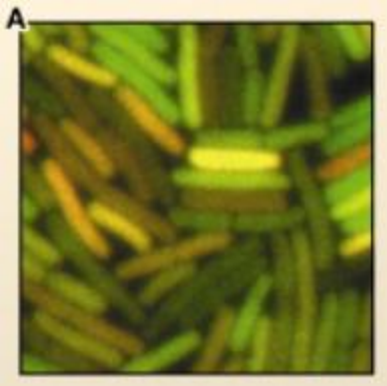
SIMULATION OF STOCHASTIC PROCESSES IN SYSTEMS BIOLOGY

CESAR NIETO PHD

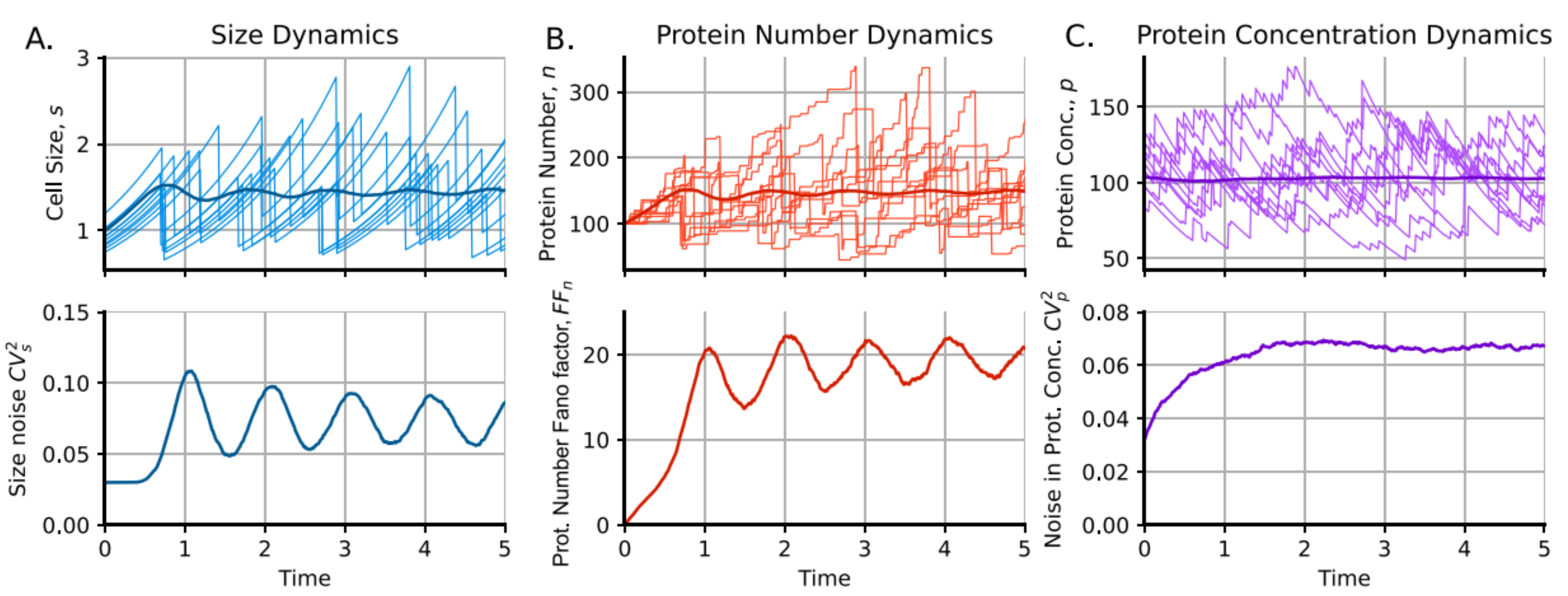
UNIVERSITY OF DELAWARE

SEPTEMBER 2023

MANY CELL PROPERTIES PRESENT STOCHASTIC VARIABILITY (NOISE)

