



# Stochastic self-regulated gene expression model

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# **Intrinsic and Extrinsic Noise Effects on Molecular Distributions in Bacteria**

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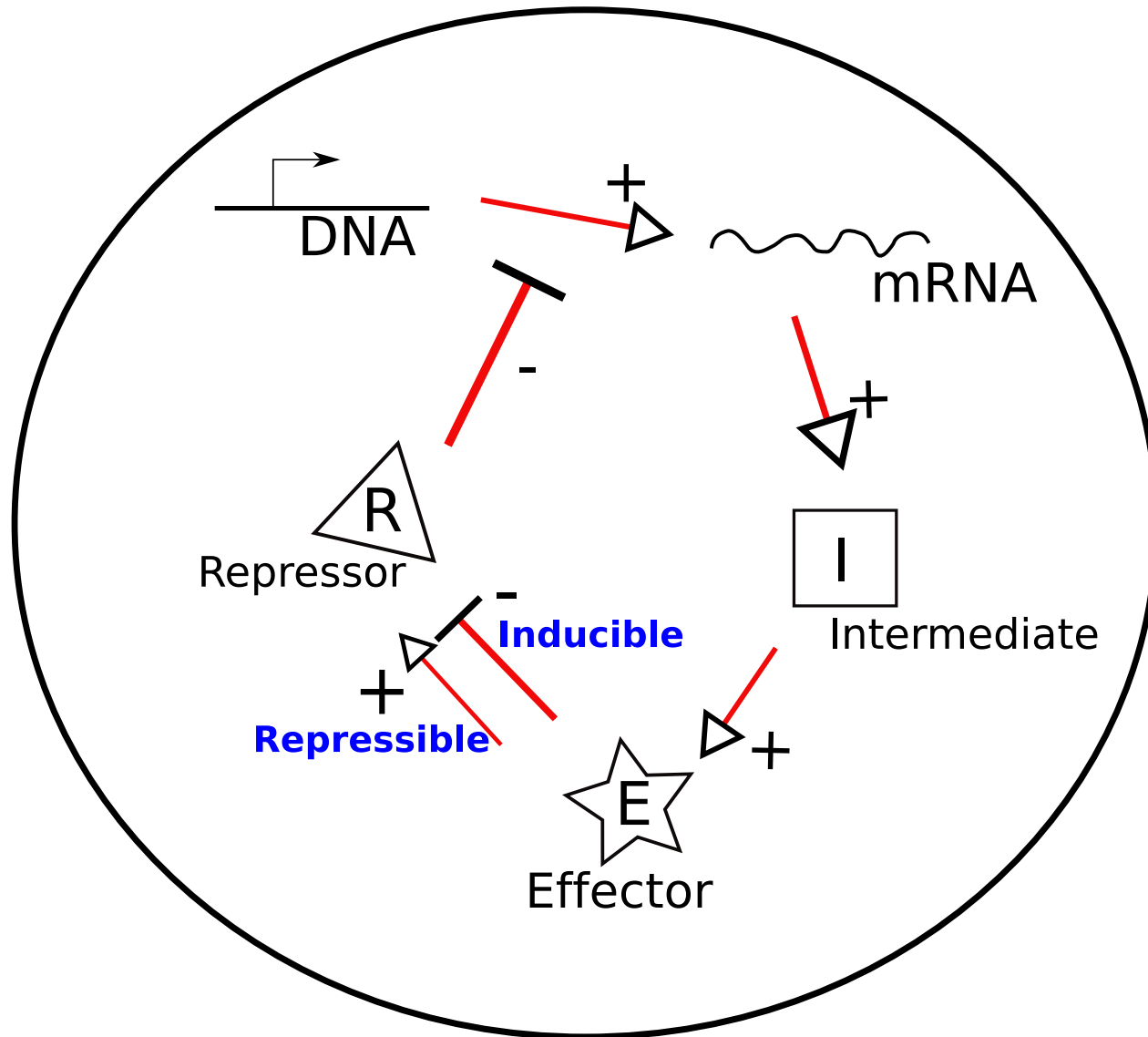
# Introduction

- Simple example of the regulatory process
- Role of noise when considering events at the single cell level
- Types of noise
  - Extrinsic vs Intrinsic

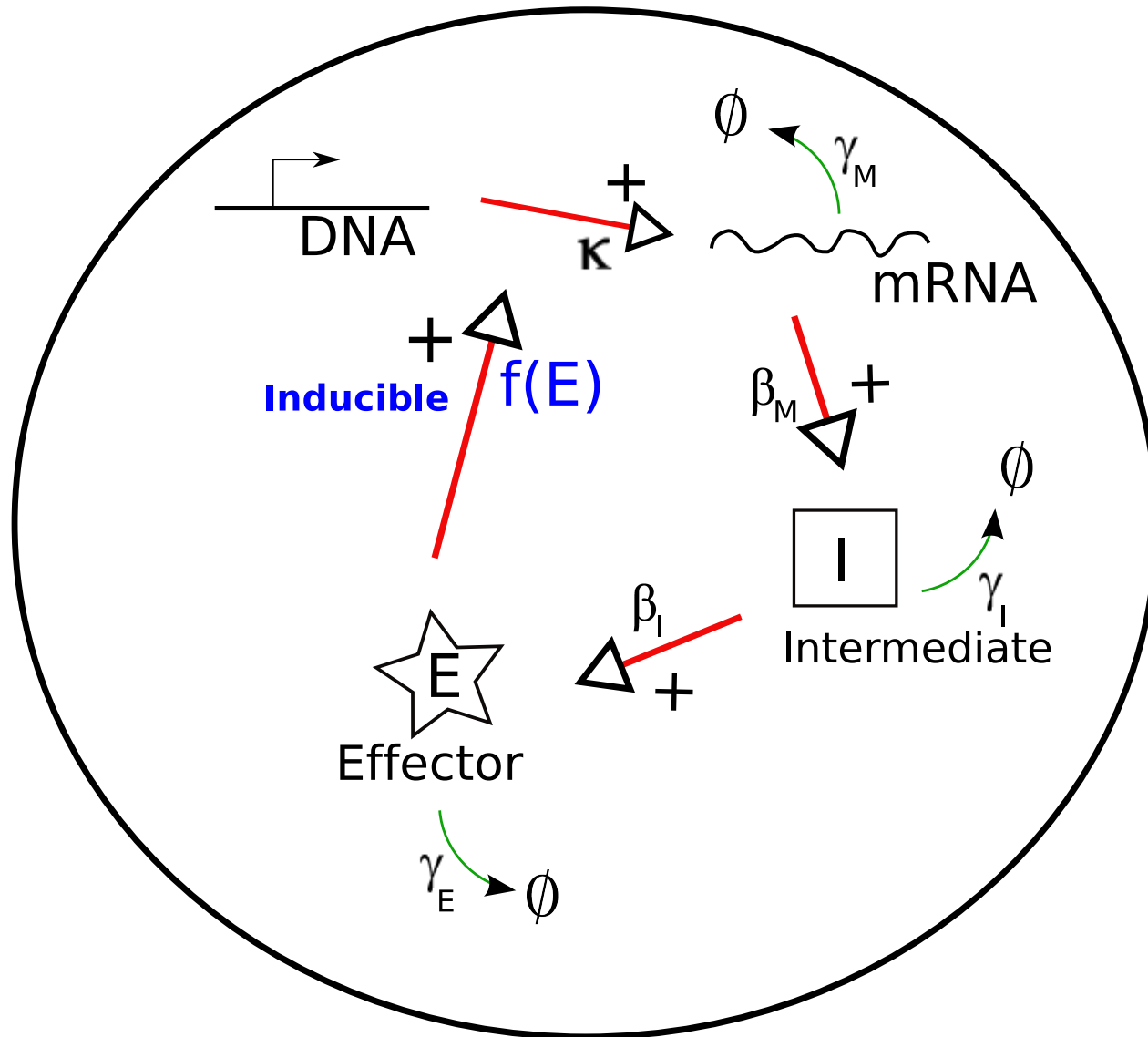
# Outline

- Quick tour of the model and the deterministic case
- What happens in the case with bursting (intrinsic noise) ?
- And then what about the effects of diffusion (extrinsic noise) ?
- Both together
- Conclusions and problems

