Stochastic Description of Systems with Delay

(Applications to Models of Protein Dynamics)

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Summary

- Motivation
- Stochastic description (master equations)
- Model for delayed degradation
    - Solution method
    - Results
- Model for delayed production
    - Solution method
    - Results
- Conclusions

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Fluctuations play an important role in many systems.

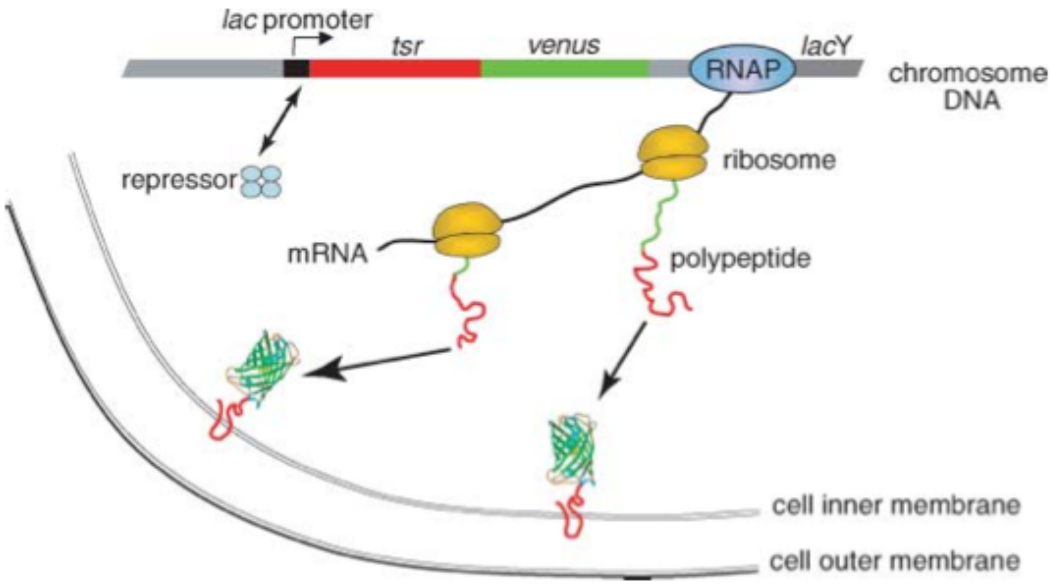
Delay in the interactions is also a common phenomenon. Can induce complex behavior such as oscillations or chaos.

Combined effect of fluctuations and delay is not completely understood.

Technical problem: Stochasticity+Delay$\rightarrow$ Non-Markovian process.

Most theoretical studies: Langevin eqs. or systems in discrete time. Models with **discrete variables but continuous in time** are the natural description of many systems: chemical reactions, protein production, population dynamics, epidemics... Some times discreteness is a mayor source of fluctuations.

We consider discrete set of states, continuous in time, for which a master equation approach is most natural.

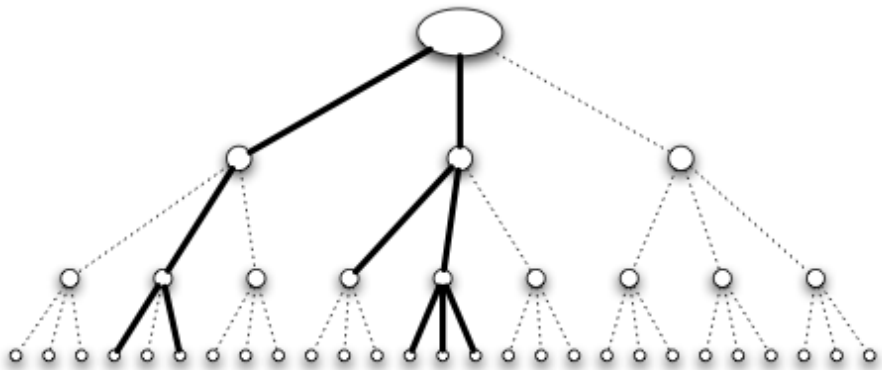


Ji Yu, et al. Science 311, 1600 (2006)

Gene → mRNA (transcription) → protein (translation)→ acts and decays
or
Gene → protein (transcription and translation), acts and decays
Stochastic processes with small number of particles ->Fluctuations are important
Delays are important!!
Heterogeneity (e.g. distribution of delay times) is important!!!

Spread of epidemics

Contagion process



There is an important stochastic component in the description
... as well as delays

Birth and death processes:

$$\varnothing \xrightarrow{C} X, \quad X \xrightarrow{D} \varnothing$$

Macroscopic variable: number n of particles of X.

D=degradation rate.
If each one of the n X-particles can die **independently** with a rate $\gamma \rightarrow D=\gamma\, n$.
(first-order reaction)

C: creation rate → Creation of a new particle is initiated with a rate *C* (proportional to system volume Ω).

If $C=C(n)$: feedback.

$C'(n)>0 \rightarrow$ Positive feedback
$C'(n)<0 \rightarrow$ Negative feedback.

Stochastic system. We look for $P(n,t)$: probability of having n particles at time t.

$$\begin{aligned} P(n,t+\Delta t) &= \sum_{n'} P(n,t+\Delta t; n',t) \\ &= \sum_{n'} P(n,t+\Delta t \mid n',t) P(n',t) \end{aligned}$$

$$\varnothing \xrightarrow{C} X, \quad X \xrightarrow{D} \varnothing$$

$n\text{-}1 \to n$ $\quad$ $n+1 \to n$ $\quad$ $n \to n$ (nothing happens)

$$P(n,t+\Delta t) = P(n-1,t)C(n-1)\Delta t + P(n+1,t)D(n+1)\Delta t + P(n,t)(1-C(n)\Delta t - D(n)\Delta t) + O(\Delta t^2)$$

$$\frac{dP(n,t)}{dt} = \left[C(n-1)P(n-1,t) - C(n)P(n,t)\right] + \left[D(n+1)P(n+1,t) - D(n)P(n,t)\right]$$

Master Equation

$$\frac{dP(n,t)}{dt} = \left(E^{-1}-1\right)\left[C(n)P(n,t)\right] + \left(E^{1}-1\right)\left[D(n)P(n,t)\right]$$

$$E^k[f(n)] \equiv f(n+k)$$

$$\varnothing \xrightarrow{C} X, \quad X \xrightarrow{D} \varnothing$$

$$\frac{dP(n,t)}{dt} = \left(E^{-1}-1\right)\left[C(n)P(n,t)\right] + \left(E^{1}-1\right)\left[D(n)P(n,t)\right]$$

$$P_{\text{st}}(n) = P_{\text{st}}(0)\prod_{k=0}^{n-1}\frac{C(k)}{D(k)}$$

$D = \gamma\, n$, constant γ

$$P_{\text{st}}(n) = \frac{P_{\text{st}}(0)}{\gamma^{n} n!}\prod_{k=0}^{n-1}C(k)$$

Constant C (no feedback)

$$P_{\text{st}}(n) = e^{-C/\gamma}\frac{(C/\gamma)^{n}}{n!}$$

Poisson distribution

$$\langle n \rangle_{\text{st}} = \sigma^{2}_{\text{st}}[n]$$

Independent particles⇒Poisson distribution

Evolution of mean values:

$$\langle f(n(t)) \rangle = \sum_{n=0}^{\infty} f(n) P(n,t)$$

$$\frac{d\langle n(t) \rangle}{dt} = \langle C(n(t)) \rangle - \langle D(n(t)) \rangle$$

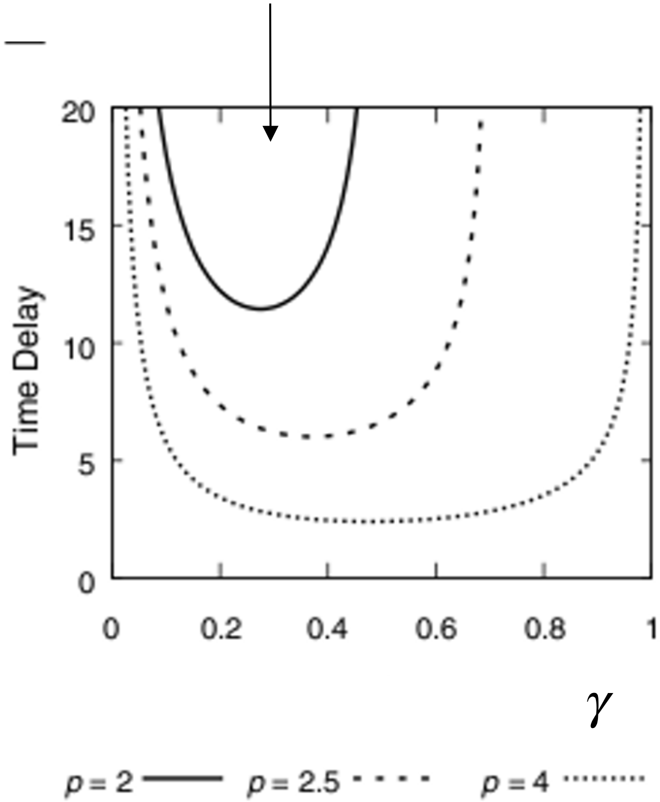
Mean-field approach (neglect fluctuations):

$$\langle f(n(t)) \rangle = f(\langle n(t) \rangle)$$

Macroscopic observable $x(t)=<n(t)>$:

$$\frac{dx(t)}{dt} = C(x(t)) - D(x(t))$$

Oscillatory regime



Hopf bifurcation line

J.J.Tyson: Biochemical oscillations, in Computational Cell Biology, Fall et al. Springer-Verlag (2004)

Negative feedback. p: Hill exponent.

$$\frac{dx(t)}{dt} = \frac{c_0}{1 + x(t)^p} - \gamma x(t)$$

Include delay:

$$\frac{dx(t)}{dt} = \frac{c_0}{1 + x(t-\tau)^p} - \gamma x(t)$$

→ Bifurcation to a limit cycle for $p>1$

Role of delay in deterministic equation: not (really) the topic of my talk.

$$\varnothing \xrightarrow{C} X, \quad X \xrightarrow{D=\gamma n} \varnothing$$

Focus on stochastic effects

If creation rate is not constant (feedback), distributions other than Poisson appear:

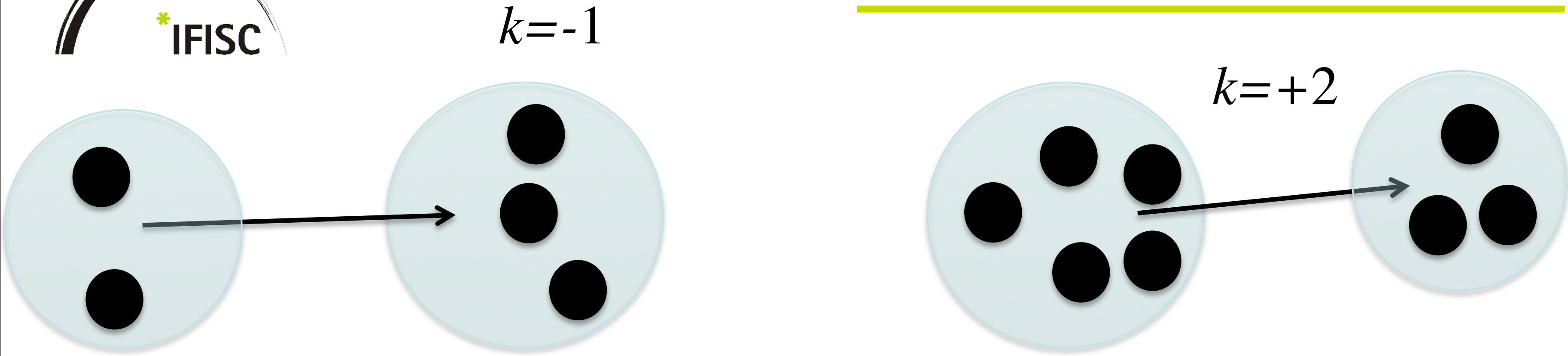
$$C(n) = \frac{c_0}{1+\epsilon n}$$

$$P_{\rm st}(n) = \frac{v^{\frac{1}{\epsilon}-1}}{I_{\frac{1}{\epsilon}-1}(2v)} \frac{v^{2n}}{n!\Gamma(n+\frac{1}{\epsilon})}, \qquad v = \sqrt{\frac{c_0}{\gamma\epsilon}}$$

$$\langle n \rangle_{\rm st} = v \frac{I_{\frac{1}{\epsilon}}(2v)}{I_{\frac{1}{\epsilon}-1}(2v)}, \qquad \sigma^2_{\rm st}[n] = \langle n \rangle_{st} - v^2 \left[\left(\frac{I_{\frac{1}{\epsilon}}(2v)}{I_{\frac{1}{\epsilon}-1}(2v)} \right)^2 - \frac{I_{\frac{1}{\epsilon}+1}(2v)}{I_{\frac{1}{\epsilon}-1}(2v)} \right]$$

As $\sigma^2_{\rm st}[n] \le \langle n \rangle_{st}$ the distribution is sub-Poissonian (negative feedback)

0.- Van Kampen expansion
(and Gaussian approximation closure scheme)



$P(n,t)$= probability of population number = n at time t

General master equation:

$$\frac{\partial P(n,t)}{\partial t} = \sum_k (E^k - 1)\left[C_k(n;\Omega)P(n,t)\right]$$

$E^k[f(n)] \equiv f(n+k)$ Step operator

$C_k(n;\Omega)$ Rates: number of "particles" decreases (increases) by k

Examples of rates.

n=number of X particles

$$\varnothing \xrightarrow{C_{-1}=c_{-1}\Omega} X, \quad X \xrightarrow{C_1=c_1 n} \varnothing,$$

$$X + X \xrightarrow{C_2 = \frac{k}{\Omega} n(n-1)} \varnothing,$$

$$C_k(n;\Omega) = \sum_a C_k^a(\Omega) n^a$$

$$C_k^a(\Omega) = \Omega^{1-a} \tilde{C}_k^a(\Omega) = \Omega^{1-a} \left(c_{k,0}^a + c_{k,1}^a \Omega^{-1} + c_{k,2}^a \Omega^{-2} + \dots \right)$$

van Kampen's (wonderful) ansatz:

$$n(t) = \Omega\phi(t) + \Omega^{1/2}\xi(t)$$

Macroscopic equation:
$$\frac{d\phi(t)}{dt} = f(\phi) = \sum_{a,k} k c_{k,0}^{a} \phi^{a}.$$

Fokker-Planck equation for fluctuations:

$$\frac{\partial \Pi(\xi,t)}{\partial t} = f'(\phi)\frac{\partial(\xi\Pi)}{\partial \xi} + g(\phi)\frac{\partial^2 \Pi}{\partial \xi^2} + O(\Omega^{-\frac{1}{2}}),$$

Solution for $\Pi(\xi,t)$ is a Gaussian distribution

Commercial

Assume Gaussian distribution from the beginning.
-On the Gaussian approximation for master equations, L. Lafuerza and R. T., J. Stat. Phys. **140**, 917 (2010)

Close equations for first two moments using Gaussian distribution

$$\frac{d\langle n\rangle}{dt}=-\sum_k\langle kC_k(n;\Omega)\rangle,\quad \frac{d\langle n^2\rangle}{dt}=\sum_k\langle k(k-n)C_k(n;\Omega)\rangle.$$

Moment	Gaussian approximation
$\langle n^3\rangle$	$3\langle n^2\rangle\langle n\rangle-2\langle n\rangle^3$
$\langle n^4\rangle$	$3\langle n^2\rangle^2-2\langle n\rangle^4$
$\langle n^5\rangle$	$15\langle n^2\rangle^2\langle n\rangle-20\langle n^2\rangle\langle n\rangle^3+6\langle n\rangle^5$
$\langle n^6\rangle$	$15\langle n^2\rangle^3-30\langle n^2\rangle\langle n\rangle^4+45\langle n\rangle^6$

1.-Delayed degradation

Simplest possible process including delayed degradation:

$$\varnothing \xrightarrow{C} X, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

Delay time τ is distributed according to $f(\tau)$

$$F(t) = 1 - \hat{F}(t) = \mathrm{Prob}(\tau < t) = \int_0^t d\tau \; f(\tau)$$

Equivalent to degradation at a rate $\gamma(a)$ depending on age *a* of the particle

$$X \xrightarrow{\gamma(a)} \varnothing$$

$\gamma(a)$=Conditional failure rate

$$\gamma(a)da = \text{Prob[dying at time(a,a+da) | particle alive at time a]}$$

$$= \text{Prob}[\tau \in (a+da) \,|\, \text{particle alive at time a}]$$

$$= \frac{f(a)da}{\int_a^\infty da' f(a')} = \frac{f(a)da}{\hat{F}(a)}$$

$$f(\tau) = \gamma(\tau) e^{-\int_0^\tau da\, \gamma(a)}$$

Two different points of view: particle is born with a random death date built-in, or probability of dying depends on age.

If $\gamma(a)$ is a constant (first-order reaction), then $f(\tau)$ is an exponential distribution.

Some delays can be represented by multistep first-order reactions:

$$X \underset{\tau}{\Rightarrow} \varnothing, \quad \text{equivalent to} \quad X \xrightarrow{\gamma_1} X_1 \xrightarrow{\gamma_2} X_2 \cdots X_{m-1} \xrightarrow{\gamma_m} \varnothing$$

if:

$$\mathcal{F}(s) \equiv \int_0^\infty dt\, e^{-st} f(t) = \prod_{i=1}^{m} \frac{\gamma_i}{\gamma_i + s}$$

e.g. $\gamma_i = \gamma, \ \forall i$:

$$f(\tau) = \frac{\gamma^m \tau^{m-1}}{(m-1)!} e^{-\gamma\tau}$$

but, in general:

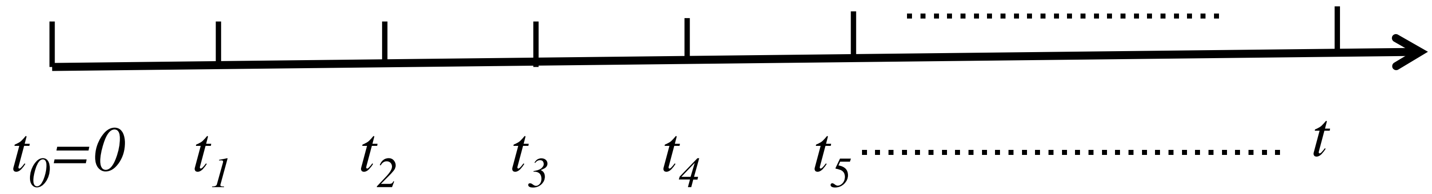
$$\frac{\sigma[\tau]}{\langle\tau\rangle} = \frac{\sqrt{\sum \frac{1}{\gamma_i^2}}}{\sum \frac{1}{\gamma_i}} \leq 1$$

Restrictive

$$\varnothing \xrightarrow{C} X, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

Determine $P(n,t)$ in the non-feedback case: $C(t)$.

$$\Delta t = t / M$$



$$P(0,t) = \lim_{M\to\infty} \prod_{i=0}^{M-1} \left[1 - C\Delta t + C\Delta t F(t - t_i) + o(\Delta t)\right] \equiv \lim_{M\to\infty} \prod_{i=0}^{M-1} \left[1 - C\hat{F}(t - t_i)\Delta t + o(\Delta t)\right]$$

No particle is born

A particle is born with a lifetime less than $t\text{-}t_i$

$$P(n,t) = \lim_{M\to\infty} \sum_{i_1=0}^{M-1} \sum_{i_2=i_1+1}^{M-1} \cdots \sum_{i_n=i_{n-1}+1}^{M-1} \prod_{l=1}^{n} \left[C\Delta t \hat{F}\left(t - t_{i_l}\right)\right] \prod_{\substack{0\le j\le M-1 \\ j\ne i_1, i_2, \ldots, i_n}} \left[1 - C\Delta t \hat{F}(t - t_{i_j})\right]$$

In the limit $M \to \infty$

$$P(n,t) = e^{-\langle n(t)\rangle} \frac{\langle n(t)\rangle^n}{n!},$$

$$\langle n(t)\rangle = \int_0^t dt' C(t') \hat{F}(t-t').$$

$$C = \text{constant} \Rightarrow \langle n(t)\rangle \to \langle n\rangle_{\text{st}} = C\langle \tau \rangle$$

