Intrinsic and Extrinsic Noise Effects on Molecular Distributions in Bacteria

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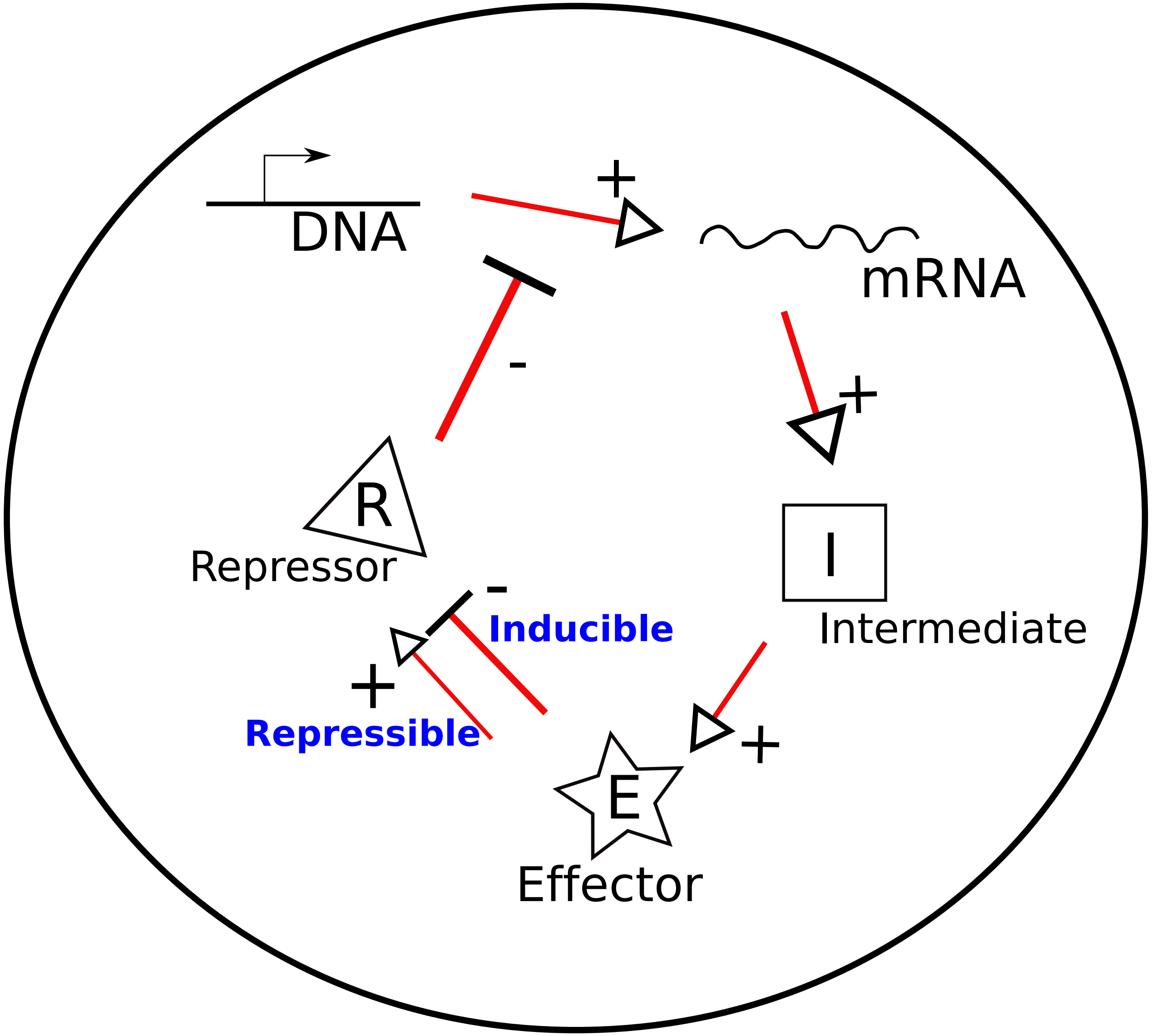
Introduction