# Central dogma



# Central dogma



# Deterministic situation: Many cells

Through **rescaling** parameters and variables, the equations read  $(M, I, E) \rightarrow (x_1, x_2, x_3)$

$$\frac{dx_1}{dt} = \gamma_1[\kappa_d f(x_3) - x_1]$$

$$\frac{dx_2}{dt} = \gamma_2(x_1 - x_2)$$

$$\frac{dx_3}{dt} = \gamma_3(x_2 - x_3)$$

And

$$f(x) = \frac{1 + x^n}{K + x^n}$$

# Deterministic situation: Many cells

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$$\frac{dx_1}{dt} = \gamma_1 [\kappa_d f(x_1) - x_1] = 0$$

$$\frac{dx_2}{dt} = \gamma_2 (x_1 - x_2) = 0$$

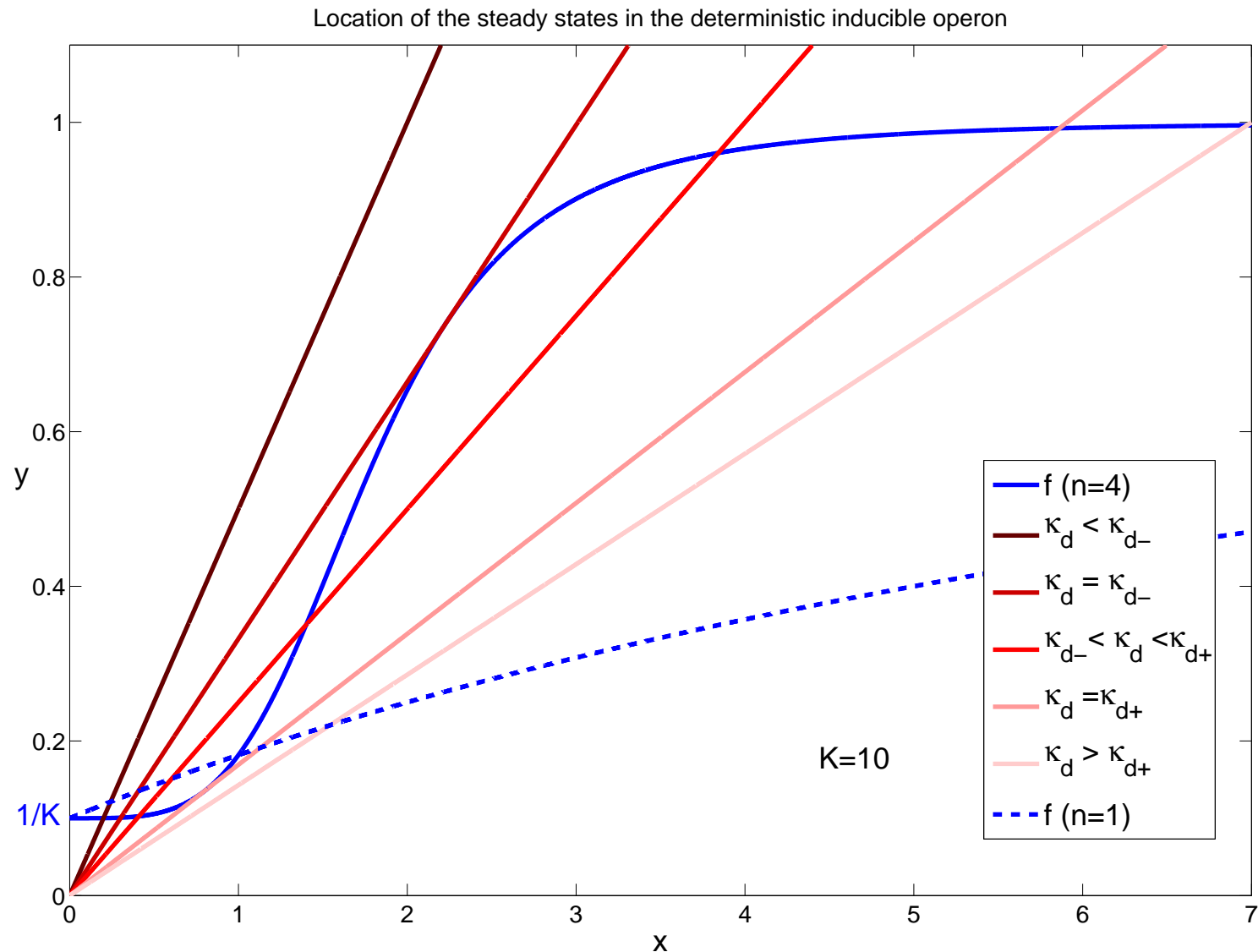
$$\frac{dx_3}{dt} = \gamma_3 (x_2 - x_3) = 0$$