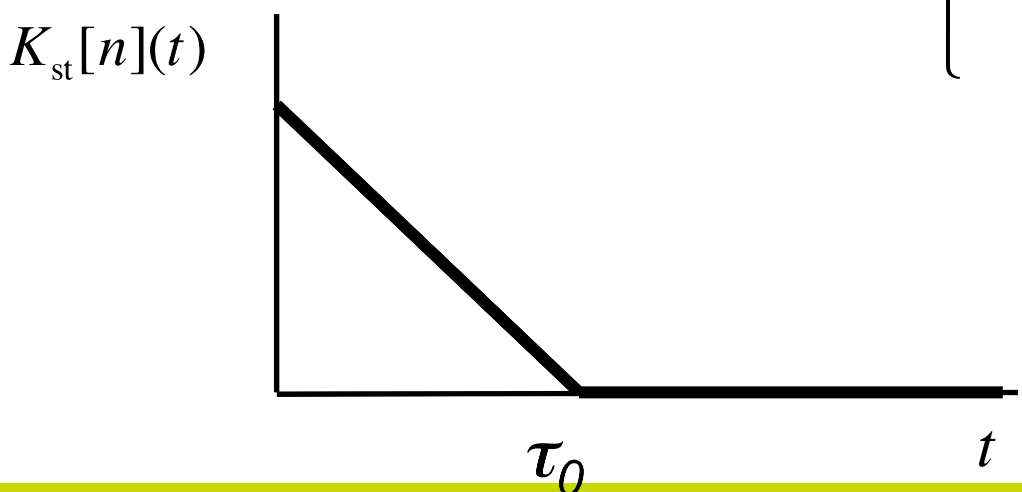
A Poisson distribution at all times.

Correlation function:

$$K[n](t',t+t') = \langle n(t')n(t'+t)\rangle - \langle n(t')\rangle\langle n(t'+t)\rangle = \int_0^{t'} dt''\, C(t'')\hat{F}(t'+t-t'')$$

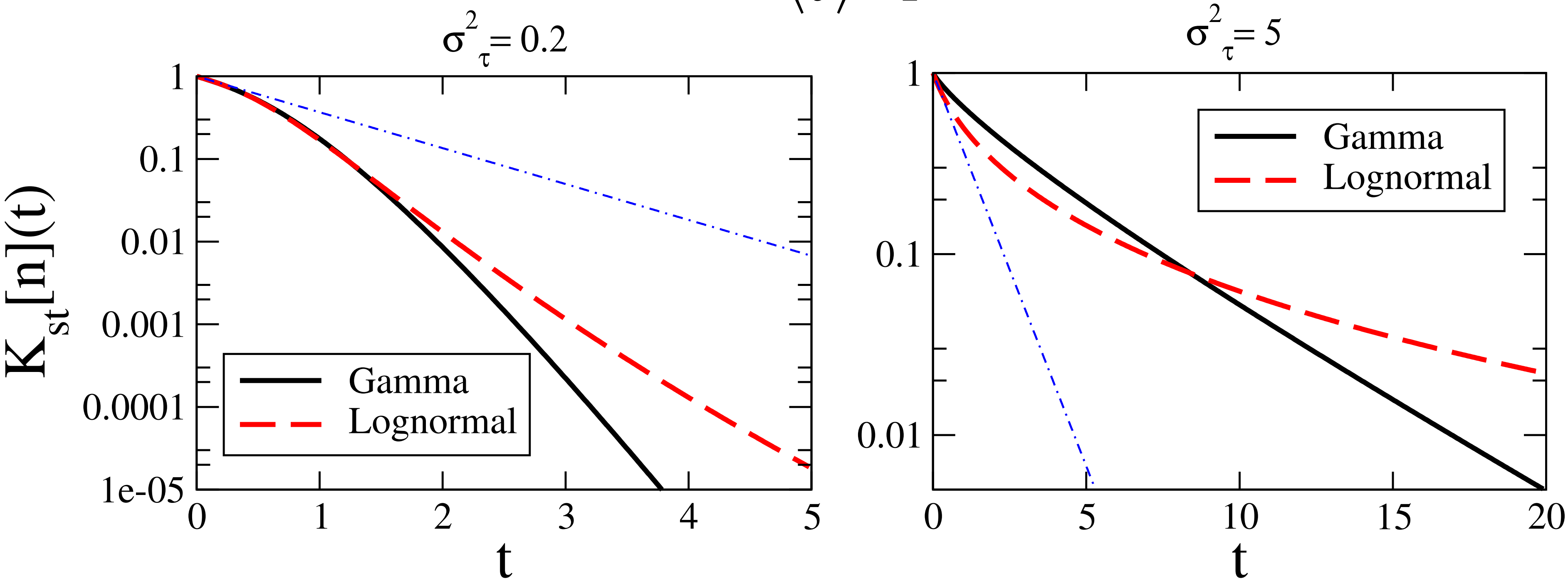
$$f(\tau) = \gamma e^{-\gamma\tau} \Rightarrow K_{\text{st}}[n](t) = \frac{C}{\gamma} e^{-\gamma/t}$$

$$f(\tau) = \delta(\tau-\tau_0) \Rightarrow K_{\text{st}}[n](t) = \begin{cases} C(\tau_0 - t), & t < \tau_0 \\ 0, & t > \tau_0 \end{cases}$$



$$\varnothing \xrightarrow{C} X, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

$$\langle \tau \rangle = 1$$



Different correlation functions can appear because of the delay distribution

Delayed degradation: $\varnothing \xrightarrow{C} X, \quad X \xrightarrow{\gamma} \varnothing, \quad X \underset{\tau}{\overset{D}{\Rightarrow}} \varnothing$

-Creation at a rate C (not necessarily constant).

-Instantaneous degradation at constant rate γ.

-Delayed degradation initiated at a constant rate D but taking a time τ to complete.

-Again, we assume that τ has a probability distribution $f(\tau)$.

As a model for protein production [Bratsun et al. PNAS **102**:14593 (2005)].
-Transcription and translation steps lumped into a single process.
-Instantaneous degradation: dilution due to cell growth, proteins leaving the cell, etc.
-Delayed degradation (proteases).

Delayed degradation: $\varnothing \xrightarrow{C} X,\quad X \xrightarrow{\gamma} \varnothing,\quad X \overset{D}{\underset{\tau}{\Rightarrow}} \varnothing$

We need to specify if particles that initiated delayed degradation can undergo instantaneous degradation. We allow it at a rate γ'. The process is equivalent to:

$$\varnothing \xrightarrow{C} X_A,\quad X_A \xrightarrow{\gamma} \varnothing,\quad X_A \xrightarrow{D} X_I,\quad X_I \underset{\tau}{\Rightarrow} \varnothing,\quad X_I \xrightarrow{\gamma'} \varnothing$$

In general we can take $\gamma' = 0$ setting:

$$f(\tau) \to e^{-\gamma'\tau} f(\tau) + e^{-\gamma'\tau}\gamma'\hat{F}(\tau)$$

1.- A particle has a lifetime τ and survives up to this time with prob. $e^{-\gamma'\tau}$

2.- Lifetime larger than τ (prob $\hat{F}(\tau)$), survives up to τ (prob. $e^{-\gamma'\tau}$), undergoes instaneous degradation γ'.

Furthermore, if D and γ are independent of n, the process is equivalent to the previous simple case

$$\varnothing \xrightarrow{C} X, \quad X \xrightarrow{\gamma} \varnothing, \quad X \underset{\tau}{\overset{D}{\Rightarrow}} \varnothing \qquad \text{equivalent to} \qquad \varnothing \xrightarrow{C} X, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

with a modified delay distribution:

$$f(\tau) = e^{-(\gamma+D)\tau}\gamma + \int_0^{\tau} dt' e^{-(\gamma+D)t'} D f(\tau - t')$$

A particle can die at τ because:

1) Survives (does not die or is infected before) up to τ and is degraded
2) instantaneously at time τ
2) Survives up to time t' and then gets infected at time $t' < \tau$ with a life time τ-t'

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

This means that that $P(n;t)$ follows a Poisson distribution.

In particular, if $f(t)=\delta(t-\tau)$, (fixed delay) we obtain:

$$\langle n(t)\rangle = \langle n_A(t)\rangle + \langle n_I(t)\rangle$$

$$\langle n_A(t)\rangle = \frac{C}{\gamma+D}\left(1-e^{-(\gamma+D)t}\right)$$

$$\langle n_I(t)\rangle = \begin{cases} \dfrac{CD}{\gamma+D-\gamma'}\left[\dfrac{1-e^{-\gamma' t}}{\gamma'} - \dfrac{1-e^{-(\gamma+D)t}}{\gamma+D}\right], & 0\le t\le\tau, \\[2ex] \dfrac{CD}{\gamma+D}\left[\dfrac{1-e^{-\gamma'\tau}}{\gamma'} + \dfrac{(1-e^{\tau(\gamma+D-\gamma')})}{\gamma+D-\gamma'}e^{-at}\right], & t\ge\tau. \end{cases}$$

$\gamma'=0$, Miekisz et al. Bull. Math. Biol. **79**: 2231-2247 (2011).
Lafuerza and Toral, Phys. Rev. **E84**:051121 (2011).

More general results valid for arbitrary distribution $f(t)$.

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

Can also compute time correlations in steady state:

$$K_{\text{st}}[n](t) = \langle n_A \rangle_{\text{st}} e^{-(D+\gamma)t} + \begin{cases} \langle n_I \rangle_{\text{st}} \dfrac{e^{-\gamma' t} - e^{-\gamma' \tau}}{1 - e^{-\gamma' \tau}} + D \dfrac{e^{-\gamma' t} - e^{-(D+\gamma)t}}{D + \gamma - \gamma'}, & 0 \le t \le \tau, \\ \dfrac{CD}{D+\gamma} \dfrac{e^{(D+\gamma-\gamma')\tau} - 1}{D + \gamma - \gamma'} e^{-(D+\gamma)t}, & t \ge \tau, \end{cases}$$

It turns out that $K_{\text{st}}[n](t)$ decreases monotonically with t (no signature of stochastic oscillations).