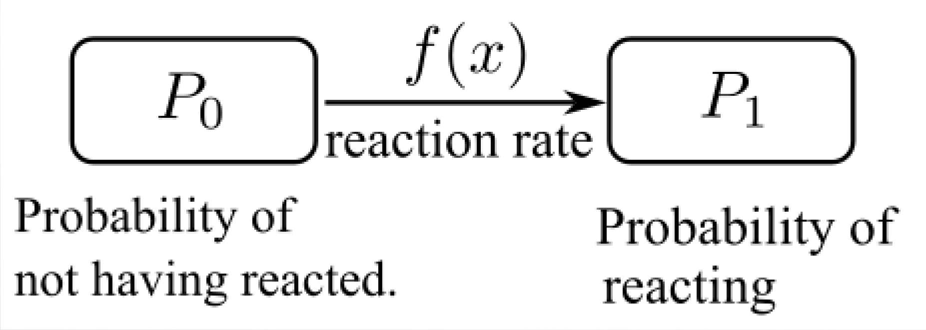


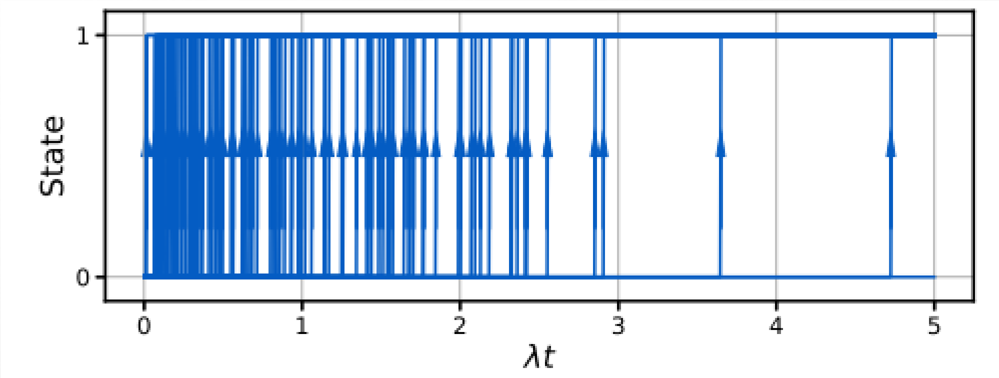
Raj A, et al Cell. 2008 Oct 17;135(2):216-26.



César Nieto et al 2023 Phys. Biol. 20 045006

SINGLE STEP PROCESS



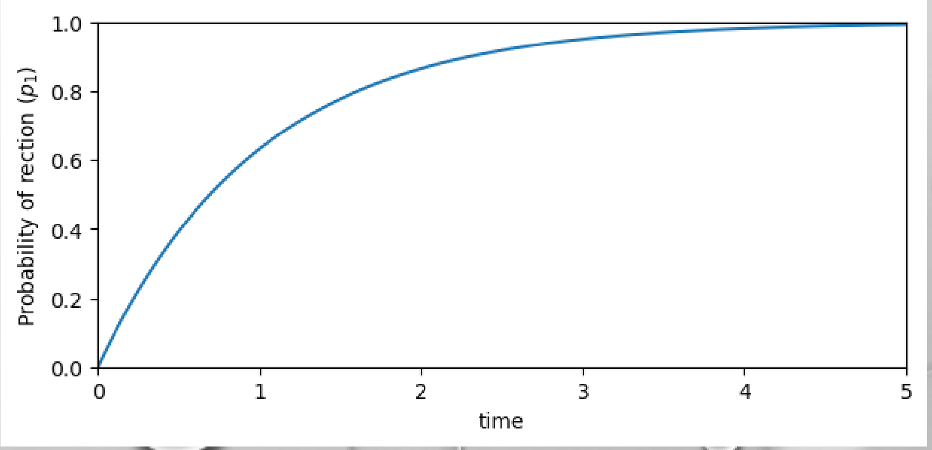


In the case of constant reaction rate $f(x, t) = \lambda$

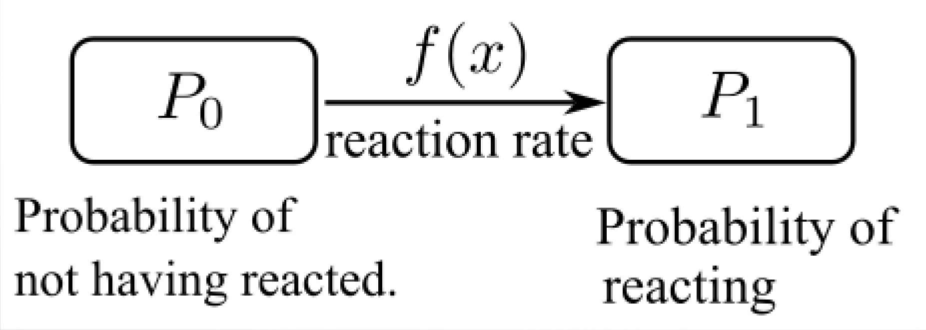
$$\begin{aligned} \frac{dp_0}{dt} &= -\lambda p_0 \\ \frac{dp_1}{dt} &= \lambda p_0 \end{aligned}$$

With solutions

$$\begin{aligned} p_0(t) &= \exp(-\lambda t) \\ p_1(t) &= 1 - \exp(-\lambda t) \end{aligned}$$