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

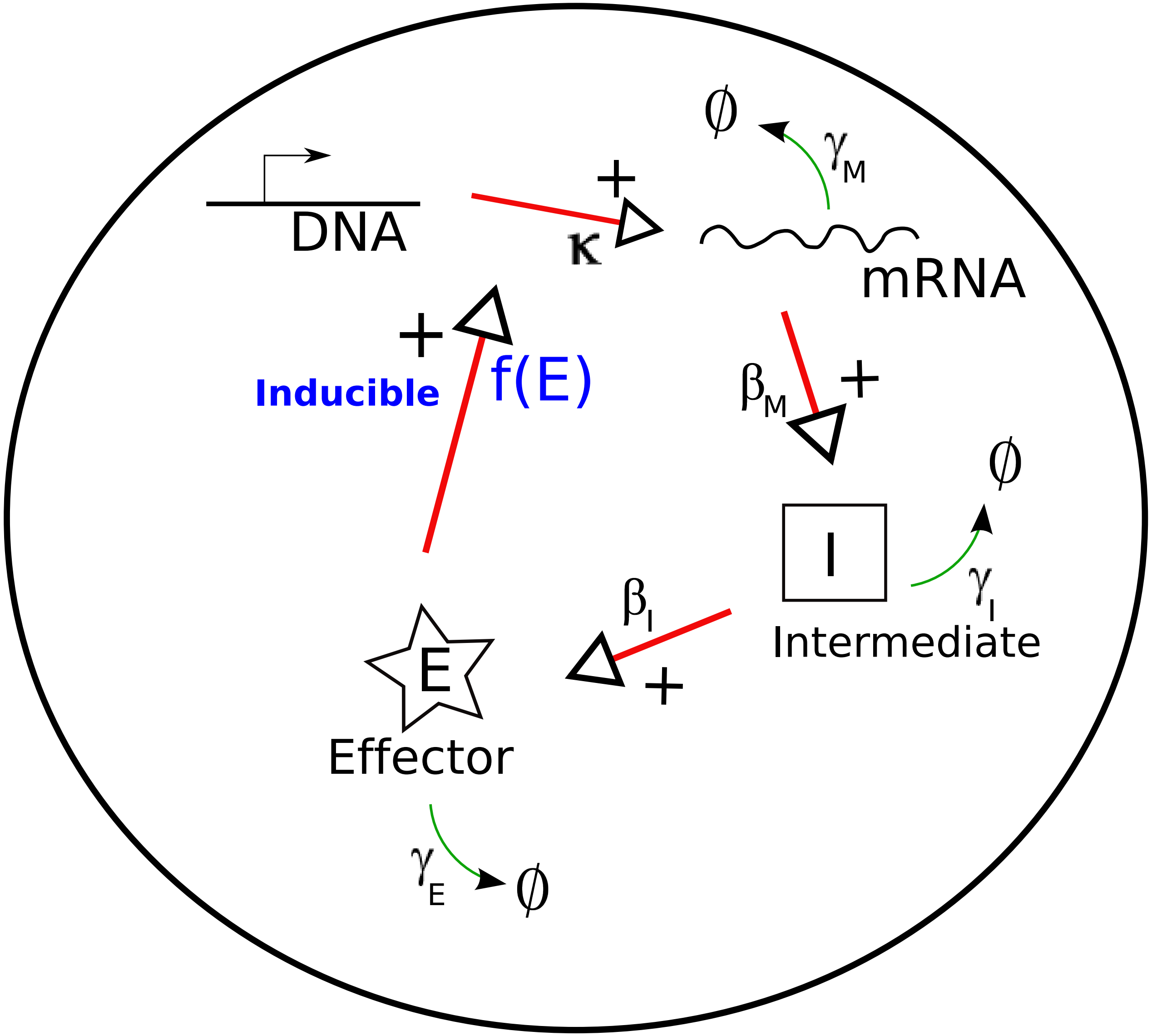
Outline

- 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 $(M, I, E) \rightarrow (x_1, x_2, x_3)$

$$\begin{aligned}
\frac{dx_1}{dt} &= \gamma_1[\kappa_d f(x_3) - x_1] \\
\frac{dx_2}{dt} &= \gamma_2(x_1 - x_2) \\
\frac{dx_3}{dt} &= \gamma_3(x_2 - x_3)
\end{aligned}$$