Details in: L. Lafuerza and R. Toral, Phil. Trans. R. Soc. **A371**, 20120458 (2013)

Delayed degradation: $\emptyset \xrightarrow{C} X, \quad X \xrightarrow{\gamma} \emptyset, \quad X \underset{\tau}{\overset{D}{\Rightarrow}} \emptyset$

Naïve arguments will lead to:

$$\frac{dx(t)}{dt} = C - \gamma x(t) - Dx(t-\tau)$$

So, oscillations seem to be able to appear due to delay degradation.

But we have seen that this simple argument is not correct.

What can be done if D, C, γ are not constants (feedback)?

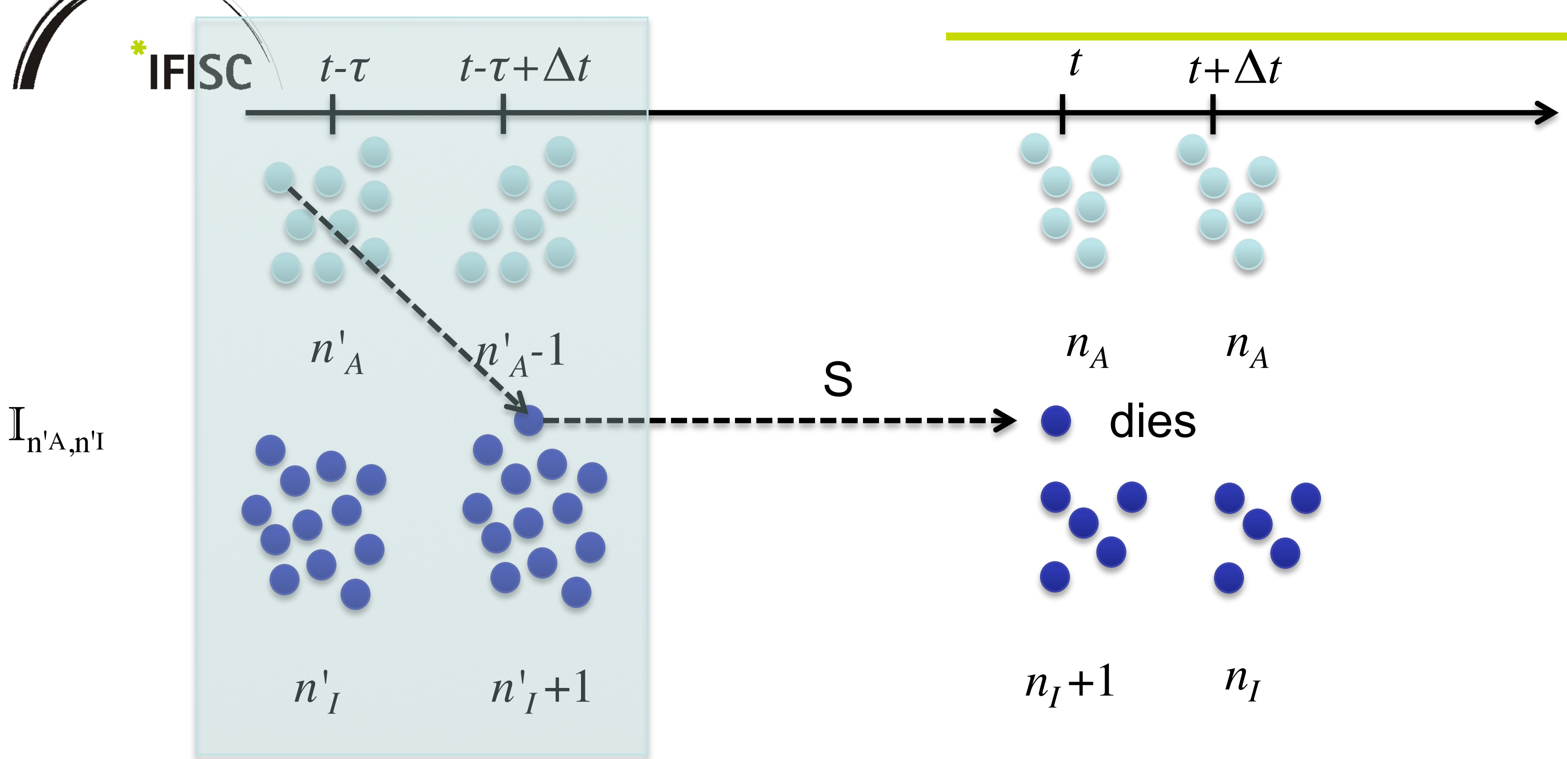
$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

Master eq.: $$P(n,t+\Delta t) = \sum_{n'} P(n,t+\Delta t; n',t)$$

$$n = (n_A, n_I)$$

All problems come from the process: $X_I \underset{\tau}{\Rightarrow} \varnothing$

$X_I \Rightarrow \varnothing$
τ



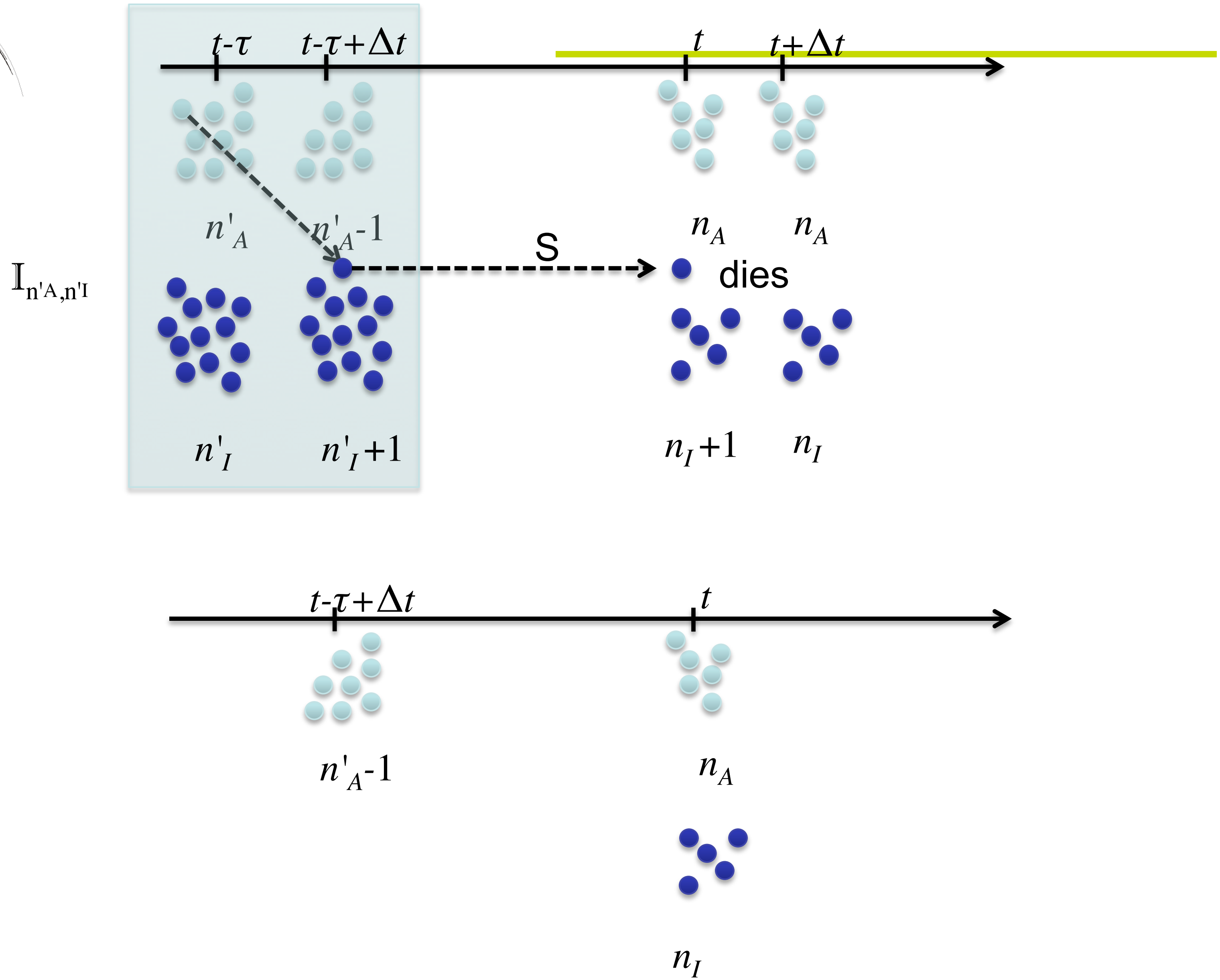
$$P(n_A, n_I, t+\Delta t; n_A, n_I+1, t; S; I_{n_{A'},n_{I'}}) =$$

$$P(n_A, n_I, t+\Delta t \mid n_A, n_I+1, t; S; I_{n_{A'},n_{I'}})$$

$$\times P(n_A, n_I+1, t \mid S; I_{n_{A'},n_{I'}})$$

$$\times P(S \mid I_{n_{A'},n_{I'}})$$

$$\times P(I_{n_{A'},n_{I'}})$$



$$P(n_A, n_I + 1, t \mid S; I_{n_{A'}, n_{I'}}) = P(n_A, n_I, t \mid n'_A - 1, t - \tau + \Delta t)$$

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

$$\frac{dP(n_A,n_I,t)}{dt} = (E_A^{-1}-1)CP(n_A,n_I,t) + (E_A-1)\gamma n_A P(n_A,n_I,t) +$$
$$(E_A E_I^{-1}-1)Dn_A P(n_A,n_I,t) + (E_I-1)\gamma' n_I P(n_A,n_I,t) +$$
$$(E_I-1)\sum_{n_{A'}=0}^{\infty} P(n_A,n_I-1,t \mid n_{A'}-1,t-\tau)Dn_{A'}P(n_{A'},t-\tau)e^{-\gamma'\tau}$$

↑↑

Non-Markovian term

We were then able to prove that if D, γ and C are constants, then n_A and n_I follow independent Poisson distributions at all times and to find the average values $\langle n_A(t) \rangle$, $\langle n_I(t) \rangle$.