And

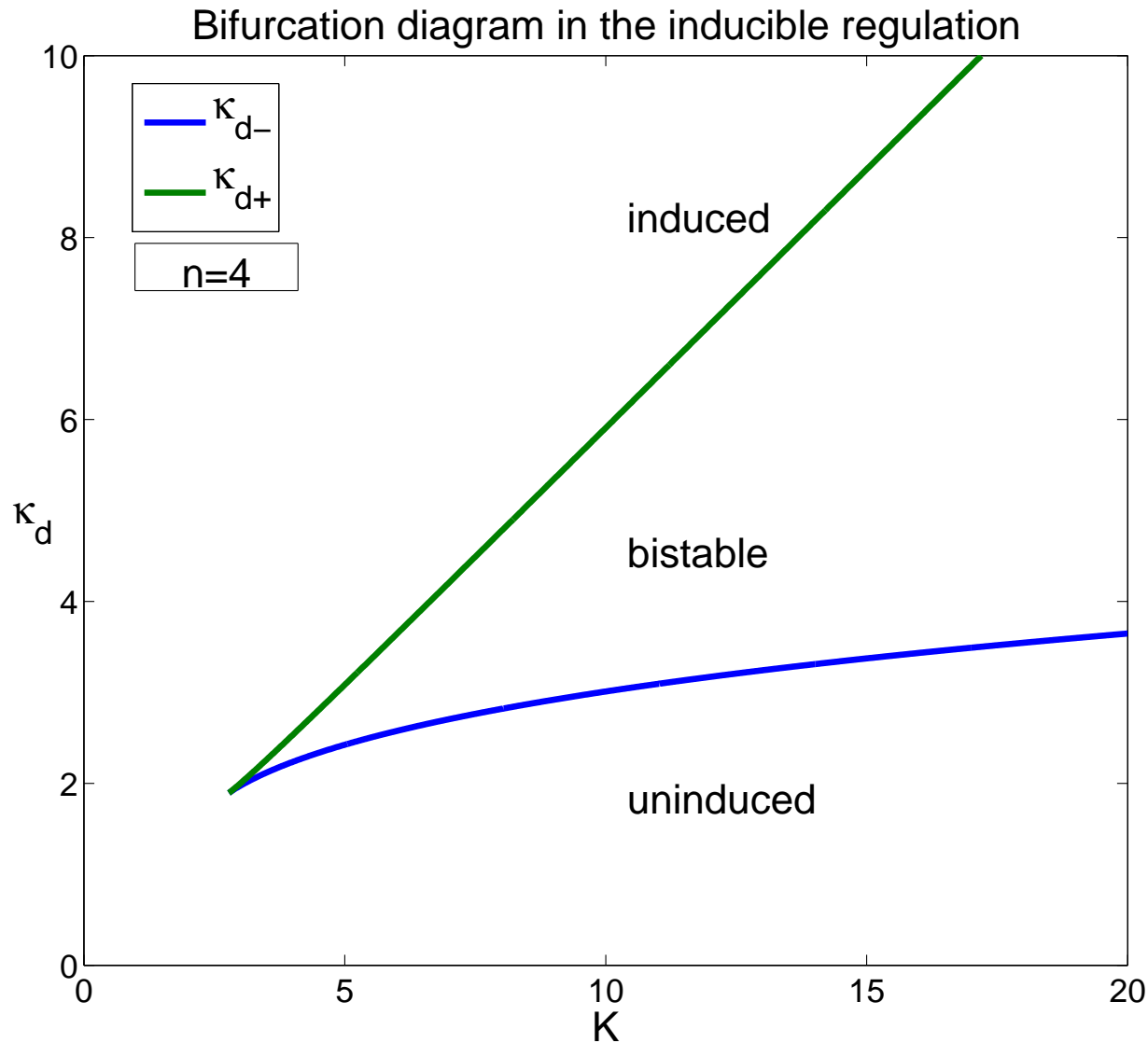
$$f(x) = \frac{1 + x^n}{K + x^n}$$



# Deterministic inducible regulation



# Dependence of bistability on $\kappa_d$ and $K$



# Fast and slow variables

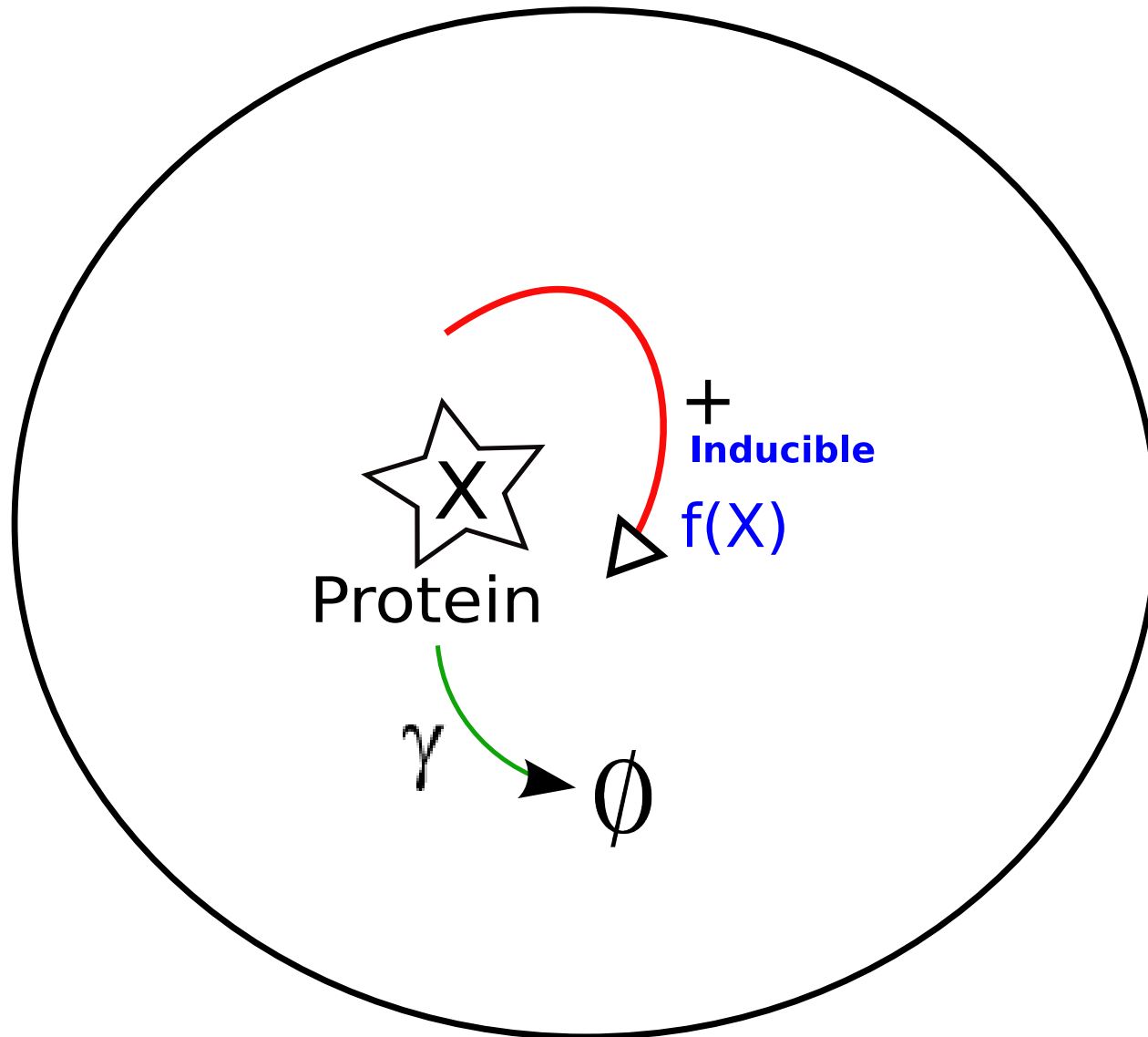
Typically the degradation rate of mRNA is much greater than that of either the intermediate or effector so  $x_1 \simeq \kappa_d f(x_3)$  and equations reduce to

$$\begin{aligned}\frac{dx_2}{dt} &= \gamma_2[\kappa_d f(x_3) - x_2] \\ \frac{dx_3}{dt} &= \gamma_3(x_2 - x_3)\end{aligned}$$

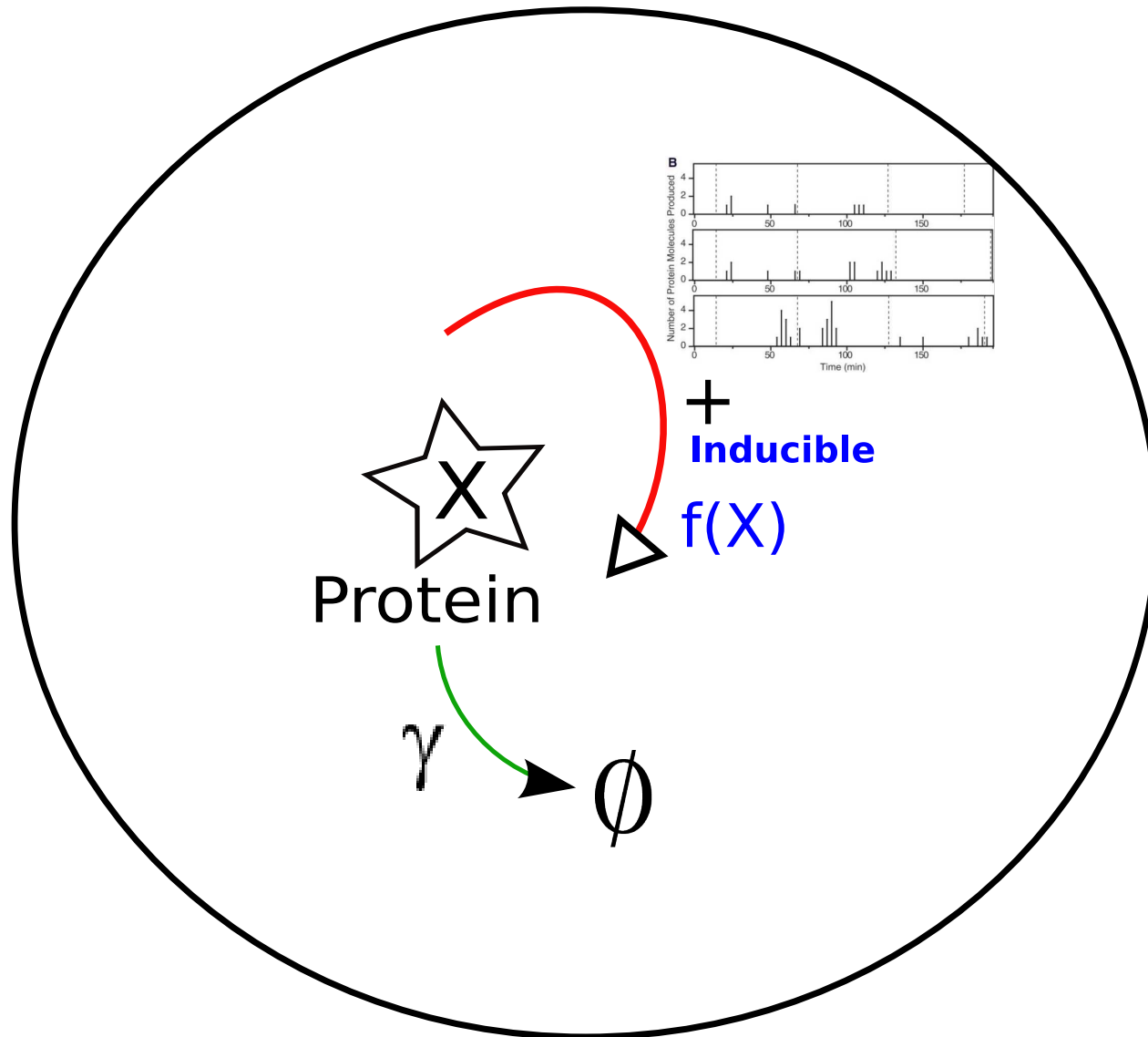
With either intermediate or effector dynamics additionally dominating because of time scales we have