And

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

Deterministic situation: Many cells

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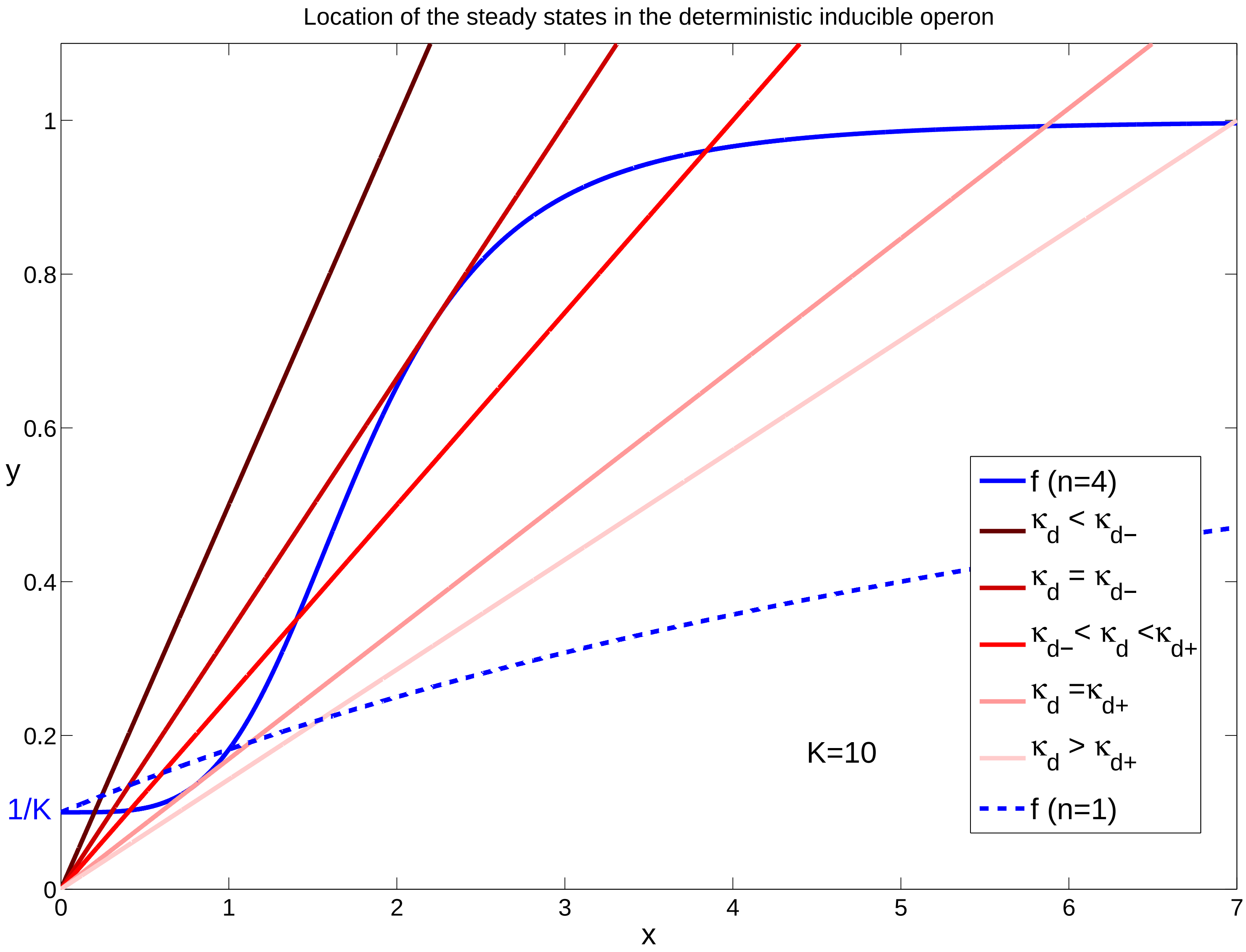
$$
\begin{aligned}
\frac{dx_1}{dt} &= \gamma_1 [\kappa_d f(x_1) - x_1] = 0 \\
\frac{dx_2}{dt} &= \gamma_2 (x_1 - x_2) = 0 \\
\frac{dx_3}{dt} &= \gamma_3 (x_2 - x_3) = 0
\end{aligned}
$$