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

Introduce additional Markov auxiliary variable Z (Miekisz et al, 2011):

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I + Z, \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

If fixed delay τ and no instantaneous degradation $\gamma'=0$, then

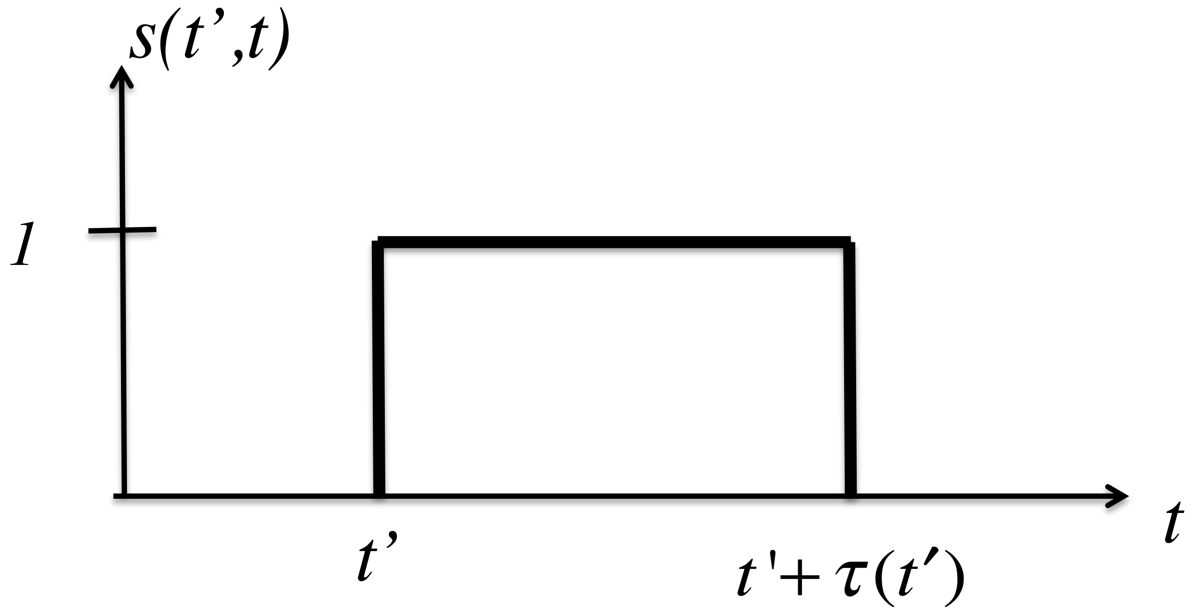
$$n_I(t) = n_Z(t) - n_Z(t-\tau)$$

$$\emptyset \xrightarrow{C} X_A,\quad X_A \xrightarrow{\gamma} \emptyset,\quad X_A \xrightarrow{D} X_I, +Z \quad X_I \underset{\tau}{\Rightarrow} \emptyset,\quad X_I \xrightarrow{\gamma'} \emptyset$$

More general relation: $$n_I(t) = \int_{-\infty}^{t} dt' \frac{dn_Z(t')}{dt'} s(t',t)$$

Given t' obtain $\tau(t')$ from $f(\tau)$. Define: $$s(t',t) = \begin{cases} 1 & t \in (t', t'+\tau(t')) \\ 0 & \text{else} \end{cases}$$

Indicator function of a particle that is infected at time t' and survives up to $t'+\tau(t')$



$$\varnothing \xrightarrow{C} X_A,\quad X_A \xrightarrow{\gamma} \varnothing,\quad X_A \xrightarrow{D} X_I, +Z \quad X_I \underset{\tau}{\Rightarrow} \varnothing,\quad X_I \xrightarrow{\gamma'} \varnothing$$

$$\langle s(t_1,t)\rangle = \hat{F}(t-t_1)$$

$$\langle s(t_1,t)s(t_2,t')\rangle = \begin{cases} \langle s(t_1,t)\rangle\langle s(t_2,t')\rangle & \text{if } t_1 \neq t_2 \\ \langle s(t_1,\max\{t,t'\})\rangle & \text{if } t_1 = t_2, \end{cases}$$

n_A, n_Z follow Markovian dynamics

$$\frac{dP(n_A,n_Z,t)}{dt} = (E_A^{-1}-1)C(n_A)P(n_A,n_z,t) + (E_A-1)\gamma n_A P(n_A,n_Z,t) + (E_A E_Z^{-1}-1)D(n_A)P(n_A,n_Z,t)$$

$$n_I(t) = \int_{-\infty}^{t} dt' \frac{dn_Z(t')}{dt'} s(t',t)$$

Exact results in the case of constant rates C, γ, γ', D:

-Both n_A and n_I follow independent Poisson distributions

$$\langle n_A(t) \rangle = \sigma^2[n_A(t)] \equiv x_A(t)$$

$$\langle n_I(t) \rangle = \sigma^2[n_I(t)] \equiv x_I(t)$$

-Average values satisfy delay equations:

$$\frac{dx_A(t)}{dt} = C - ax_A(t)$$

$$\frac{dx_I(t)}{dt} = -\gamma' x_I(t) + Dx_A(t) - D\int dt' e^{-\gamma'(t-t')} x_A(t') f(t-t')$$

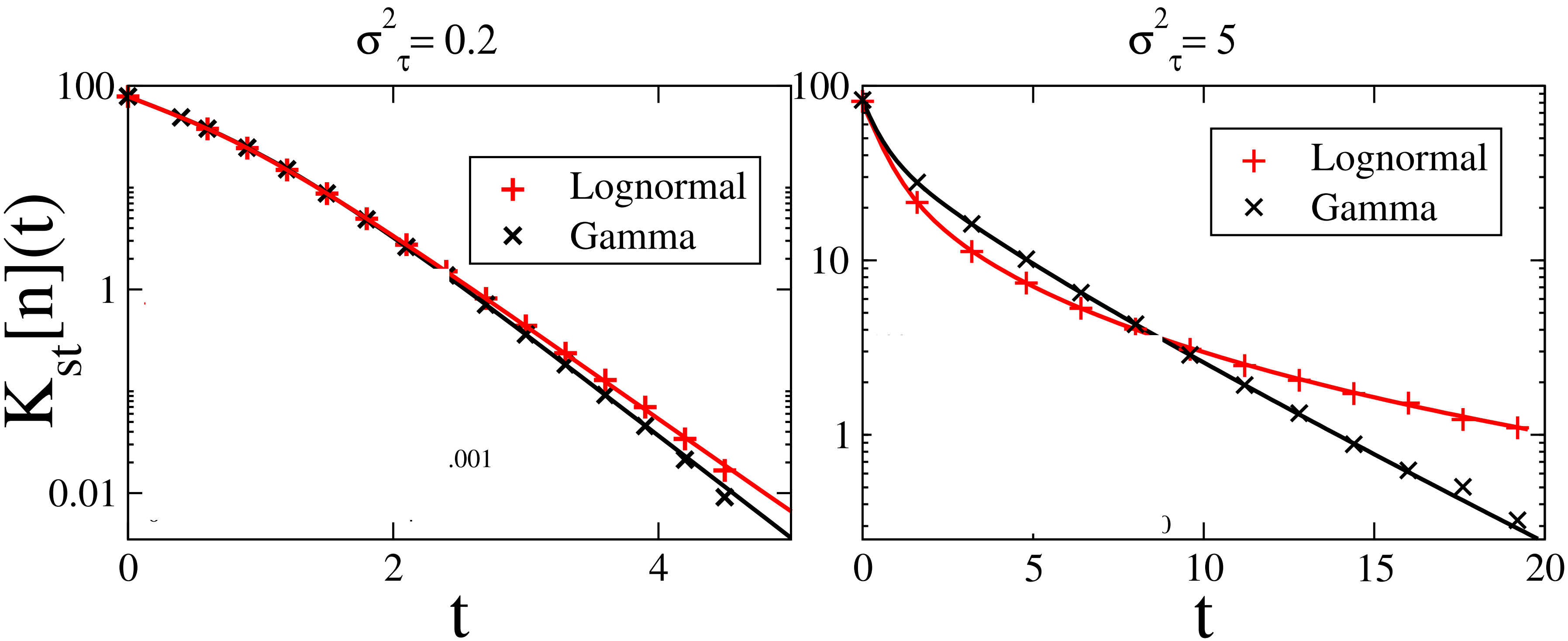
-Not possible to write down a closed equation for $x(t)=x_A(t)+x_I(t)$.

$$\frac{dx(t)}{dt} = C - \gamma x(t) - Dx(t-\tau)$$

There are no delay-induced oscillations neither for $x_A(t)$ nor $x_I(t)$ nor $x(t)$.

If $C(n_A)$, $\gamma(n_A)$, $D(n_A)$, we can use approximate techniques (van Kampen):

$$n_{A,Z} = \Omega\phi_{A,Z} + \Omega^{1/2}\xi_{A,Z}$$



$$\langle\tau\rangle = 1$$

$$C(n_A) = \frac{c\Omega}{1+\left(\epsilon\frac{n_A}{\Omega}\right)^2}, \quad \epsilon = 0.4, \quad c = 1, \quad \Omega = 100, \quad D = 1, \quad \gamma = 1$$

It is also possible to treat the case of full feedback:

$$\varnothing \xrightarrow{C(n)} X, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

Being n the total number of particles

This includes the more general case

$$\varnothing \xrightarrow{C} X_A, \quad X_A \xrightarrow{\gamma} \varnothing, \quad X_A \xrightarrow{D} X_I, +Z \quad X_I \underset{\tau}{\Rightarrow} \varnothing, \quad X_I \xrightarrow{\gamma'} \varnothing$$

If γ, γ', D do not depend on n.