SINGLE STEP PROCESS

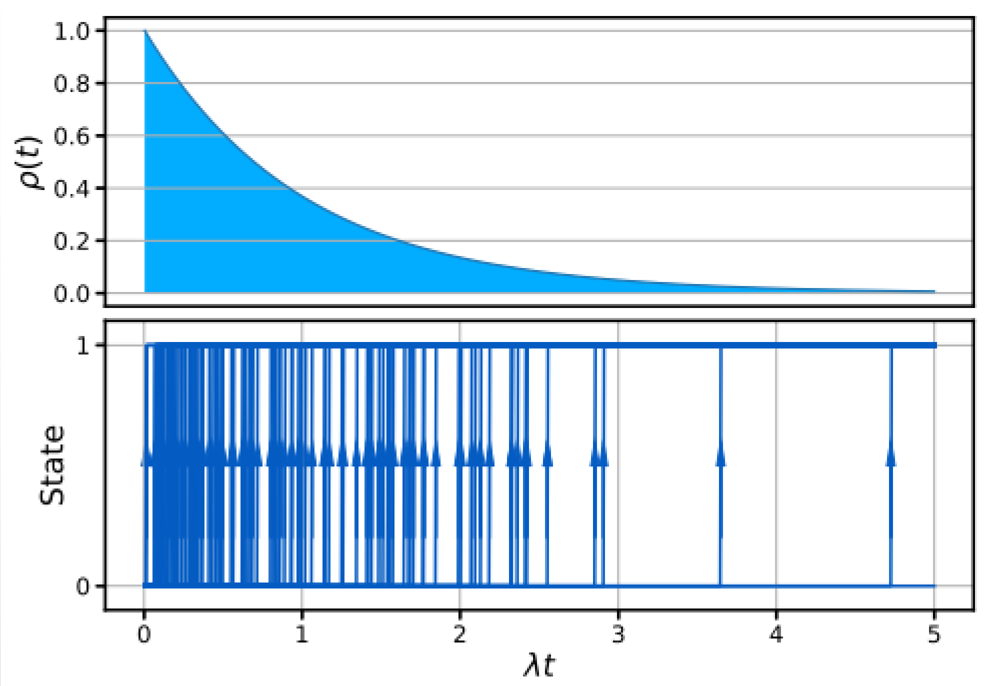


The probability density function satisfies

$$\rho(t) = \frac{dp_1}{dt}$$

$$p_1(t) = \int_0^t \rho(\tau)d\tau$$

$$\rho(t) = \lambda e^{-\lambda t}$$



METHODS FOR SIMULATION OF THE SINGLE STEP PROCESS

Time step simulation:

1. Define an infinitesimal time step Δt such as $\lambda\Delta t \ll 1$
2. The process occur with probability $\lambda\Delta t$

Activities:

1. Program a script that simulates a single-step process with $\lambda=1$, $\Delta t=0.001$ and t from 0 to 5
2. Iterate the simulator for 1000 cells and save the data in a dataframe of pandas. Plot the first 10 trajectories.
3. Using the simulated data, estimate the mean state over time. Can you estimate it analytically? Compare.
4. Plot a histogram of the First passage time. Compare it with the analytical result.
5. Compare these statistics with the known analytical solutions. What happens if $\Delta t>0.001$?

Homework: Observe what happens if $\lambda=t$

GILLESPIE ALGORITHM

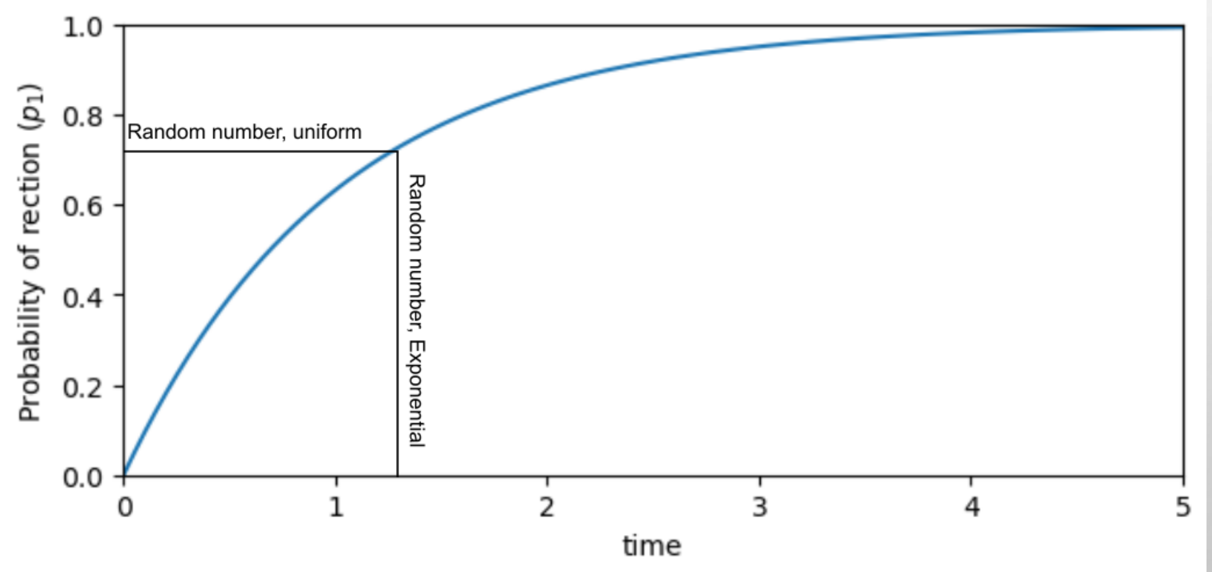
$$r \sim U(0,1)$$

We equate the random number and the Cumulative function:

$$r = 1 - e^{-\lambda t}$$

Solving for t:

$$t_r = -\frac{1}{\lambda}\ln(1-r) = -\frac{1}{\lambda}\ln(r)$$



Activity:

1. Generate 1000 random numbers with exponential distribution for λ= 1, 15, 32. Compare the histograms with the analytical expression for the distribution.
2. Homework: Generate random numbers with propensity λ=t. What is the theoretical distribution?

SIMULATING TRAJECTORIES FOR THE SINGLE STEP PROCESS

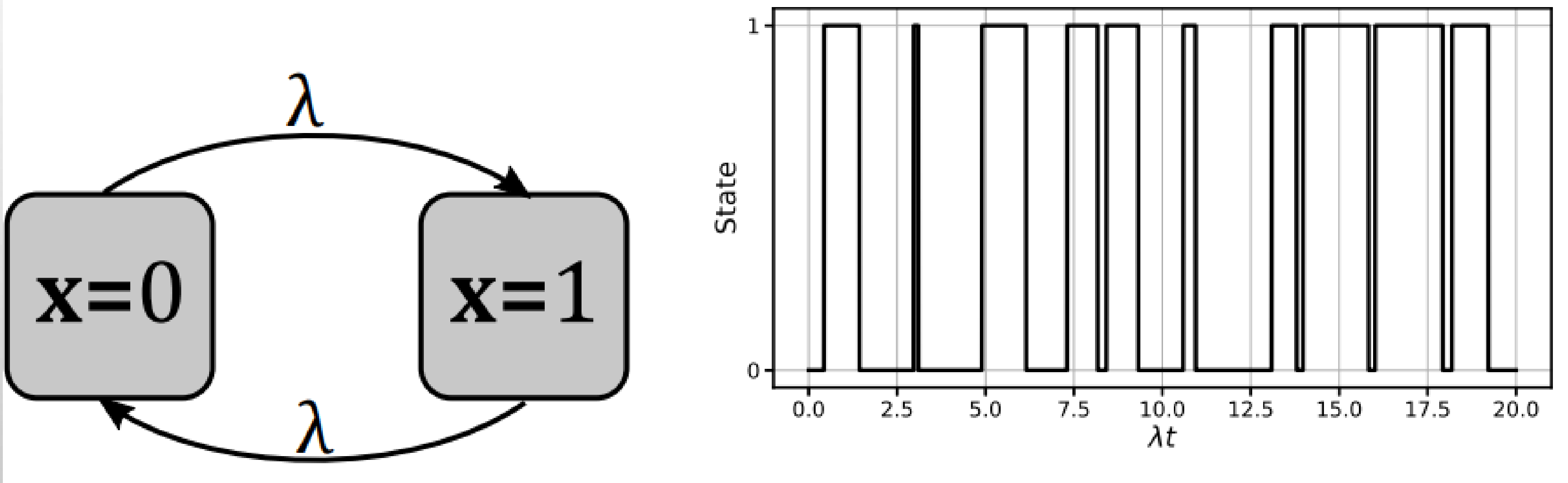
Calculating reaction times is not enough. Sometimes it is needed to plot trajectories. To do it, I suggest:

1. Estimate the reaction time.
2. Define a data acquisition frequency Δt. This does not have to be infinitesimal. I recommend that you
Have a maximum time $\Delta t \sim tmax/500$.
3. Start the data acquisition. Increment the time by steps Δt. If the time is less than tr, the state is 0 otherwise, it is 1.
4. Save the data and plot!

Activity:
Simulate 1000 trajectories. Plot similar statistics as you did in the Δt simulation.

TELEGRAPHIC WAVE

A telegraphic wave is a two states process with possibility of a reverse transition.



