lim_{t\to\infty} f(x,t\,|x_0,t_0) = \frac{1}{\sqrt{\pi\sigma^2\theta}}\exp\left\{-\frac{(x-\mu\theta)^2}{\sigma^2\theta}\right\}$$

$$EV_t = \mu\theta-(\mu\theta-x_0)\,e^{-t/\theta}$$

$$VarV_t = \frac{\sigma^2\theta}{2}\left(1-e^{-2t/\theta}\right)$$



Analytical results: underthreshold behaviour 3/3

- Feller process (model with reversal potential)

$$f(x,t\,|y,0) = \frac{2}{\sigma^2(\mu-V_I)\left(e^{-t/\theta}-1\right)}\left(\frac{x-V_I}{y-V_I}\right)^{\left(\frac{(\mu\theta-V_I)}{\sigma^2\theta}-\frac{1}{2}\right)}\exp\left(-\frac{2\left(x-V_I+(y-V_I)e^{-t/\theta}\right)}{\sigma^2(\mu\theta-V_I)\left(e^{-t/\theta}-1\right)\theta}\right)I_{\frac{(\mu\theta-V_I)}{\sigma^2\theta}}\left(\frac{4\sqrt{x-V_I+(y-V_I)e^{-t/\theta}}}{\sigma^2\theta(\mu\theta-V_I)\left(e^{-t/\theta}-1\right)}\right)$$

$$EV_t = V_0\exp^{-\frac{t}{\theta}}+\mu\left(1-e^{-t/\theta}\right)$$

$$VarV_t = \sigma^2\theta\left(1-e^{-t/\theta}\right)\left\{\frac{\mu-V_I}{2}\left(1-e^{-t/\theta}\right)+(y-\mu)\,e^{-t/\theta}\right\}$$

- Comments
  - Transition probability densities of temporary homogeneous processes are generally available although sometimes have "unpleasant" expressions
  - More refined models may introduce serious mathematical difficulties without important consequences on the results.
  - A good model should be a good compromise between realism and mathematical tractability

Introduction of the boundary

- The diffusion process describes the under-threshold behavior
- To describe the inter-times between action potentials (spikes)
  - We introduce a boundary assuming that a spike is elicited as soon as the diffusion process attains the boundary

    Mathematically this means to switch to a **nonlinear problem**: the FIRST PASSAGE TIME PROBLEM

    $$T = \inf\{t>0 : V_t < S(t)\}$$

  - After each spike we assume that the membrane potential is instantaneously reset to its resting value

    Mathematically this implies to assume that Inter-spikes Intervals (ISIs) constitute a **renewal process**.

Shape of the boundary

- Constant boundary: mathematical simplification
- Time dependent boundary
  - To consider the absolute and relative refractoriness (the threshold attains very high values immediately after a spike then decreases under the constant reference value and oscillates toward this constant)
  - Threshold with fatigue (responsible for progressive decrease of excitability during high frequency firing, as observed experimentally Chacron et al. 2003, 2004) No renewal property
  - To introduce variability of the input (i.e. periodic threshold)
- Noisy boundary

Time dependent boundaries: the constrained process is no more time homogeneous. Furthermore the renewal hypothesis loses significance

The first passage time problem

- Analytical methods
  - A few closed form solution (of scarce interest for application)
    - Wiener process with linear boundary or Daniels boundary
    - OU process with hyperbolic boundary
  - Laplace transform of FPT density is available in many instances when the boundary is constant (but it is rarely invertible)
  - Various methods allow to determine analitical expression for the moments (but the results are very complex)
  - Approximate solutions
- Numerical methods
  - Numerically solve suitable integral equations
- Simulation methods
  - Present unexpected difficulties

Integral equations for FPT probability densities

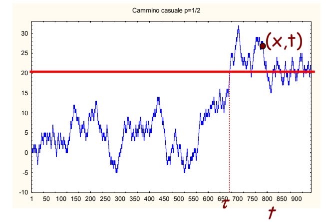
- Fortet equation: a Volterra integral equation with weakly singular kernel

$$f(x,t|x_0,t_0) = \int g(S(\tau),\tau|x_0,t_0)\, f(x,t|S(\tau),\tau)\, d\tau \quad x > S(t)$$

$$T = \inf\{t>0 : V_t > S(t)\}$$

$$f(x,t|x_0,t_0) = \frac{\partial}{\partial x} P(V_t < x | V_{t_0} = x_0)$$

$$g(S(t),t|x_0,t_0) = \frac{d(T<t|V_{t_0}=x_0)}{dt}$$



It holds also when x=S(t) (Fortet, 1943)