The trick is to write the master equation for $P(n_Z,n,t)$

$$\varnothing \xrightarrow{C(n)} X + Z, \quad X \underset{\tau}{\Rightarrow} \varnothing$$

and then relate:

$$n(t) = \int_{-\infty}^{t} dt' \frac{dn_Z(t')}{dt'} s(t',t)$$

The result is:

$$\langle n(t)\rangle = \int_{-\infty}^{t} dt_1 \langle C(n(t_1))\rangle \hat{F}(t-t_1)$$

$$\langle n(t)n(t')\rangle = \int_{-\infty}^{t} dt_1 \int_{-\infty}^{t'} dt_2 \langle C(n(t_1))C(n(t_2))\rangle \hat{F}(t-t_1)\hat{F}(t'-t_2)$$

$$+ \int_{-\infty}^{t} dt_1 \langle C(n(t_1))\rangle \hat{F}(\max\{t,t'\}-t_1)$$

Closed if $C(n)=an+b$. Otherwise, use van Kampen expansion

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2.-Delayed creation

Birth (with delay) and death processes:

$$\varnothing \underset{\tau}{\overset{C}{\Rightarrow}} X, \quad X \xrightarrow{\quad D \quad} \varnothing$$

Particle appears a time τ after initiation of the creation reaction.
τ : delay time.

$$\varnothing \xrightarrow{\quad C \quad} X^*, \quad X^* \underset{\tau}{\Rightarrow} X, \quad X \xrightarrow{\quad D \quad} \varnothing$$

Stochastic system. We look for $P(n,t)$: probability of having n X particles at time t.

$$\varnothing \overset{C}{\underset{\tau}{\Rightarrow}} X, \quad X \xrightarrow{D} \varnothing$$

No delay case: $$\frac{dP(n,t)}{dt} = (E-1)[D(n)P(n,t)] + (E^{-1}-1)[C(n)P(n,t)]$$

$$\frac{dP(n,t)}{dt} = (E-1)[D(n)P(n,t)] + (E^{-1}-1)\left[\sum_{n'=0}^{\infty} C(n')P(n',t-\tau;n,t)\right], \qquad t \geq 0$$

↑↑

Two-times distribution: Non-Markovian

Effective form:

$$\frac{dP(n,t)}{dt} = \left(E^{1}-1\right)[D(n)P(n,t)] + \left(E^{-1}-1\right)\left[\tilde{C}(n,t)P(n,t)\right]$$

$$\tilde{C}(n,t) \equiv \langle C(n'),t-\tau \mid n,t \rangle$$ Conditional average

$$\tilde{C}_{\rm st}(n) = \lim_{t\to\infty} \tilde{C}(n,t) \qquad P_{\rm st}(n) = \frac{P_{\rm st}(0)}{\gamma^n n!} \prod_{k=0}^{n-1} \tilde{C}_{\rm st}(k)$$

Need an approximation to compute: $\tilde{C}_{\mathrm{st}}(n) \equiv \langle C(n'), -\tau \mid n \rangle_{\mathrm{st}}$

$$\frac{dP(n,t)}{dt} = (E-1)[D(n)P(n,t)] + (E^{-1}-1)\left[\sum_{n'=0}^{\infty} C(n')P(n',t-\tau;n,t)\right], \qquad t \geq 0$$

We use van Kampen's expansion: $n = \Omega\phi + \Omega^{1/2}\xi$

Assume: $C(n) = \Omega\Phi\left(\frac{n}{\Omega}\right)$

Expand consistently at all orders in Ω^k:

$$\frac{d\phi(t)}{dt} = -\gamma\phi(t) + \Phi\big(\phi(t-\tau)\big)$$

$$\frac{d\langle \xi,t \mid \xi',t' \rangle}{dt} = -\gamma\langle \xi,t \mid \xi',t' \rangle + \Phi'\big(\phi(t-\tau)\big)\langle \xi,t-\tau \mid \xi',t' \rangle, \qquad t \geq t'$$

In the steady state (assumed unique and constant):

$$\frac{d\phi(t)}{dt} = -\gamma\phi(t) + \Phi\big(\phi(t-\tau)\big) = 0 \longrightarrow \gamma\phi_{\text{st}} = \Phi\big(\phi_{\text{st}}\big)$$

$$\frac{d\langle \xi,t \mid \xi',t' \rangle_{\text{st}}}{dt} = -\gamma\langle \xi,t \mid \xi',t' \rangle_{\text{st}} - \alpha\langle \xi,t-\tau \mid \xi',t' \rangle_{\text{st}}, \qquad \alpha = -\Phi'\big(\phi_{\text{st}}\big)$$

$$\langle \xi,t \mid \xi',t' \rangle_{\text{st}} = \xi' f(t-t') \longrightarrow \frac{df(\Delta)}{d\Delta} = -\gamma f(\Delta) - \alpha f(\Delta-\tau), \qquad \Delta = t-t' \geq 0$$

$$n(t) = \Omega\phi_{\text{st}} + \Omega^{1/2}\xi(t) \Rightarrow \langle n,t \mid n' \rangle_{\text{st}}, \forall t \geq 0$$

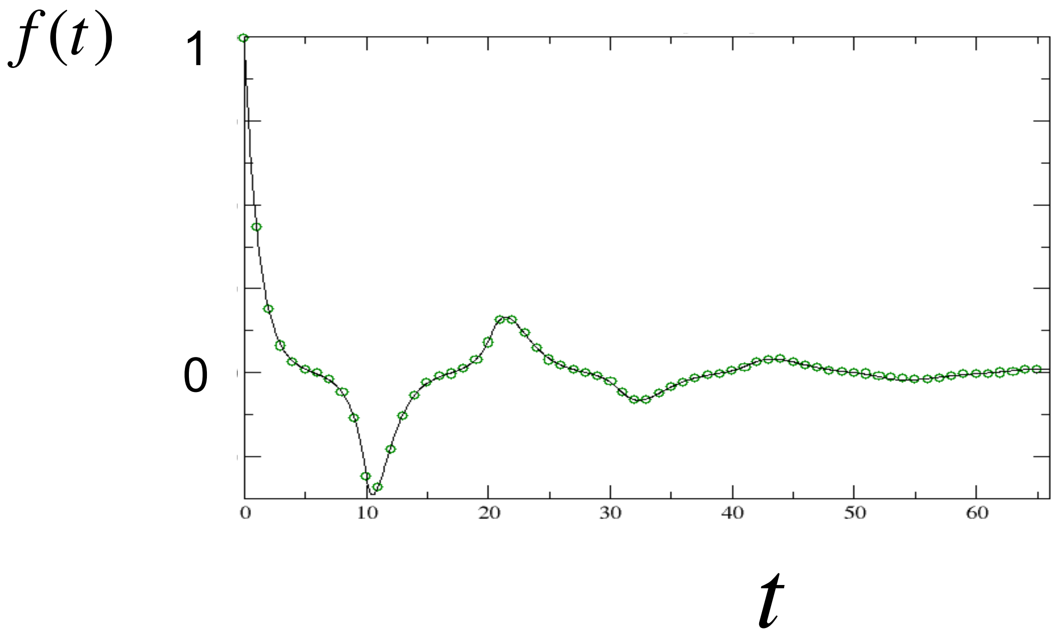
But we need $\langle n,-\tau \mid k \rangle_{\text{st}}$ backwards in time

We assume time-reversal: $\langle n,-\tau \mid k \rangle_{\text{st}} = \langle n,\tau \mid k \rangle_{\text{st}}$

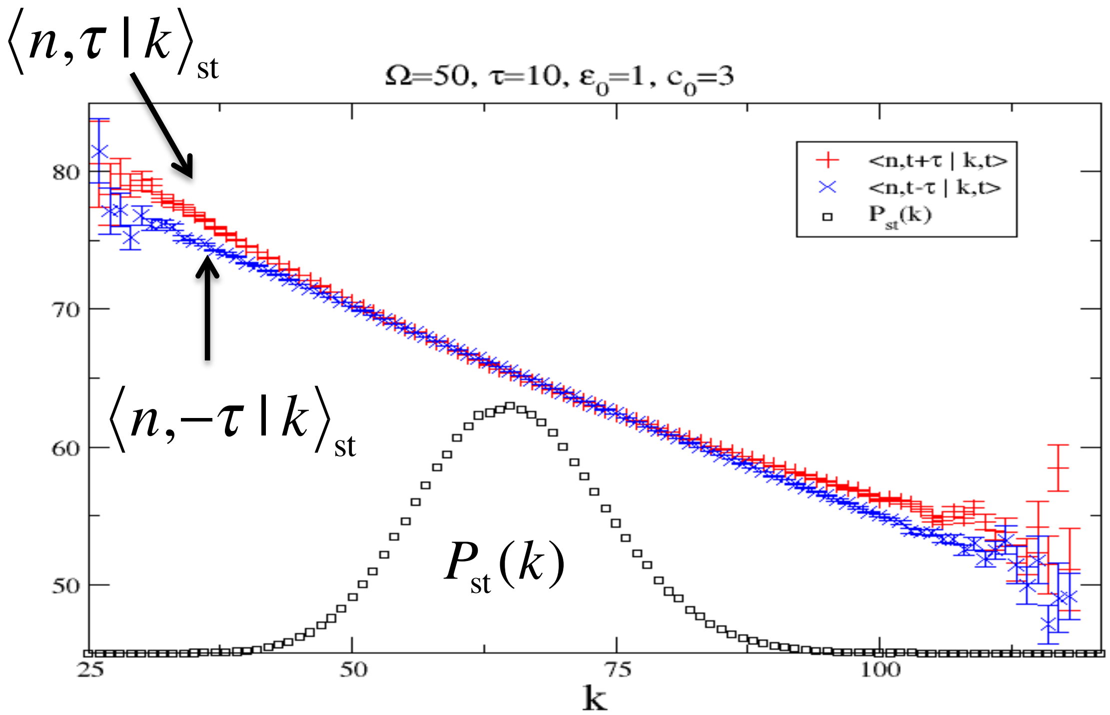
Need to find symmetric $f(\Delta) = f(-\Delta)$ solution

Symmetric solution of

$$\frac{df(t)}{dt} = -\gamma f(t) - \alpha f(t-\tau)$$
$$f(0) = 1$$



How good is the time-reversal assumption $\langle n, -\tau \mid k \rangle_{\text{st}} = \langle n, \tau \mid k \rangle_{\text{st}}$?



$$C(n) = \frac{\Omega c_0}{1 + \frac{\varepsilon_0}{\Omega} n}$$

The difference between forward and backward conditional average is small where $P_{\text{st}}(k)$ is large

General analysis: $C(n) = \Omega\Phi\left(\frac{n}{\Omega}\right)$

Split $n = \Omega\phi + \Omega^{1/2}\xi$ and use time-reversal assumption

Find steady-state value $\gamma\phi_{\mathrm{st}} = \Phi(\phi_{\mathrm{st}}) \longrightarrow \langle n\rangle_{\mathrm{st}} = \Omega\phi_{\mathrm{st}}$

and fluctuations:

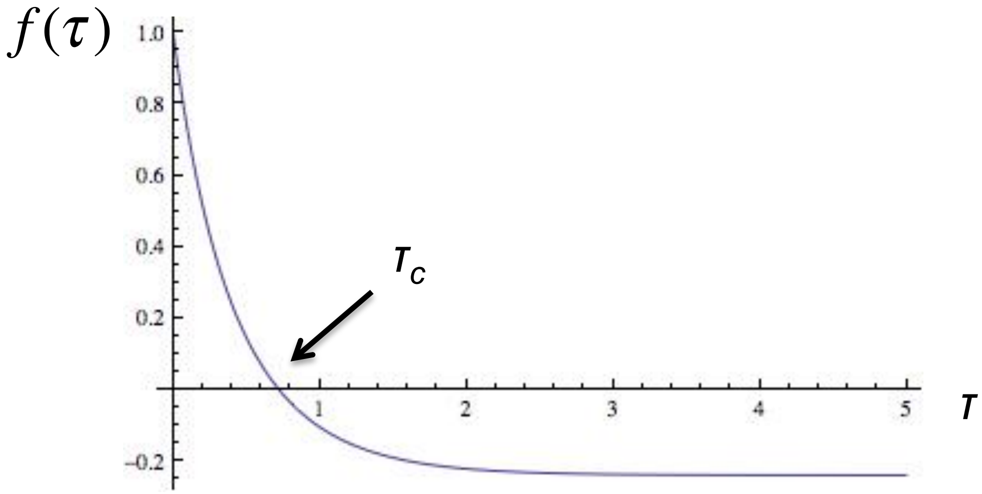
$$\sigma_{st}^2[n] = \frac{\langle n\rangle_{st}}{1-\gamma^{-1}\Phi'(\phi_{st})f(\tau)}$$

$$f(\tau) = \frac{e^{-\lambda\tau} - \zeta}{1-\zeta e^{-\lambda\tau}}$$

$$\lambda \equiv \sqrt{\gamma^2 - \Phi'(\phi_{st})^2}, \zeta \equiv \frac{-\gamma+\lambda}{\Phi'(\phi_{st})}$$

$$\Phi'(\phi_{st})f(\tau) \begin{cases} <0 & \text{Subpoissonian fluctuations:} \quad \sigma_{\mathrm{st}}^2[n] < \langle n\rangle_{\mathrm{st}} \\ =0 & \text{Poissonian fluctuations:} \quad \sigma_{\mathrm{st}}^2[n] = \langle n\rangle_{\mathrm{st}} \\ >0 & \text{Superpoissonian fluctuations:} \quad \sigma_{\mathrm{st}}^2[n] > \langle n\rangle_{\mathrm{st}} \end{cases}$$

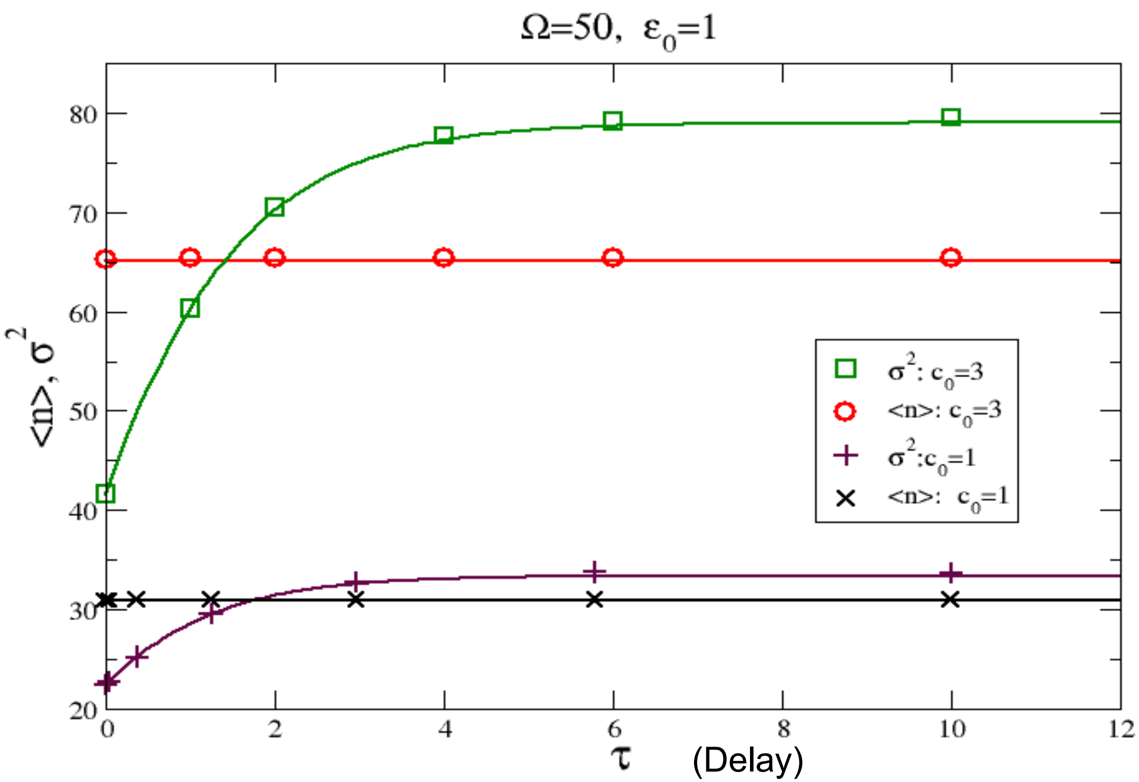
Negative feedback loop, e.g. $C(n) = \dfrac{\Omega c_0}{1 + \frac{\varepsilon_0}{\Omega} n}$ $\qquad \Phi'(\phi_{st}) < 0$



$$\tau \begin{cases} < \tau_c & \text{Subpoissonian fluctuations:} \quad \sigma^2_{\text{st}}[n] < \langle n \rangle_{\text{st}} \\ = \tau_c & \text{Poissonian fluctuations:} \quad \sigma^2_{\text{st}}[n] = \langle n \rangle_{\text{st}} \\ > \tau_c & \text{Superpoissonian fluctuations:} \quad \sigma^2_{\text{st}}[n] > \langle n \rangle_{\text{st}} \end{cases}$$

Negative feedback of the form:

$$C(n) = \frac{\Omega c_0}{1 + \frac{\varepsilon_0}{\Omega} n}$$



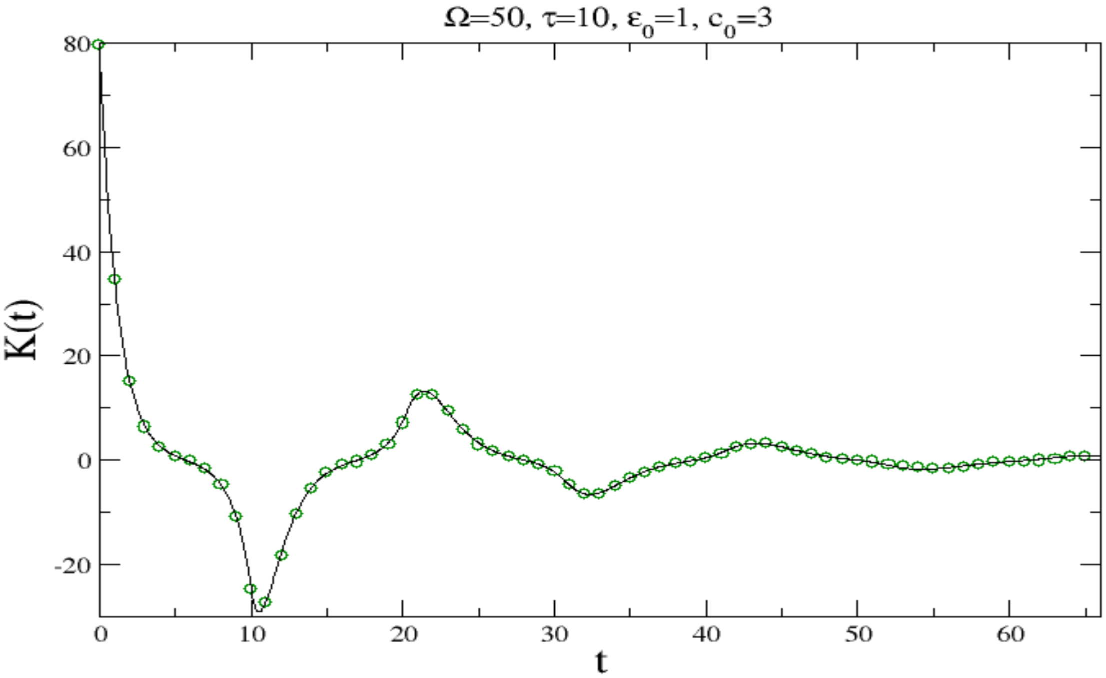
Fluctuations are amplified as the delay is increased.

System changes from sub-Poissonian $\tau = 0$) to super-Poissonian ($\tau > \tau_c$)

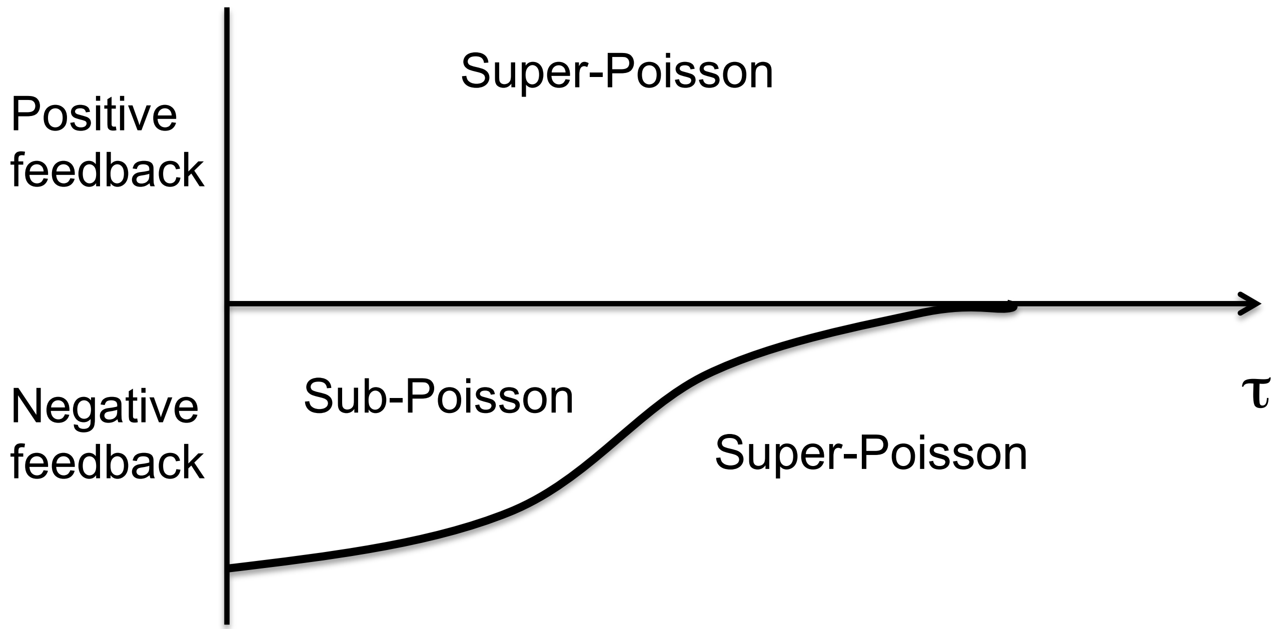
With positive feedback, system is always super-Poissonian but fluctuations decrease as the delay is increased.