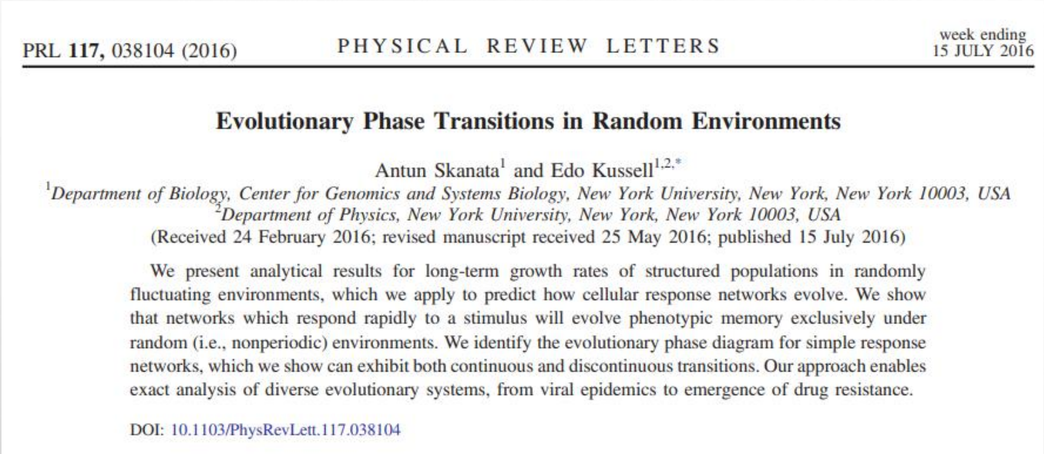
(a) Diagram for the telegraphic Markov process

(b) Example of a telegraphic stochastic path

Master equation:

$$\frac{dp_1}{dt} = \lambda p_{-1} - \lambda p_1$$
$$\frac{dp_{-1}}{dt} = \lambda p_1 - \lambda p_{-1}$$

EXAMPLE OF USES FOR THE TELEGRAPHIC WAVE



PRL 117, 038104 (2016) PHYSICAL REVIEW LETTERS week ending 15 JULY 2016

Evolutionary Phase Transitions in Random Environments

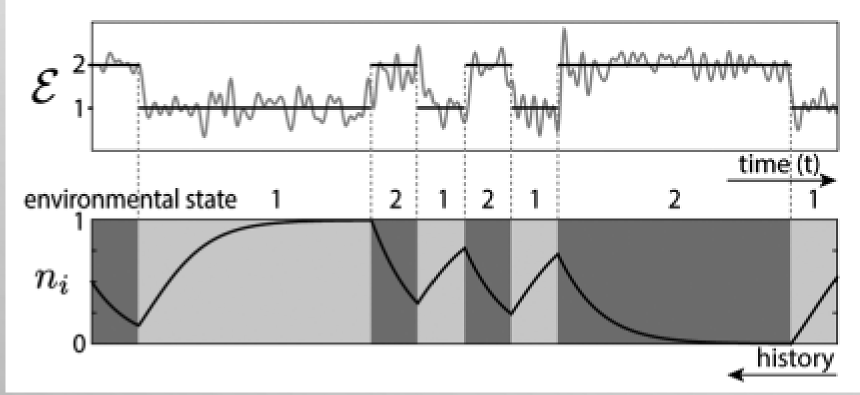
Antun Skanata[1] and Edo Kussell[1,2,*]
[1]*Department of Biology, Center for Genomics and Systems Biology, New York University, New York, New York 10003, USA*
[2]*Department of Physics, New York University, New York, New York 10003, USA*

(Received 24 February 2016; revised manuscript received 25 May 2016; published 15 July 2016)

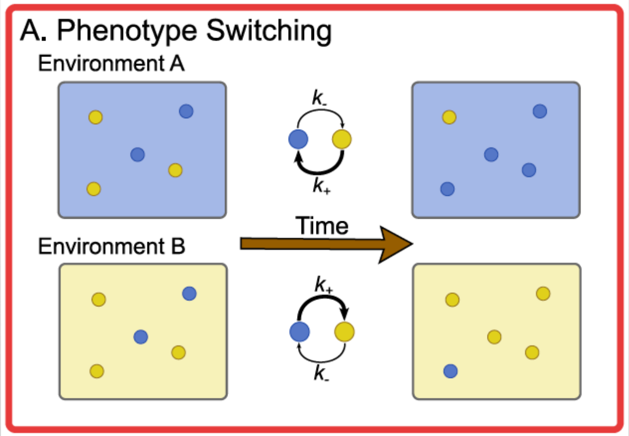
We present analytical results for long-term growth rates of structured populations in randomly fluctuating environments, which we apply to predict how cellular response networks evolve. We show that networks which respond rapidly to a stimulus will evolve phenotypic memory exclusively under random (i.e., nonperiodic) environments. We identify the evolutionary phase diagram for simple response networks, which we show can exhibit both continuous and discontinuous transitions. Our approach enables exact analysis of diverse evolutionary systems, from viral epidemics to emergence of drug resistance.