Fortet equation
constant boundary

- Fortet equation is a first kind Volterra equation
  - If the boundary is constant S(t)=S it is a convolution integral
    - Laplace transform of first passage time probability dansity may be obtained for the involved process

$$g_\alpha(S|x_0) = \frac{f_\alpha(S|x_0)}{f_\alpha(S|S)}$$

Antitrasforming

$$g_\alpha(S|x_0) \overset{\text{Wiener}}{=} e^{\left[\frac{\mu}{\sigma^2}+\sqrt{\frac{\mu}{\sigma^2}+2\alpha}\right](S-x_0)}$$

$$g_\alpha(S|x_0) \overset{\text{OU}}{=} e^{\frac{S^2-x_0^2}{2\sigma^2\theta}} \frac{D_{-\alpha\theta}\left[-x_0\sqrt{\frac{2}{\sigma^2\theta}}\right]}{D_{-\alpha\theta}\left[-S\sqrt{\frac{2}{\sigma^2\theta}}\right]}$$

Antitrasforming ??

$$g(S,t|x_0) = \frac{|S-x_0|}{\sqrt{2\pi\sigma^2(t-t_0)^3}} \exp\left(-\frac{(S-x_0-\mu(t-t_0))^2}{2\sigma^2(t-t_0)}\right)$$

Fortet equation and other integral equations
constant or time varying boundary

- Numerical solution

$$f(S(t),t|x_0,t_0) = \int_0^t g(S(\tau),\tau|x_0,t_0)\, f(S(t),t|S(\tau),\tau)\, d\tau \quad x > S(t)$$

$$f(S(t),t|S(\tau),\tau) \overset{\text{Wiener}}{=} \frac{1}{\sqrt{2\pi\sigma^2(t-\tau)}} \exp\left\{-\frac{(S(t)-S(\tau))}{2\sigma^2(t-\tau)}\right\} \sim \frac{K(t-\tau)}{\sqrt{t-\tau}}$$

- Alternative diffusion processes:

$$f(S(t),t|S(\tau),\tau) \sim \frac{K(t-\tau)}{\sqrt{t-\tau}}$$

The kernel is weakly singular: numerical difficulties arise!

Alternative integral equations (Ricciardi et. Al., Buonocore et al.)

$$g(S(t),t|x_0) = 2\psi(S(t),t|x_0) - 2\int_0^t \psi(S(t),t|S(\tau),\tau)\, g(S(\tau),u|x_0)\, d\tau$$

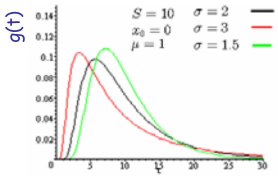
It depends from transition probability densities and from its derivatives

The kernel is regular: standard numerical methods can be applied

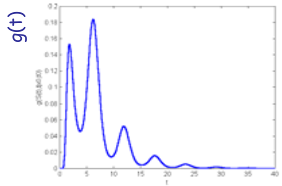
Numerical solution of FPT problem

constant or time varying boundary

FPT of a Wiener process through a constant boundary for different values of σ



FPT of an OU process through a periodic boundary



Numerical methods for FPT problem

Difficulties of numerical methods:

- they request the knowledge of the transition probability density
- Numerical problems may arise for large t
  - Adaptive step methods
  - Asymptotic properties of first passage time distribution have been studied for large S or large t.