$$\frac{dx}{dt} = \gamma \kappa_d f(x) - \gamma x$$

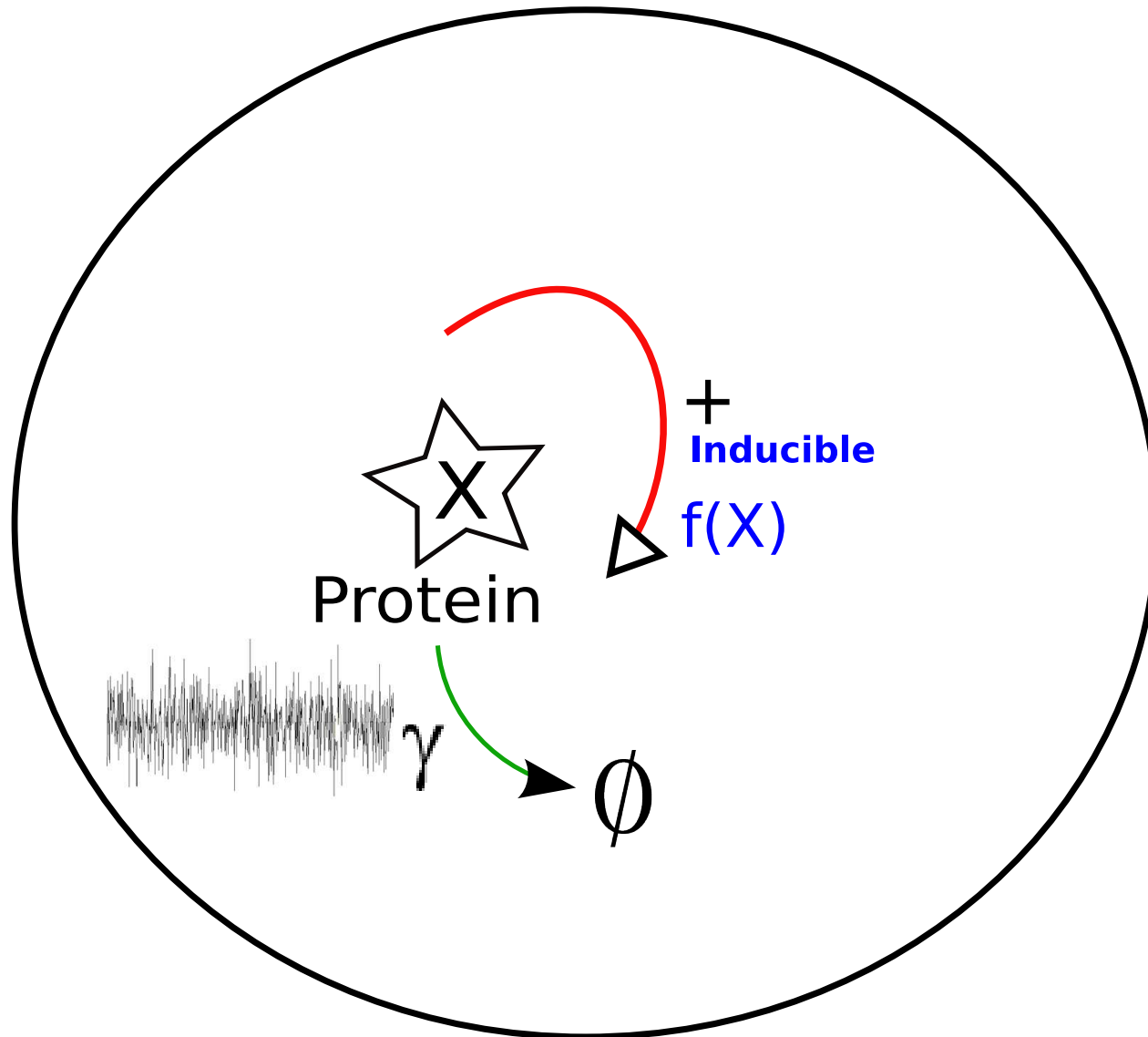
# Reduced model



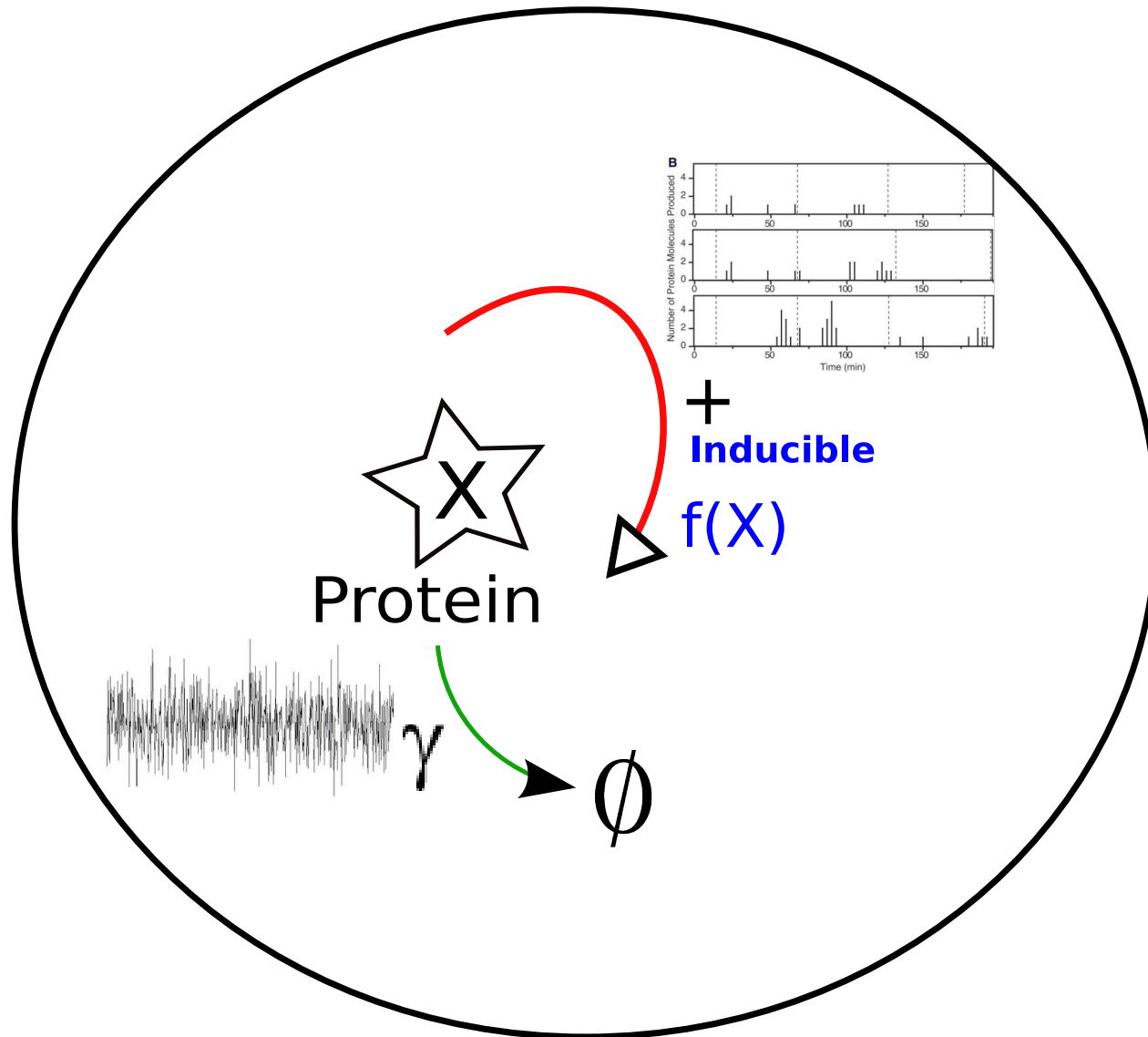
# Intrinsic noise



# Extrinsic noise

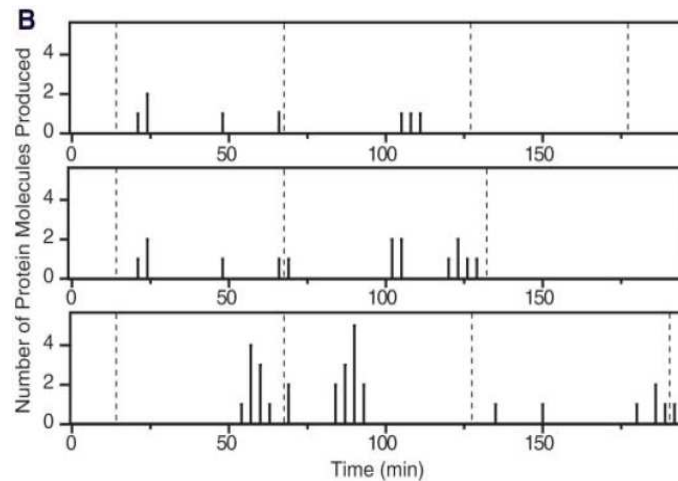


# Intrinsic and Extrinsic noise



# Bursting (intrinsic noise) in cells

- Experimentally observed that in many organisms the amplitude of protein production through bursting translation of mRNA is exponentially distributed at the single cell level
- Let the density of this distribution be  $h(y) = \frac{1}{b}e^{-y/b}$





# Bursting as a jump Markov process

- Replace the simple deterministic dynamics

$$\frac{dx}{dt} = -\gamma x + \gamma \kappa_d f(x)$$