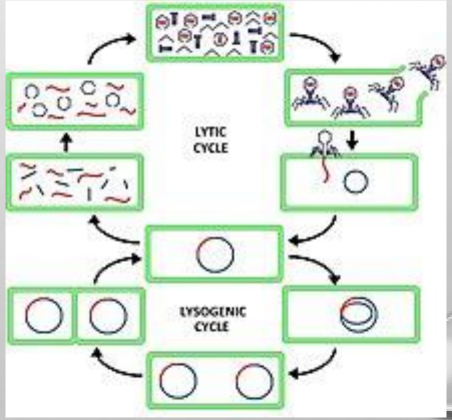
DOI: 10.1103/PhysRevLett.117.038104

Phenotypical switching: (phage lysogenic-lytic states. Bacterial persistence, Metastable systems: LAC system, GAL, etc)



Environmental transitions





TELEGRAPHIC WAVE

Master equation:

$$\frac{dp_1}{dt} = \lambda p_{-1} - \lambda p_1$$
$$\frac{dp_{-1}}{dt} = \lambda p_1 - \lambda p_{-1}$$

If we use the result

$$\begin{bmatrix} p_{-1}(t) \\ p_1(t) \end{bmatrix} = \exp \begin{bmatrix} -\lambda t & \lambda t \\ \lambda t & -\lambda t \end{bmatrix} \begin{bmatrix} 1 \\ 0 \end{bmatrix} = \frac{1}{2} \begin{bmatrix} 1+\exp(-2\lambda t) & 1-\exp(-2\lambda t) \\ 1-\exp(-2\lambda t) & 1+\exp(-2\lambda t) \end{bmatrix} \begin{bmatrix} 1 \\ 0 \end{bmatrix}$$

Obtaining:

$$\begin{aligned} p_{-1}(t) &= \tfrac{1+\exp(-2\lambda t)}{2} \\ p_1(t) &= \tfrac{1-\exp(-2\lambda t)}{2} \end{aligned}$$

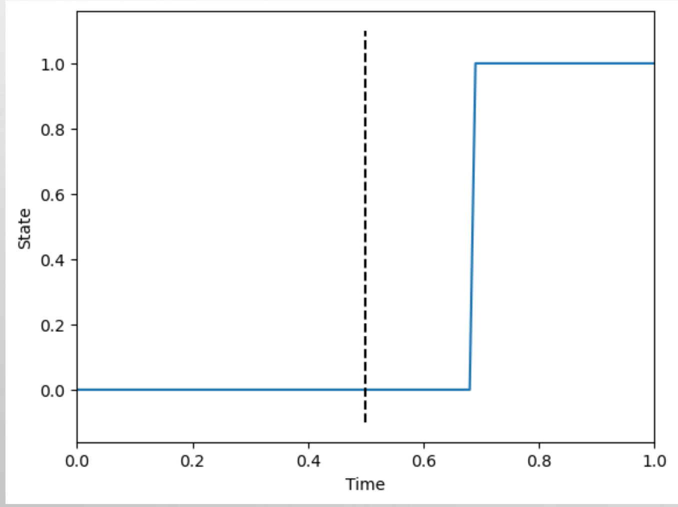
Obtaining the moment dynamics:

$$\begin{aligned} \langle x(t) \rangle &= (-1)p_{-1}(t) + (1)p_{-1}(t) = -\exp(-2\lambda t) \\ \langle x^2(t) \rangle &= (-1)^2 p_{-1}(t) + (1)^2 p_{-1}(t) = 1 \\ \mathrm{var}(x) &= \langle x^2(t) \rangle - \langle x(t) \rangle^2 = 1 - \exp(-4\lambda t) \end{aligned}$$

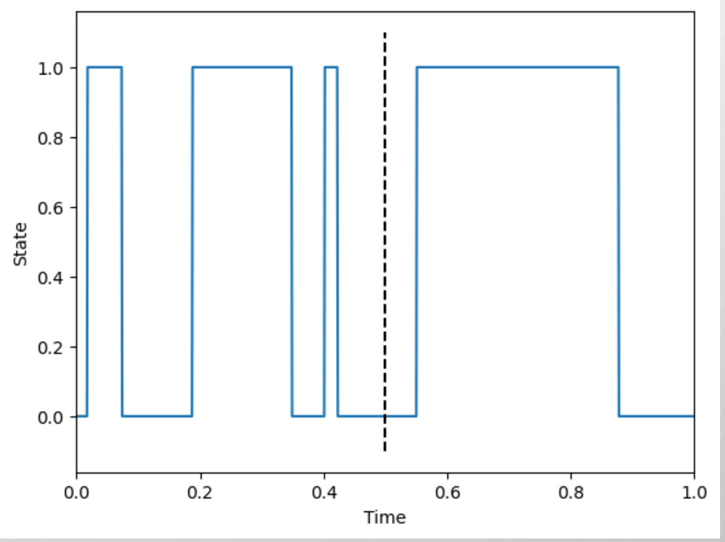
SIMULATION TELEGRAPHIC WAVE

Define the initial conditions, estimate the time to reaction using Gillespie formula:

Case 1: The state switch occurs after the max time:
Do nothing, export data.