If the process admits steady state distribution the first passage time distribution, for large S it holds (Nobile et al., 1985)

$$g(S,t|x_0) \sim \frac{1}{ET}\exp\left(-\frac{t}{ET}\right)$$

For various instants t the first-passage time p.d.f. $g(4,t|0)$ has been estimated by means of the numerical procedure The results are listed under $\tilde{g}$. In column 3 $g^* = [t_1(4|0)]^{-1}\exp\{-[t_1(4|0)]^{-1}$ with $t_1(4|0) = 2018.39$

t	$\tilde{g}$	g^*
6	0.493983×10^{-3}	0.493973×10^{-3}
15	0.491770×10^{-3}	0.491776×10^{-3}
30	0.488129×10^{-3}	0.488134×10^{-3}
90	0.473834×10^{-3}	0.473837×10^{-3}
180	0.453173×10^{-3}	0.453173×10^{-3}
270	0.433413×10^{-3}	0.433410×10^{-3}
360	0.414515×10^{-3}	0.414509×10^{-3}
450	0.396440×10^{-3}	0.396432×10^{-3}

FPT moments 1/3

constant boundary

- Different methods can be applied to determine mean and variance of T, when S is constant
  - Derivation of FPT Laplace transform $E[T^n(S,x_0)] = (-)^n \left.\frac{\partial^n g_\lambda(S|x_0)}{\partial\lambda^n}\right|_{\lambda=0}$
  - Siegert method (if steady state distribution W(x) exists)

$$E[T^n(S,x_0)] = \int_{-\infty}^{S} \frac{2dy}{\sigma^2(y)W(y)} \int_{-\infty}^{y} W(z)E\left[T^{n-1}(S,z)\right] dz$$

Wiener

$$E[T_S(x_0)] = \frac{S-x_0}{\mu};$$

$$E\left[T_S^2(x_0)\right] = \left(\frac{x_0-S}{\mu}\right)^2 - \frac{(x_0-S)\,\sigma^2}{\mu^3}$$

$\Rightarrow$ If $m \le 0 \Rightarrow ET$ diverges

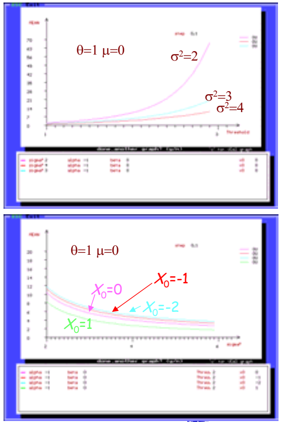
FPT moments 2/3

Orstein-Uhlenbeck

$$E[T_S(x_0)] = \frac{1}{2}\left[\sum_{n=1}^{\infty}\frac{S^{2n}}{n(2n-1)!!} - \sum_{n=1}^{\infty}\frac{x_0^{2n}}{n(2n-1)!!}\right] + \left(\frac{\pi}{2}\right)^{\frac{1}{2}}\left[S\Phi\left(\frac{1}{2},\frac{3}{2};\frac{S^2}{2}\right) - x_0\Phi\left(\frac{1}{2},\frac{3}{2};\frac{x_0^2}{2}\right)\right]$$

$$\begin{aligned} E\left[T_S^2(x_0)\right] = & \left[\sum_{n=1}^{\infty}\frac{x_0^{2n}}{n(2n-1)!!} - \sum_{n=1}^{\infty}\frac{S^{2n}}{n(2n-1)!!}\right]\times\left[-\left(\frac{\pi}{2}\right)^{\frac{1}{2}} S\Phi\left(\frac{1}{2},\frac{3}{2};\frac{S^2}{2}\right) - \frac{1}{2}\sum_{n=1}^{\infty}\frac{S^{2n}}{n(2n-1)!!}\right] \\ & - \left[x_0\Phi\left(\frac{1}{2},\frac{3}{2};\frac{x_0^2}{2}\right) - S\Phi\left(\frac{1}{2},\frac{3}{2};\frac{S^2}{2}\right)\right]\times\left[(2\pi)^{\frac{1}{2}} - \left(\frac{\pi}{2}\right)^{\frac{1}{2}}\sum_{n=1}^{\infty}\frac{1}{n(2n+1)} + \left(\frac{\pi}{2}\right)^{\frac{1}{2}}\sum_{n=1}^{\infty}\frac{S^{2n}}{n(2n-1)!!}\right. \\ & \left. + \pi S\Phi\left(\frac{1}{2},\frac{3}{2};\frac{S^2}{2}\right)\right] + \frac{1}{2}\left[\sum_{n=2}^{\infty}\frac{x_0^{2n}}{n(2n-1)!!}\sum_{k=1}^{n-1}\frac{1}{k} - \sum_{n=2}^{\infty}\frac{S^{2n}}{n(2n-1)!!}\sum_{k=1}^{n-1}\frac{1}{k}\right] + (2\pi)^{\frac{1}{2}}\left[\sum_{n=1}^{\infty}\frac{(-S)^{2n+1}}{n!2^n(2n+1)}\right. \\ & \left. \times\sum_{k=1}^{n}\frac{1}{2k-1} - \sum_{n=1}^{\infty}\frac{(-x_0)^{2n+1}}{n!2^n(2n+1)}\sum_{k=1}^{n}\frac{1}{2k-1}\right] \end{aligned}$$