with

$$\frac{dx}{dt} = -\gamma x + \Xi(h, \gamma \kappa_b f(x))$$

where  $\Xi(h, \varphi)$  is a jump Markov process occurring at a rate  $\varphi$  and distributed with density  $h$

# Evolution equation for density of $x$

The evolution equation for the density  $u(t, x)$  of  $x$  is

$$\frac{\partial u(t, x)}{\partial t} - \gamma \frac{\partial(xu(t, x))}{\partial x} = -\alpha f(x)u(t, x) + \alpha \int_0^x f(y)u(t, y)h(x-y)dy$$

(differential Chapman-Kolmogorov equation) so the stationary density  $u_*(x)$  satisfies

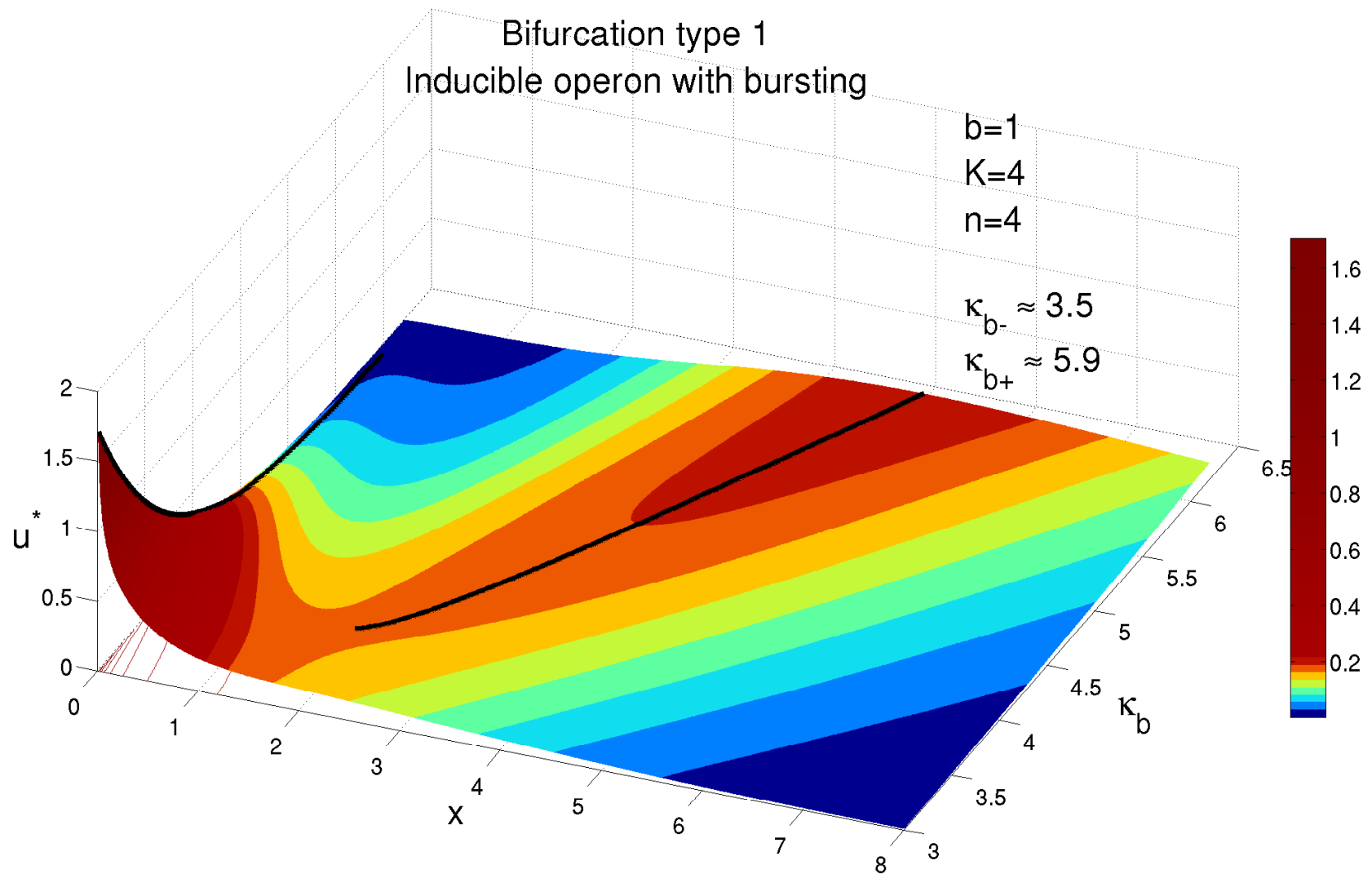
$$-\gamma \frac{d(xu_*(x))}{dx} = -\alpha f(x)u_*(x) + \alpha \int_0^x f(y)u_*(y)h(x-y)dy$$