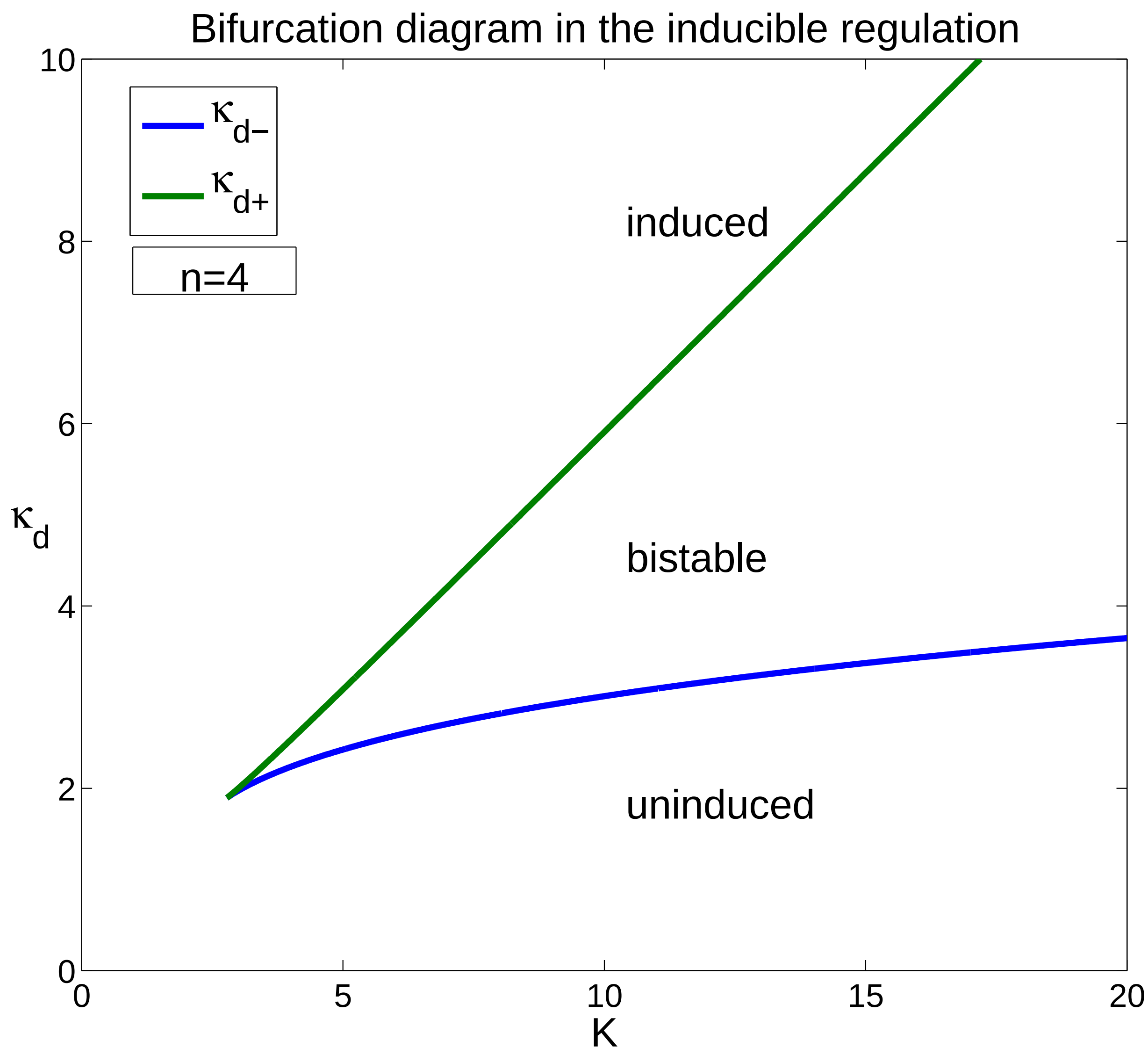
And

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

Deterministic inducible regulation



Dependence of bistability on κ_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

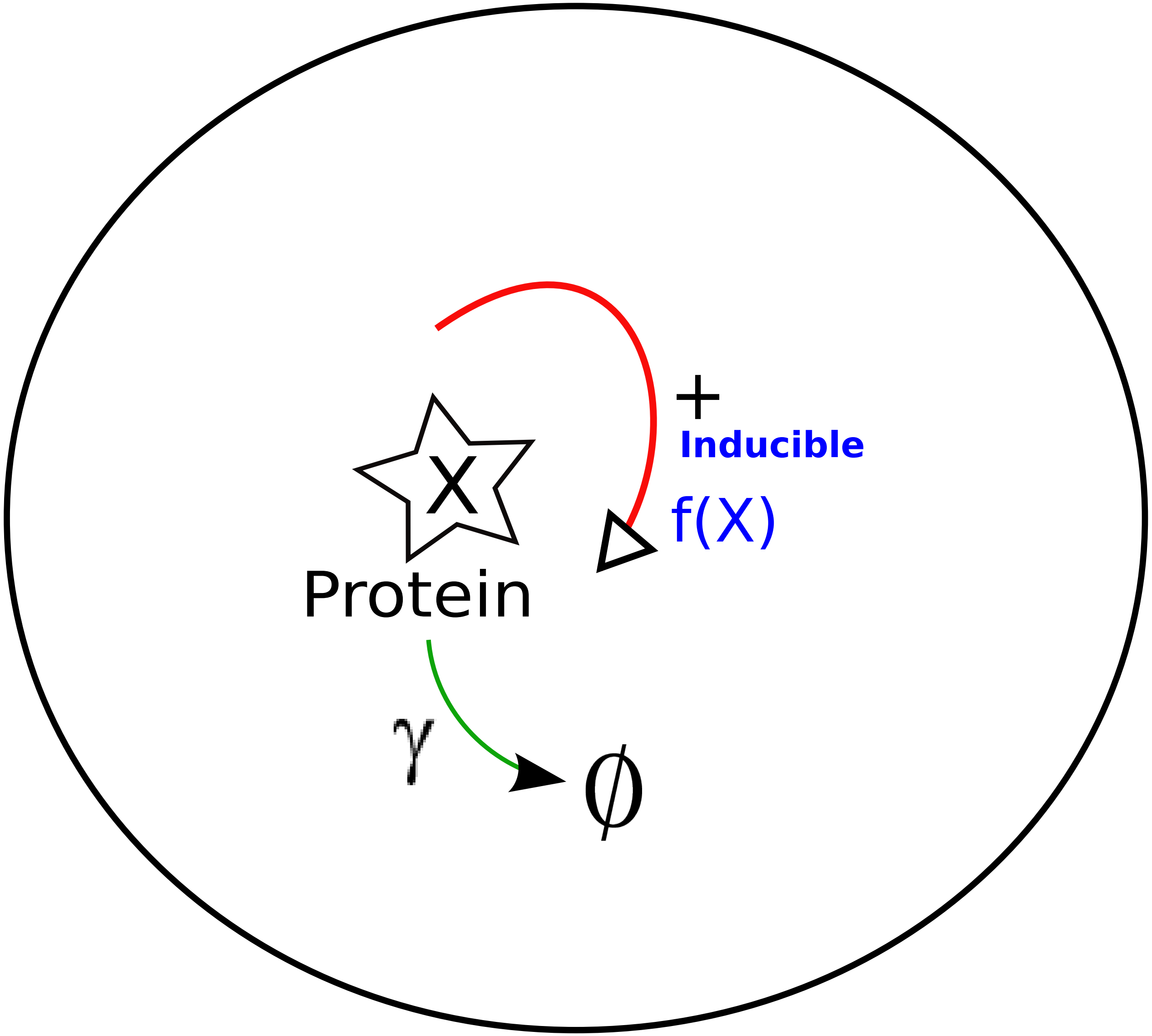
$$\frac{dx_2}{dt} = \gamma_2[\kappa_d f(x_3) - x_2]$$