Computational problems may arise



FPT moments 3/3

- Moments computation difficulties
  - The analytic expression obtained deriving the Laplace transform involves sums and differences of infinite sums. Truncation problems arise in correspondence of some parameters ranges (negative variance can result from these differences!)
  - The Siegert method request the integration of lower order moments
  - The complexity of moments expression descourage the use of moment method for parameter estimation purposes

Practical rules:

- Use different methods and compare results to guarantee reliability
- Check analitic monotonicity properties of the obtained values

Simulation methods for FPT problems 1/3

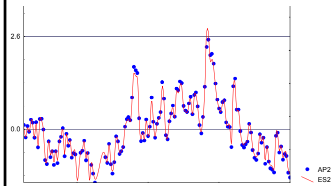
$$dX_t = (-aX_t + b)dt + \sigma dW_t$$

k=0,1,2,…

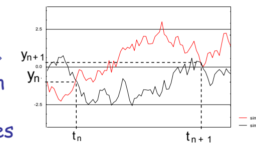
$$X(t_{k+1}) - X(t_k) = (-aX(t_k) + b)h + \sigma(W(t_{k+1}) - W(t_k))$$

$$\hat{X}(t_{k+1}) = (1 - ah)\hat{X}(t_k) + bh + \sigma \Delta W_k$$

Crossing in a discretization interval could be undetected!



Brownian bridges processes



Simulation algorithm for FPT problems 2/3

1. t_1=h, k=1
2. Simulate $\hat{X}_{t_k}$, if $\hat{x}_{t_k} > S$ stop T=t_1/2 else
   - Check for the presence of an hidden crossing in (t_0,t_1): if an hidden crossing has happened stop T=t_i/2
   - else . t_k+1=t_k+h and go to 2.

- To check for an **hidden crossing**:
  - estimate the crossing probability P for the Bridge
  - Generate a random number u from U~U[0,1]
  - if P< u recognize an hidden crossing

Estimation of hidden crossing probabilities:

- Approximate formulae for numerical evaluation
- totally simulative algorithm: generate N paths of the Bridge and count the number L of paths that crossed S: L/N gives a MonteCarlo estimation of hidden crossings.

Simulation algorithm for FPT problems 3/3

- Difficulties
  - The case of time depending drift and diffusion coefficient request special care
  - The case of rare crossings request very long simulation time (one should use adaptive step methods)
- Disadvantages of the simulation approach:
  - Detection of multimodal distribution requests more attention
  - Histograms are only approximations of the FPT distribution, sensibility analysis is made difficult

Model study: numerical, analytical or simulative

Which method use for the analysis?

A merge of all the possibilities

Analitycal methods are available only for specific instances but they allow to check reliability of other methods

Asymptotic methods: allow a better understanding of the role of each parameter

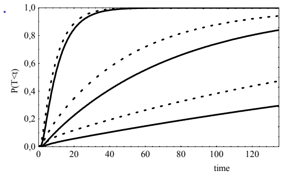
Numerical methods: give precise evaluations of FPT distribution (i.e. they allow to recognize the values from which an asyptotic behavior holds)

Simulation: the most used approach but care should be devoted to the study of the reliability of the algorithms

Comparison between different diffusion models

- To compare features of different models one has to fix the parameters of the 2 models according to suitable criteria (Lansky et al 1995)
  - Parameters of the diffusion deduced from identical mean membrane potential behavior
  - Parameters of the diffusion deduced from their discontinuos models
  - Parameters induced by the same ISI densities
- Stochastic ordering of FPT allows:
  - To compare different diffusion models features
  - To perform a sensibility analysis on characterizing the processes