# Evolution equation for density of $x$

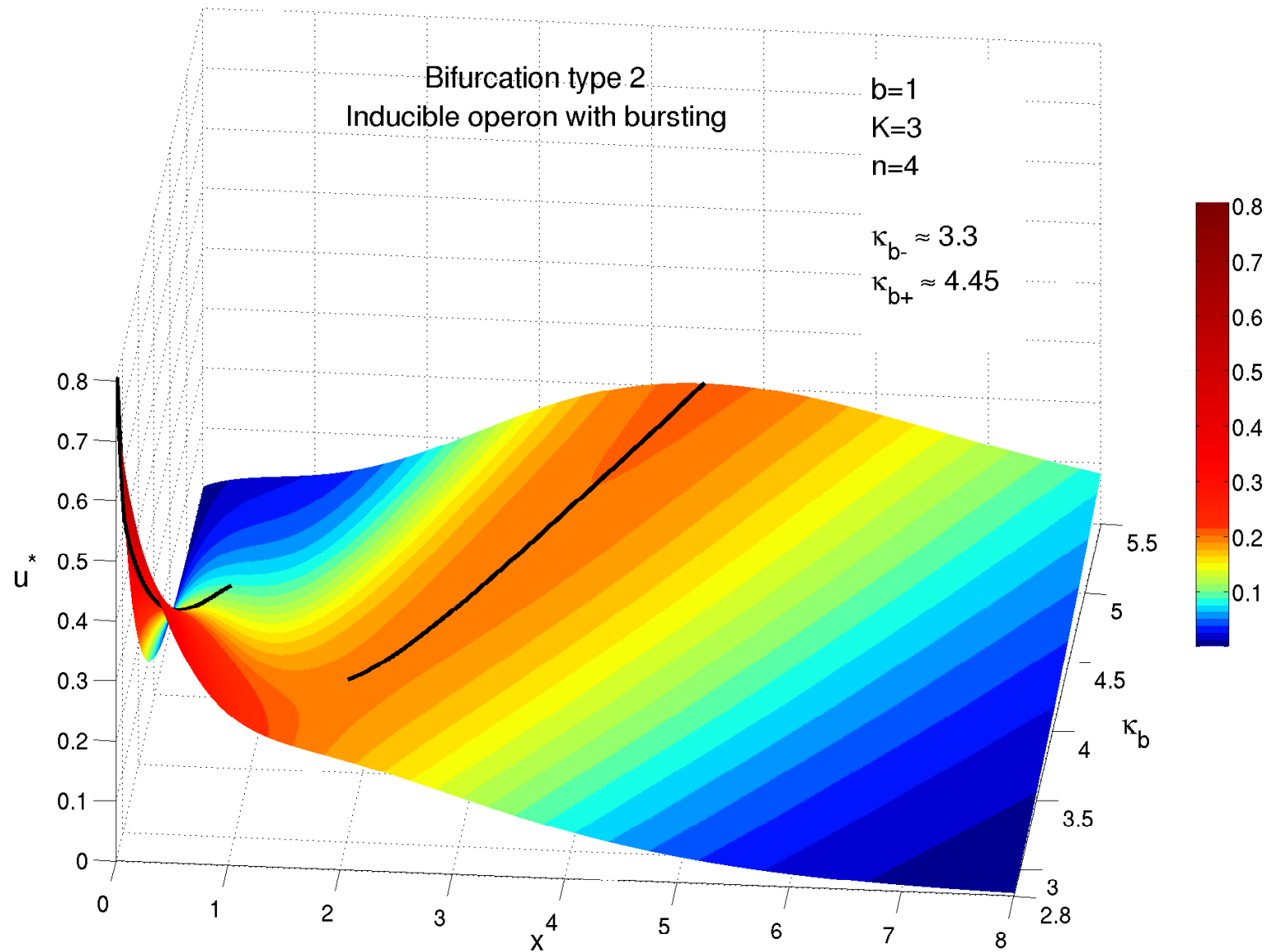
The evolution equation for the density  $u(t, x)$  of  $x$  is

$$\frac{\partial u(t, x)}{\partial t} + \gamma \frac{d(xu_*(x))}{dx} = -\alpha f(x)u_*(x) + \alpha \int_0^x f(y)u_*(y)h(x - y)dy \quad (1)$$

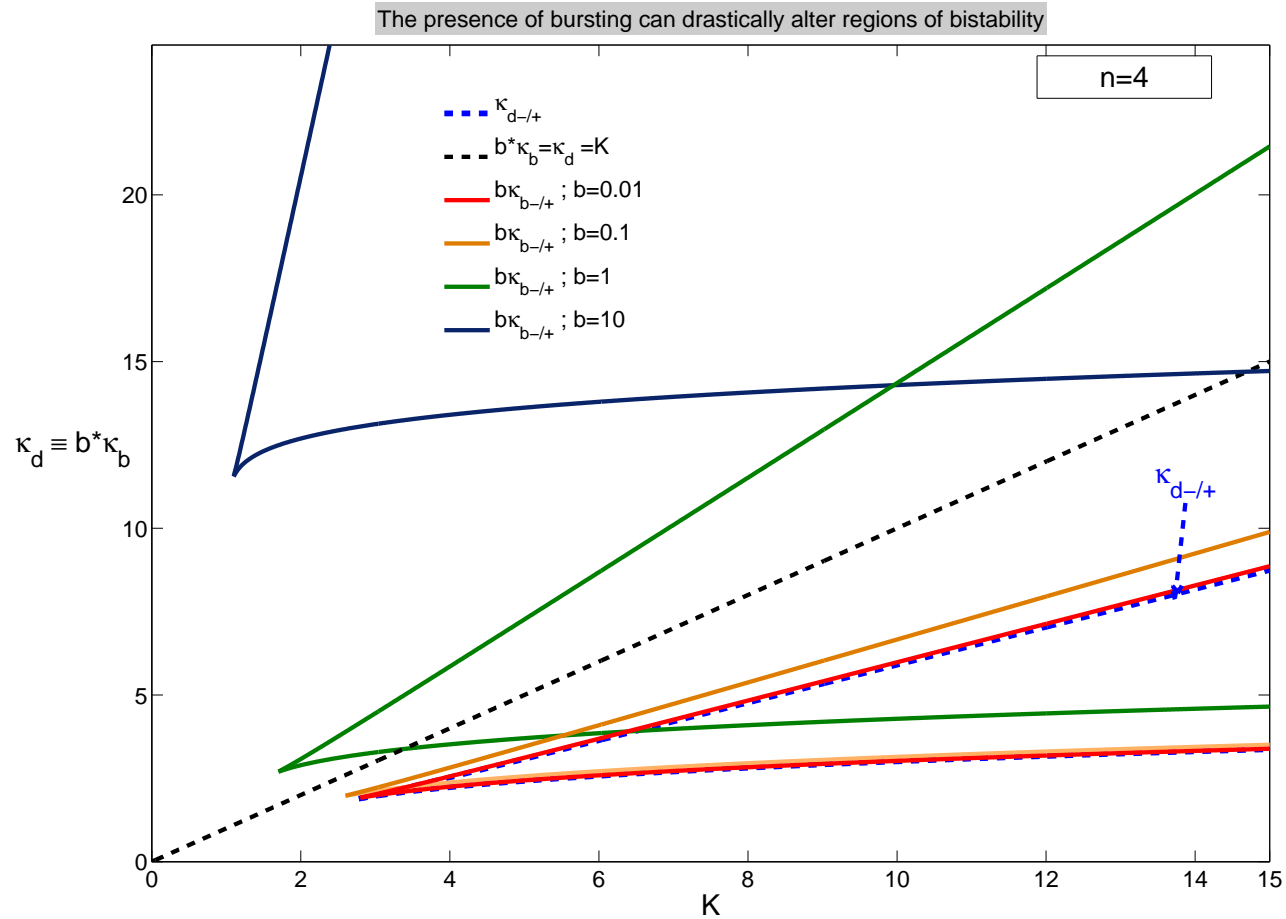
# Stationary density as a function of $\kappa_b$