→ Increasing delay has opposite effects for positive and negative feedback.

Correlation function: $K(t) = \langle n(t+t')n(t')\rangle_{st} - \langle n\rangle_{st}^2 = \sigma_{st}^2 f(t)$



The correlation function displays a clear non-monotonic character due to the presence of delay. This is a signature of stochastic oscillations.
Solid line: theory. Dots: numerical simulations.



For negative feedback: An increase of the delay reduces fluctuations, turning them from sub-Poissonian to super-Poissonian. For fixed delay, an increase of the negative feedback finally leads to increase the fluctuations

For positive feedback, system is always super-Poissonian but fluctuations decrease as the delay is increased.

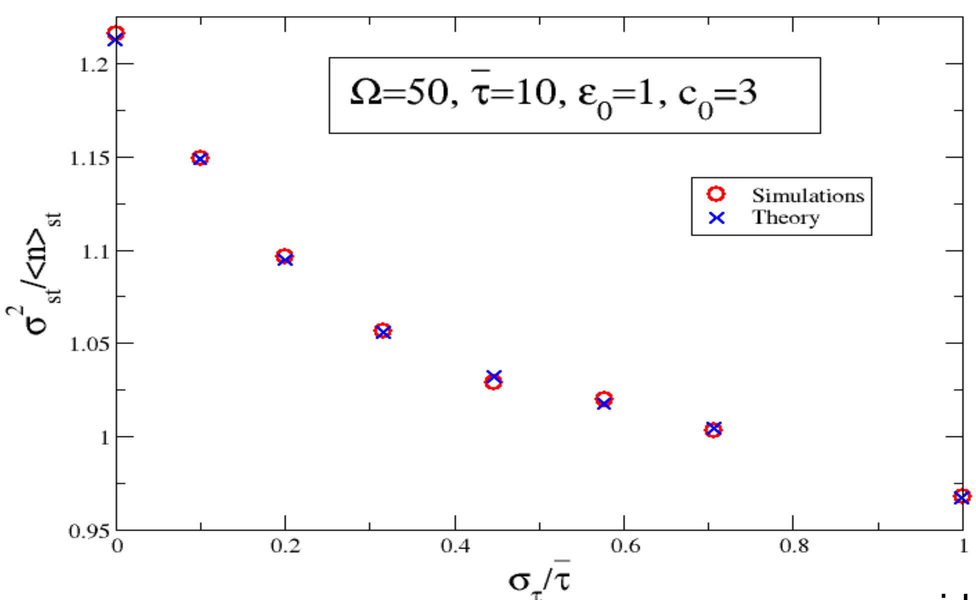
→ Increasing delay has opposite effects for positive and negative feedback.

In the case of distributed delay $p(\tau)$, same applies, but now;

$$\sigma_{st}^2[n] = \frac{\langle n \rangle_{st}}{1-\gamma^{-1}\Phi'(\phi_{st}) f(\tau)} \quad \Rightarrow \quad \sigma_{st}^2 = \frac{\langle n \rangle_{st}}{1-\gamma^{-1}\Phi'(\phi_{st})\int d\tau\, p(\tau) f(\tau)}$$

With $f(t)$ the symmetric solution of:

$$\frac{df(t)}{dt} = -\gamma f(t) + \Phi'(\phi_{st}) \int \mathrm{d}\tau\, p(\tau) f(t-\tau)$$



As the delay becomes more spread, its effect decreases.

we consider $p(\tau) = \frac{\tau^{m-1}}{(m-1)!} e^{-b\tau} b^m$ (Gamma distribution)

Transcription-translation model [Thattai and Oudernaarden (2001)] :

$$\varnothing \xrightarrow{C} Y^* \overset{\tau_1}{\Rightarrow} Y, \quad Y \xrightarrow{\omega m} X^* \overset{\tau_2}{\Rightarrow} X, \quad X \xrightarrow{\gamma_n n} \varnothing, \quad Y \xrightarrow{\gamma_m m} \varnothing$$

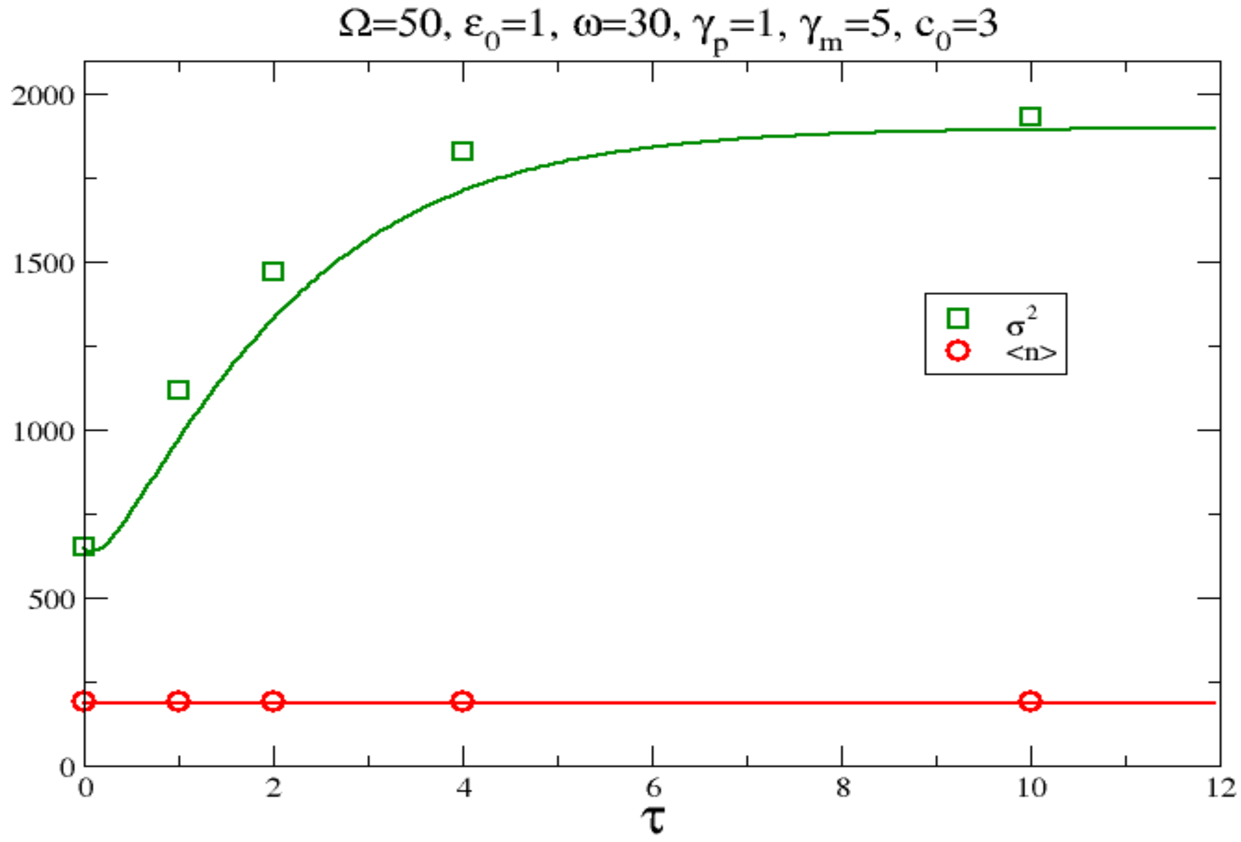
Use van Kampen's expansion: assume

$$n = \Omega \varphi_n + \Omega^{1/2} \xi_n$$
$$m = \Omega \varphi_m + \Omega^{1/2} \xi_m,$$
$$C(n) = \Omega\, \Phi(n/\Omega)$$

and derive a linear Fokker-Planck equation. Solve the equations for the first moments under the assumption of time-reversal.

$$\langle n \rangle_{st} = \Omega \phi_{n,st}$$

$$\frac{\sigma^2_{st}[n]}{\langle n \rangle_{st}} = 1 + \frac{\dfrac{\omega}{\gamma_m}}{1 + \dfrac{\gamma_n}{\gamma_m} + \dfrac{\alpha}{\gamma_m} f_m(\tau)} \frac{1 - \dfrac{\alpha}{\gamma_n} f_n(\tau)\left(1 + \dfrac{\alpha}{\gamma_m} f_m(\tau)\right)}{1 + \dfrac{\alpha}{\gamma_m}\left(\dfrac{\omega}{\gamma_n} f_n(\tau) + f_m(\tau)\right)}$$



Again the fluctuations increase (decrease) with the delay in the case of negative (positive) feedback.

Results are qualitatively similar to the one-step case.

- We have presented rather general methods to solve stochastic processes with delay described by master equations.

-We have considered first the case of delayed degradation. We have solved it exactly in the case of constant rates and proved that it leads always to a Poisson distribution in the steady state. Therefore, no delay-induced oscillations are present in this simple model (contrary to intuitive analysis).

- In the case of delayed production with negative feedback, we show how the delay induces a change from sub-Poissonian to super-Poissonian statistics → Delay increases fluctuations.
In the positive feedback case, delay decreases the fluctuations.

-The methods also allows us to consider situations with a distribution of delay. As the delay distribution widens, its effects decrease.

Thank you!

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