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

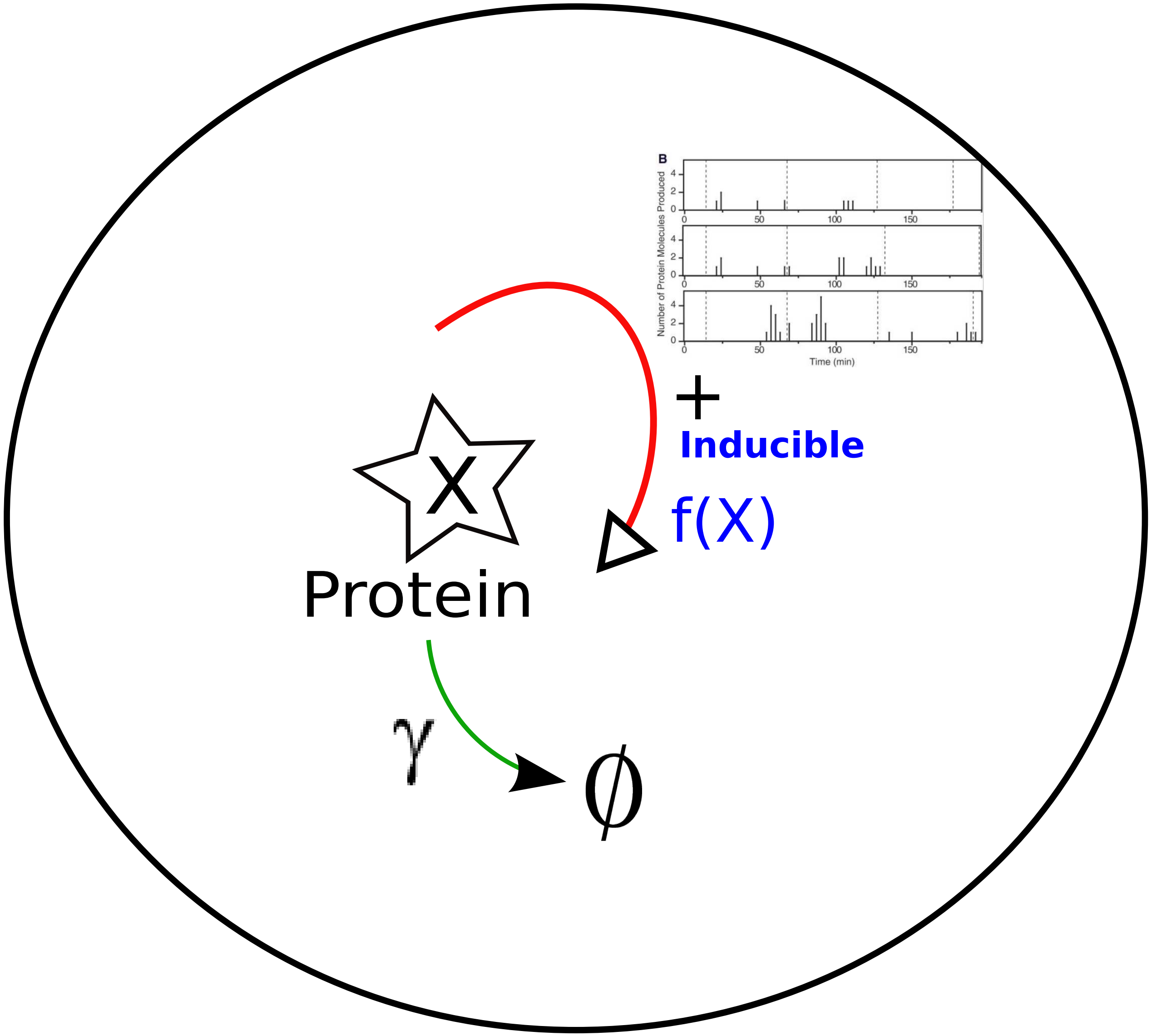
With either intermediate or effector dynamics additionally dominating because of time scales we have