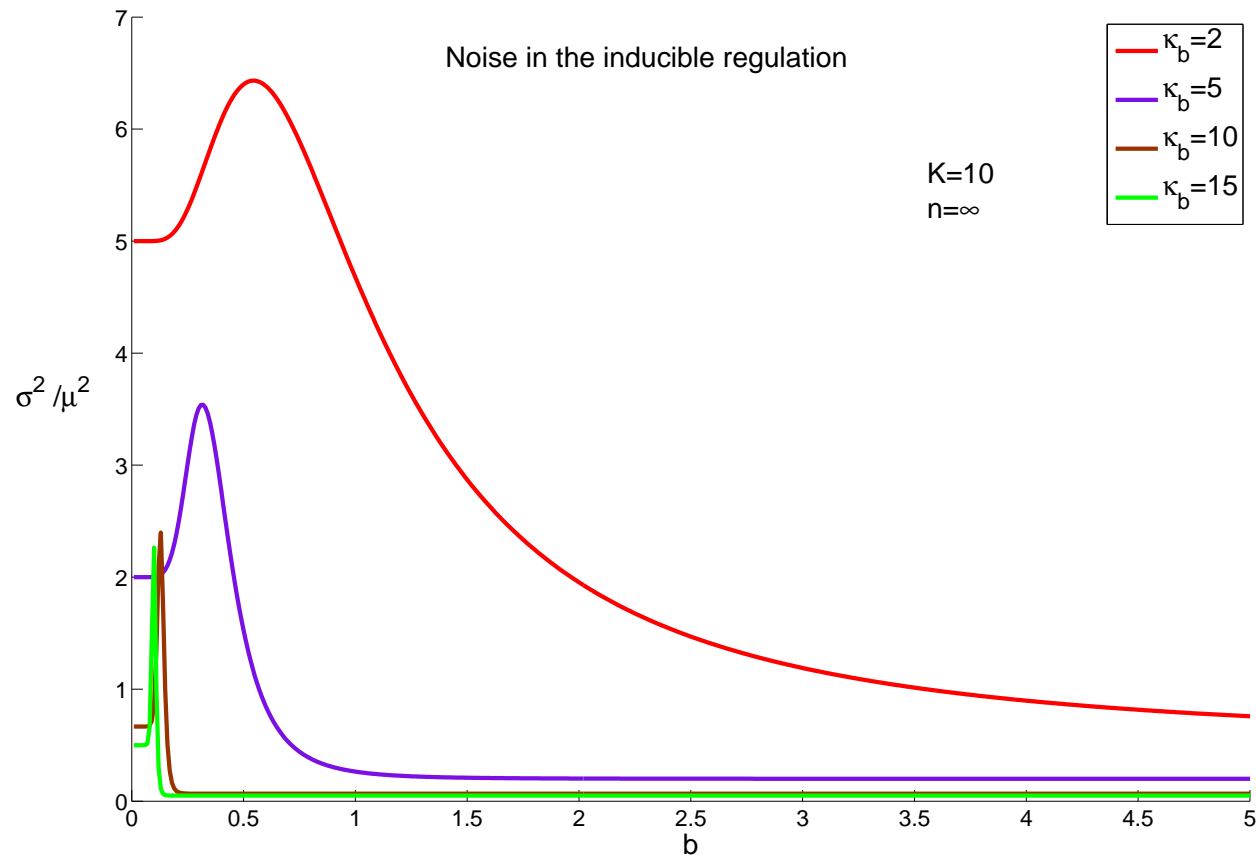
# Stationary density as a function of $\kappa_b$



# Effects of bursting



# Noise induced by bursting



# Diffusion (extrinsic noise) in cells

- We consider the fluctuations that appear in the degradation rate  $\gamma$  of the generic equation.
- From standard chemical kinetic arguments (Oppenheim (1969), J. Chem. Phys. **50**, 460-466), if the fluctuations are Gaussian distributed the mean numbers of molecules decaying in a time  $dt$  is simply  $\gamma x dt$  and the standard deviation of these numbers is given by  $\gamma \sqrt{x} / \sqrt{2}$



# Extrinsic noise as a white noise process

- Replace the simple deterministic dynamics

$$\frac{dx}{dt} = -\gamma x + \gamma \kappa_d f(x)$$

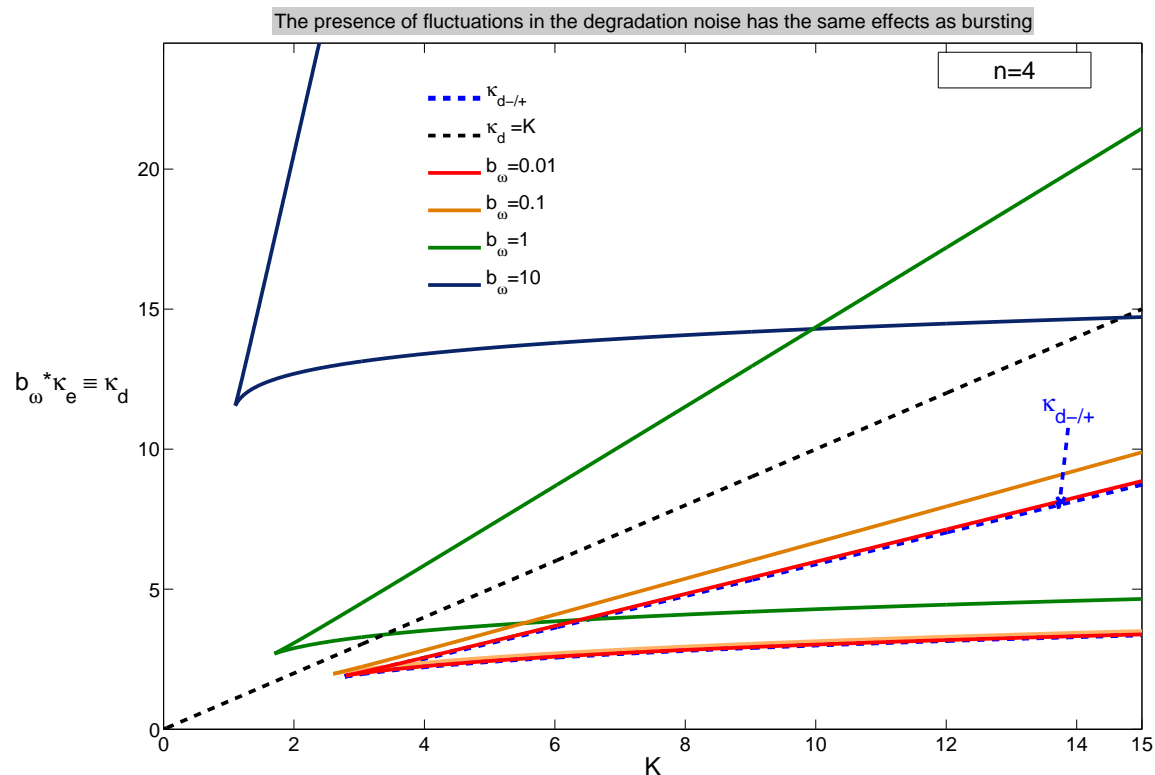
with

$$dx = [\gamma \kappa_d f(x) - \gamma x]dt + \sigma \sqrt{x}dw$$

where  $dw$  is a standard white noise process

# Extrinsic noise $\sim$ intrinsic noise

- Let replace the average burst amplitude  $b$  with  $b \rightarrow \sigma^2/2\gamma \equiv b_w$  and  $\kappa_b \rightarrow \kappa_e = 2\gamma\kappa_d/\sigma^2 \equiv \kappa_d/b_w$ , then the stationary density in the case of extrinsic noise has the **same form** as in the case of intrinsic noise.