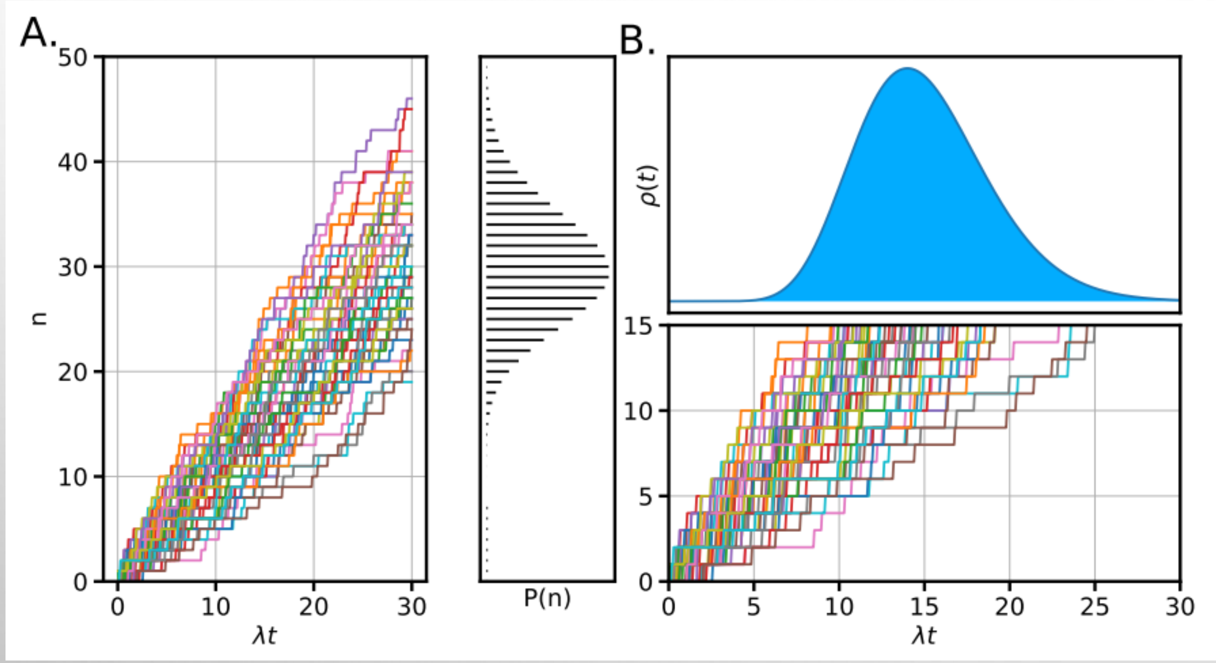
Case 2: There one or more switches before t max:
Perform the switches while t<tmax. Export data



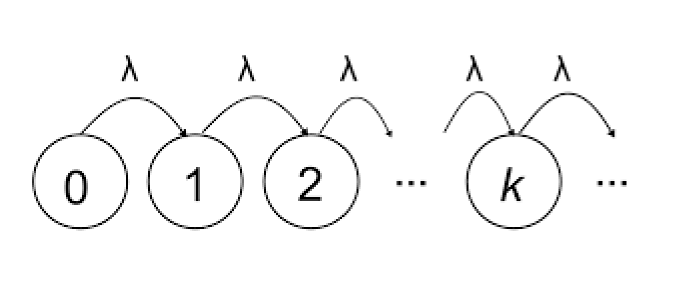
Activity:
Simulate 1000 trajectories of the telegraphic wave using Gillespie algorithm.
Obtain the moments of the trajectories and compare with analytical solutions.

Homework:
How can you

POISSON PROCESS



In a Poisson Process, Different single steps process occur one after other at a constant rate.

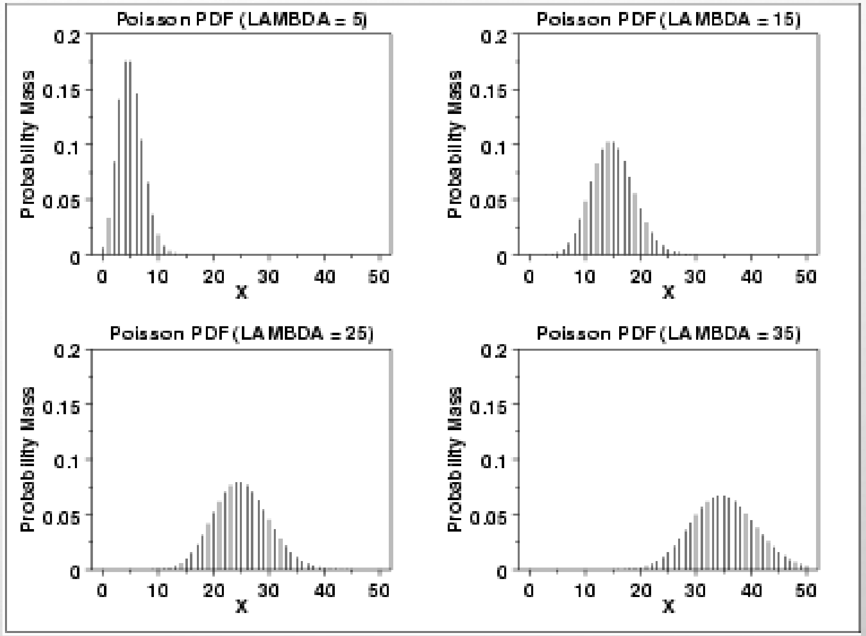


The Associated master equation follows:

$$
\begin{aligned}
\frac{dp_0}{dt} &= -\lambda p_0 \\
\frac{dp_1}{dt} &= \lambda p_0 - \lambda p_1 \\
&\vdots \\
\frac{dp_n}{dt} &= \lambda p_{n-1} - \lambda p_n
\end{aligned}
$$

THE SOLUTION OF THE SYSTEM IS THE POISSON DISTRIBUTION

$$
\begin{aligned}
p_0(t) &= \exp(-\lambda t)\theta(t) \\
p_1(t) &= \int_{-\infty}^{t} e^{-\lambda(t-\tau)} p_0(\tau) d\tau = \lambda t \exp(-\lambda t)\theta(t) \\
&\vdots \\
p_n(t) &= \int_{-\infty}^{t} e^{-\lambda(t-\tau)} p_{n-1}(\tau) d\tau = (\lambda t)^n \frac{\exp(-\lambda t)}{n!}\theta(t)
\end{aligned}
$$



Fundamental properties:

$\langle n \rangle = \lambda t$ $\quad\quad$ $\mathrm{var}(n) = \lambda t$

When a distribution has $FF = \frac{\mathrm{var}(n)}{\langle n \rangle} < 1$, it is sub-Poissonian.

When $FF = \frac{\mathrm{var}(n)}{\langle n \rangle} > 1$, it is Super-Poissonian

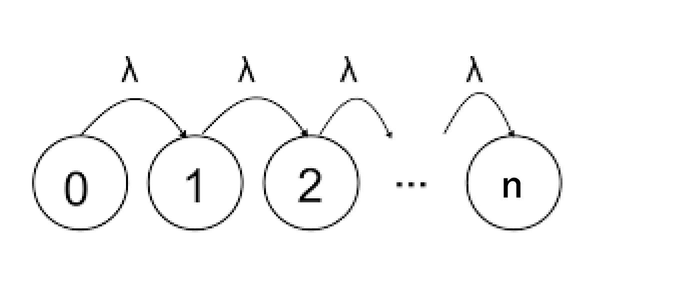
THE FIRST PASSAGE PROBLEM

To solve this problem, we make the state n an absorbent state

$$\vdots$$

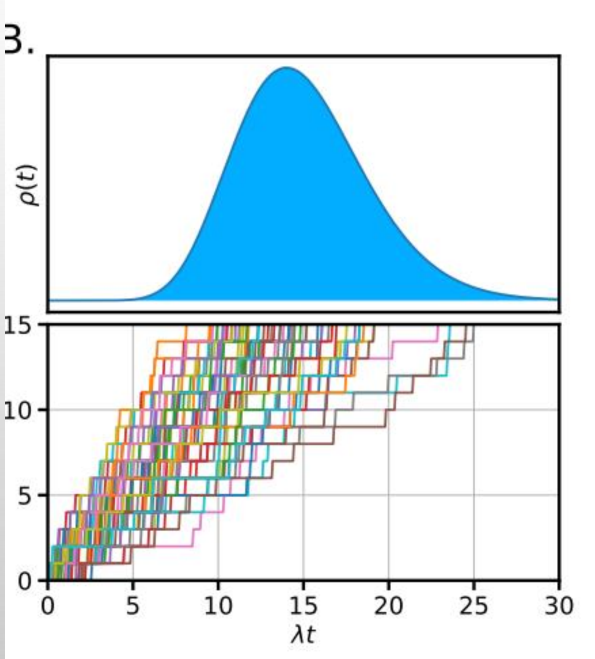
$$\frac{dp_{n-1}}{dt} = \lambda p_{n-2} - \lambda p_{n-1}$$

$$\frac{dp_n}{dt} = \lambda p_{n-1}$$



The solution is known as Erlang Distribution

$$\rho(t) = \frac{t^{n-1}\lambda^n e^{-\lambda t}}{(n-1)!}$$



Fundamental properties:

$$\langle n \rangle = \frac{n}{\lambda} \qquad \mathrm{var}(n) = \frac{n}{\lambda^2}$$

Activity: Simulate 1000 Poisson processes. Compare the properties of the simulations with the explained theoretical properties.

QUESTIONS?

CNIETO@UDEL.EDU