Comparison between FPT cumulative distributions of the OU and the reversal potential model (equal mean membrane potential behavior)



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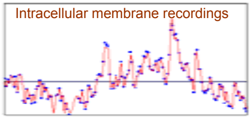
Model parameter estimation

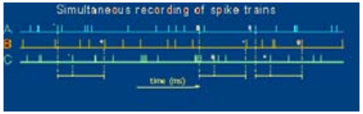
Two types of parameters

- Intrinsic parameters: S, x_0, V_I, θ can be estimated with **direct measures**
- Input parameters μ,σ^2: estimation from samples

Two types of samples:

- Intracellular membrane recordings
- ISIs time series





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Estimation problems

Intracellular recordings

- The process is observed on discretized times
- The data describe the time evolution of sample paths of diffusion processes in the **presence of an absorbing boundary**. Standard estimation methods cannot be directly applied

FPT recordings:

- Lack of closed form expressions for FPT distribution limites the use of maximum likehood approach (cf. Paninski et al. 2008 for a numerical likelihood approach)
- Moments expression are very complex (cf Inoue et al. 1995). Alternative functions less complex can be used for the moment method (Ditlevsen et al. 2007)

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Solution of the Kolmogorov equation (Wiener process $\mu=0,\sigma^2=2$) 1/2

$$\frac{\partial f}{\partial t} = \frac{\partial^2 f}{\partial x^2}$$
$$\lim_{t\to t_0} f(x,t\,|x_0,t_0) = \delta(x-x_0)$$

Take the Fourier Transform:

$$\phi(a,t) = \int_{-\infty}^{\infty} e^{i\alpha x} f(x,t)\,dx$$
$$f(x,t) = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-i\alpha x}\phi(a,t)\,d\alpha$$

The Kolmogorov equation becomes:

$$\frac{\partial\phi}{\partial t} = \int_{-\infty}^{\infty} e^{i\alpha x}\frac{\partial^2 f(x,t)}{\partial x^2}dx \overset{\text{by parts}}{=} -\alpha^2\phi(a,t)$$

Solution of the Kolmogorov equation (Wiener process $\mu=0,\sigma^2=2$) 2/2

$$\frac{1}{\phi(a,t)}\frac{\partial\phi}{\partial t} = -\alpha^2$$
$$\Longrightarrow \ln\phi(a,t) = -\alpha^2 t + H(\alpha) \Longrightarrow \phi(a,t) = \underbrace{\psi(\alpha)}_{\text{arbitrary function}} e^{-\alpha^2 t}$$

Using the initial condition

$$\lim_{t\to t_0}\phi(a,t) = e^{i\alpha(x-x_0)} \Longrightarrow \psi(\alpha) = e^{\alpha^2 t_0 + i\alpha x_0}$$

we get: $\phi(a,t) = e^{\alpha^2 t_0 + i\alpha x_0 - \alpha^2(t-t_0)}$

and

$$f(x,t\,|x0\,,t_0) = \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-i\alpha x} e^{\alpha^2 t_0 + i\alpha x_0 - \alpha^2(t-t_0)}d\alpha = \boxed{\frac{1}{\sqrt{4\pi}}\exp\left(-\frac{(x-x_0)^2}{4(t-t_0)}\right)}$$

Solution of the Kolmogorov equation (Ornstein-Uhlenbeck process $\mu=0,\sigma^2=2$)

- The transformation

$$\begin{cases} x' = \psi(x,t) = \sqrt{\frac{2}{\sigma^2}}e^{-t/\theta} \\ t' = \phi(t) = \frac{\theta}{2}e^{-2t/\theta}\end{cases} \qquad \begin{cases} x_0' = \psi(x_0,t_0) = \sqrt{\frac{2}{\sigma^2}}e^{-t_0/\theta} \\ t_0' = \phi(t_0) = \frac{\theta}{2}e^{-2t_0/\theta}\end{cases}$$

with

$$f(x,t\,|x_0,t_0) = \sqrt{\frac{2}{\sigma^2}}e^{t/\theta} f'(x',t'\,|x_0',t_0')$$

changes the Kolmogorov eq. For the O.U. process with delta initial condition into the Kolmogorov eq. for a Wiener process (Ricciardi, 1977)