# Extrinsic and intrinsic noise

- Replace the simple deterministic dynamics

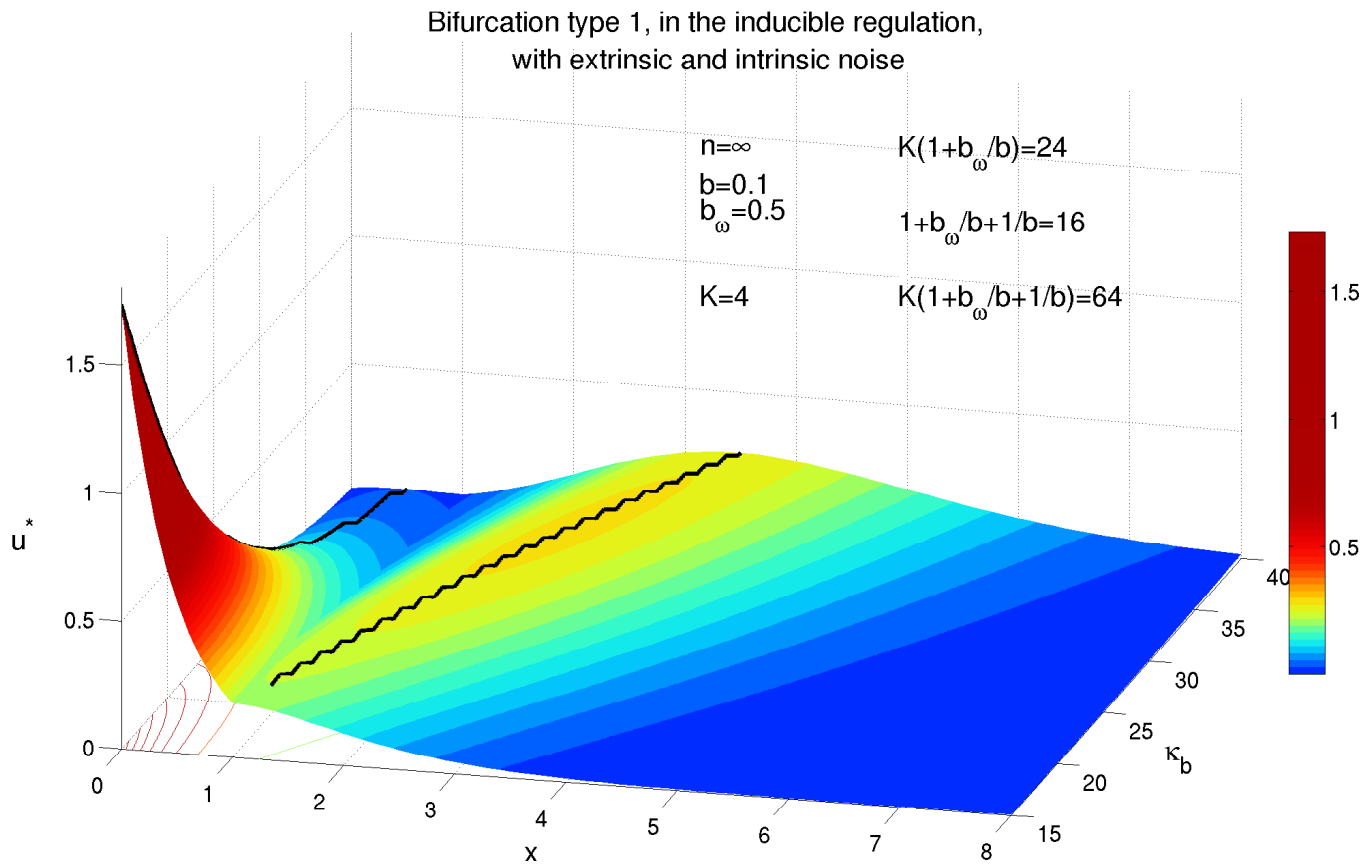
$$\frac{dx}{dt} = -\gamma x + \gamma \kappa_d f(x)$$

with

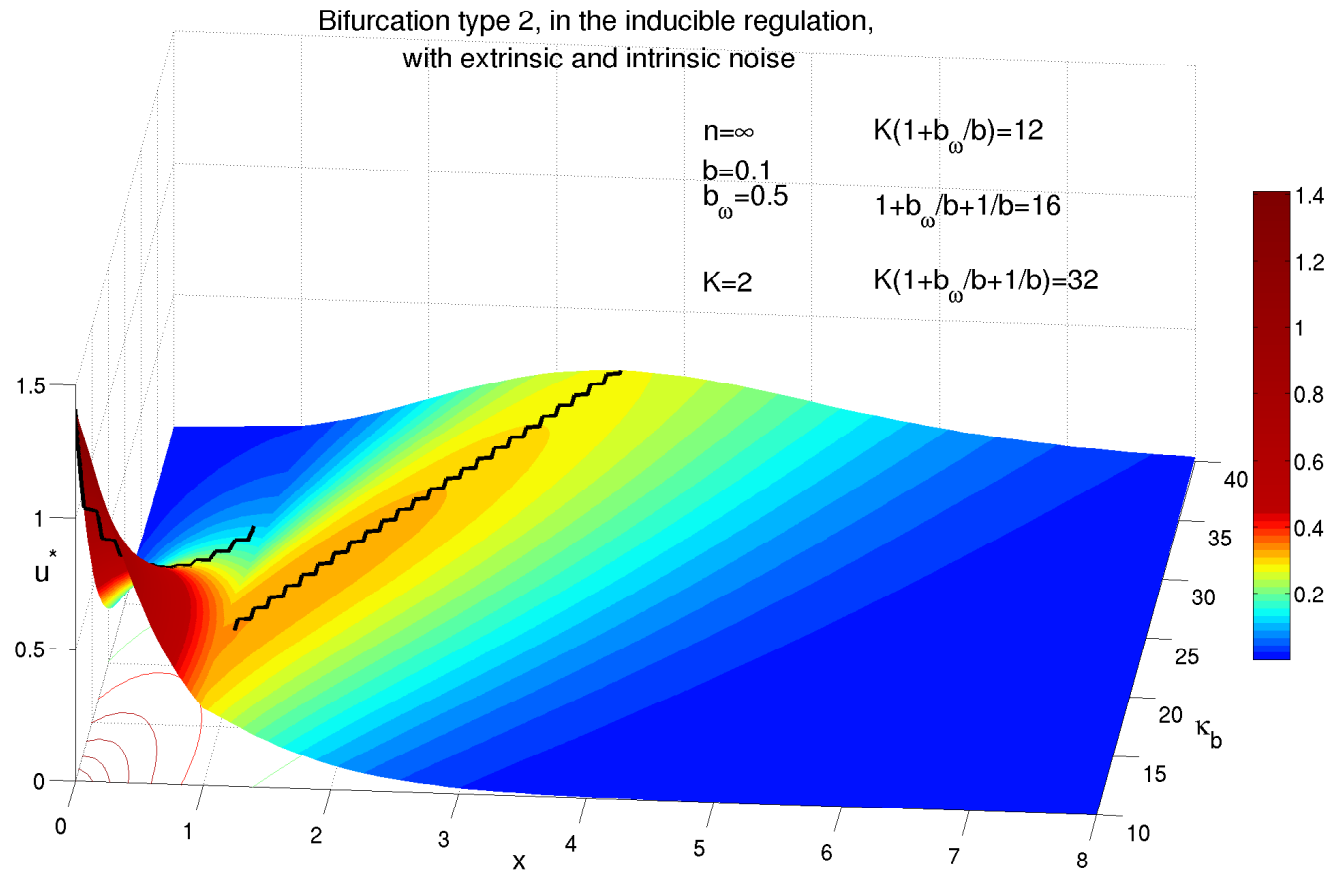
$$dx = -\gamma x dt + \Xi(h, \gamma \kappa_b f(x)) - \sigma \sqrt{x} dw,$$

where  $dw$  is a standard white noise process and  $\Xi(h, \gamma \kappa_b f(x))$  is a jump Markov process occurring at a rate  $\gamma \kappa_b f(x)$  and distributed with density  $h$

# Extrinsic and intrinsic noise



# Extrinsic and intrinsic noise



# Conclusion

- Intrinsic noise and extrinsic noise are indistinguishable from the stationary density in this model.
- The stationary densities can be much more wider (and asymmetric) than a poissonian distribution.
- Noise-enhanced bistability.
- And noise-induced bistability when  $n = 1$ .
- When both noise are present, their effect sum up additively.

# Problems and Further Studies

- Intrinsic noise should take into account transcriptional and/or translational delays.
- Extrinsic noise should take into account time correlations.
- Mean exit time and auto-correlation function should be derived to give more information on the dynamics out of equilibrium.
- The full three-stage model should be considered with noise.

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