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

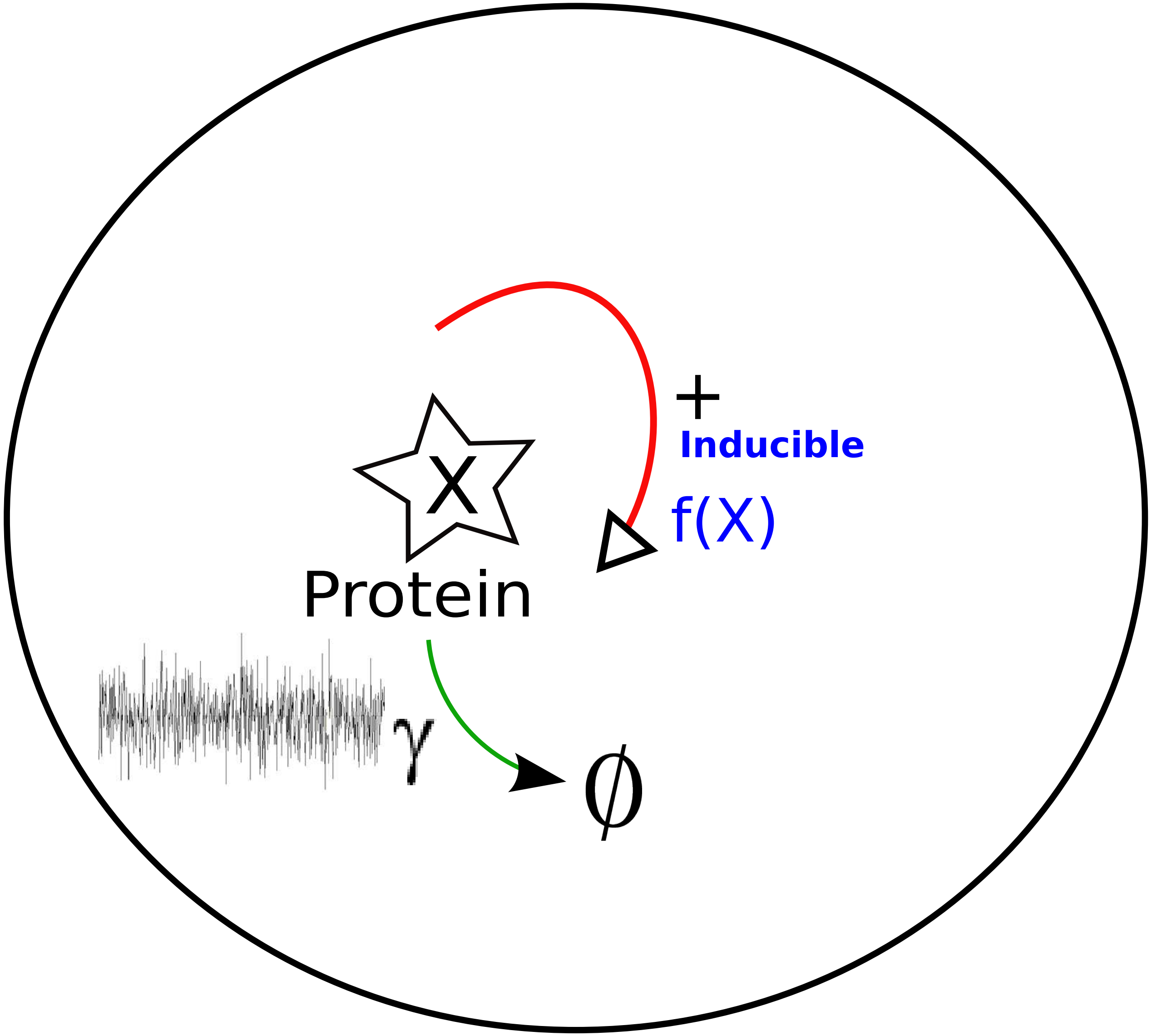
Reduced model



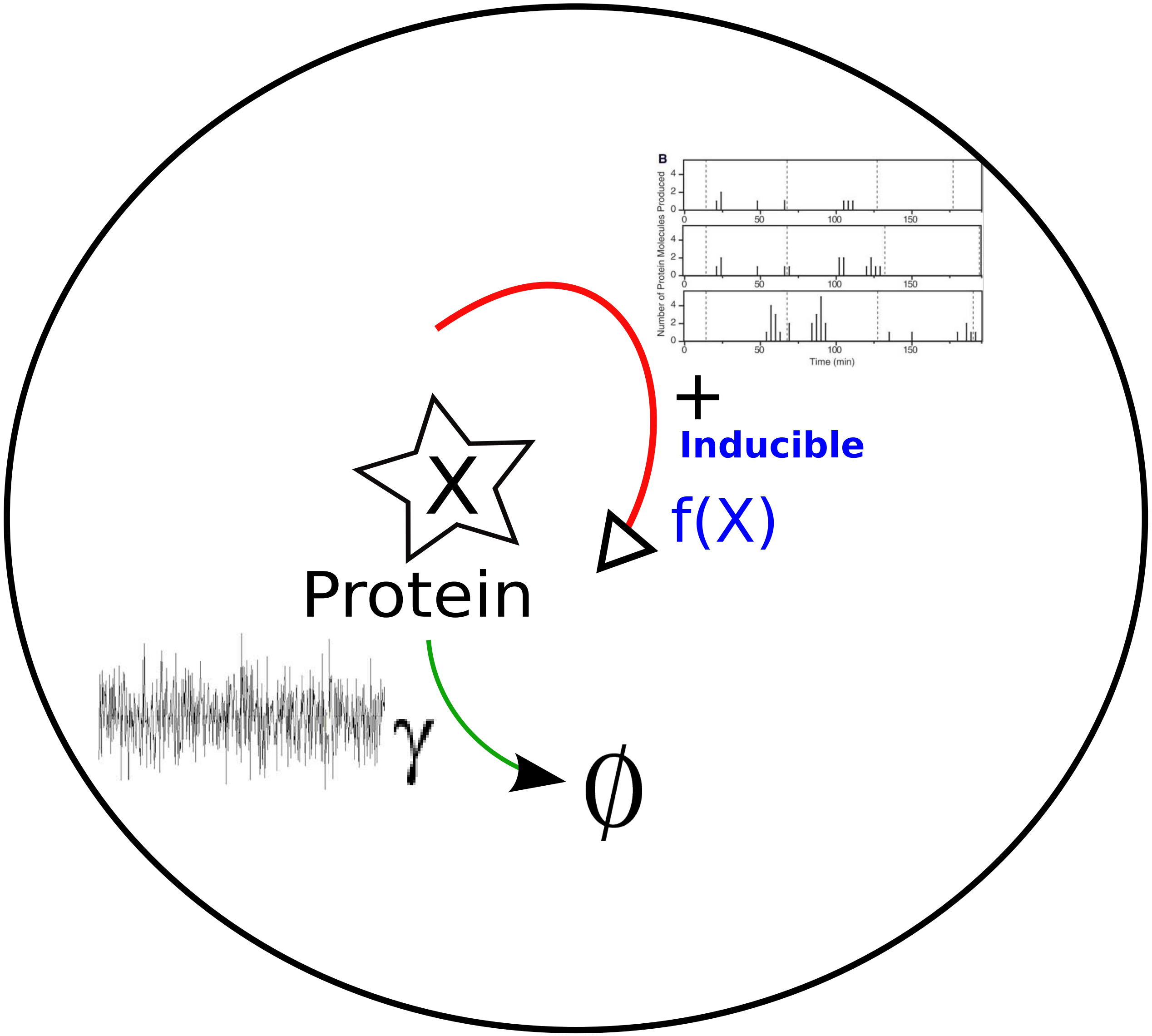
Intrinsic noise



Extrinsic noise

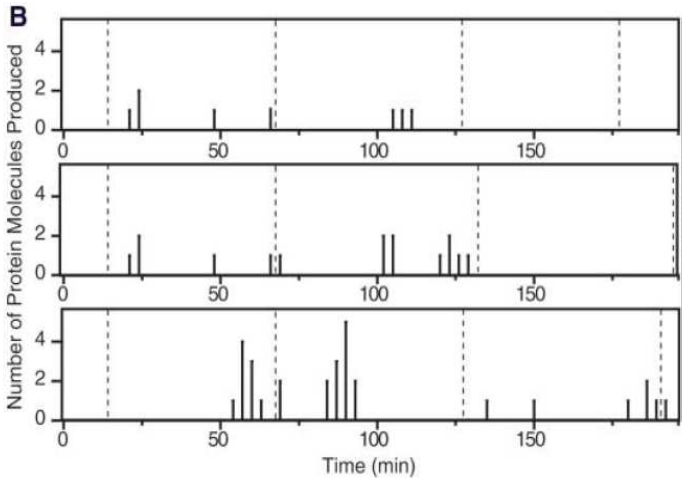


Intrinsic and Extrinsic noise



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 $h(y) = \frac{1}{b} e^{-y/b}$



Yu (2006), Science, **311**

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 φ and distributed with density h

Evolution equation for density of x

The evolution equation for the density $u(t,x)$ of x is (differential Chapman-Kolmogorov equation)

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

Evolution equation for the density of x

The evolution equation for the density $u(t,x)$ of x is (differential Chapman-Kolmogorov equation)

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

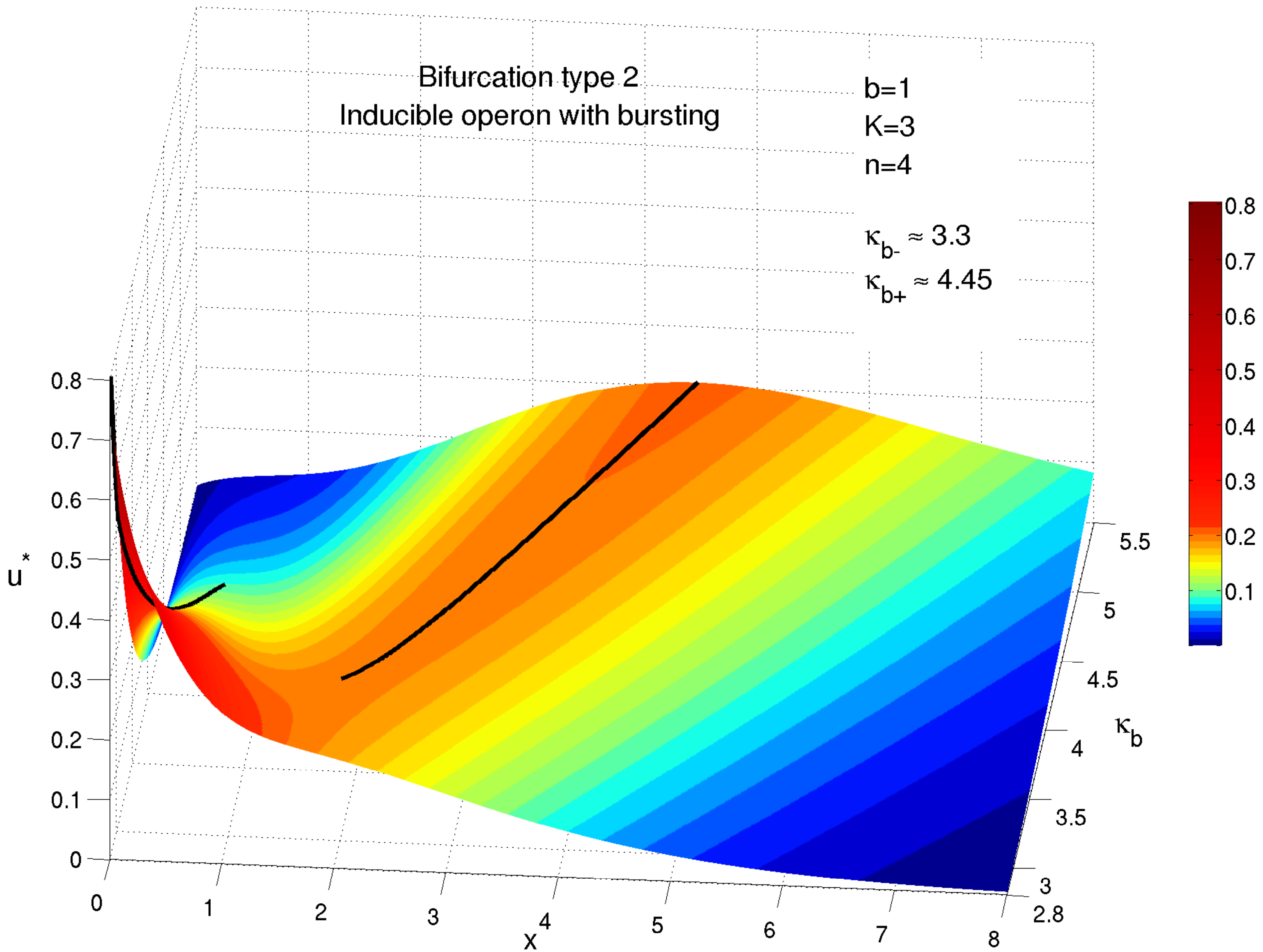
(1)

Theorem 0.1 *The unique stationary density is given by (in the inducible case)*

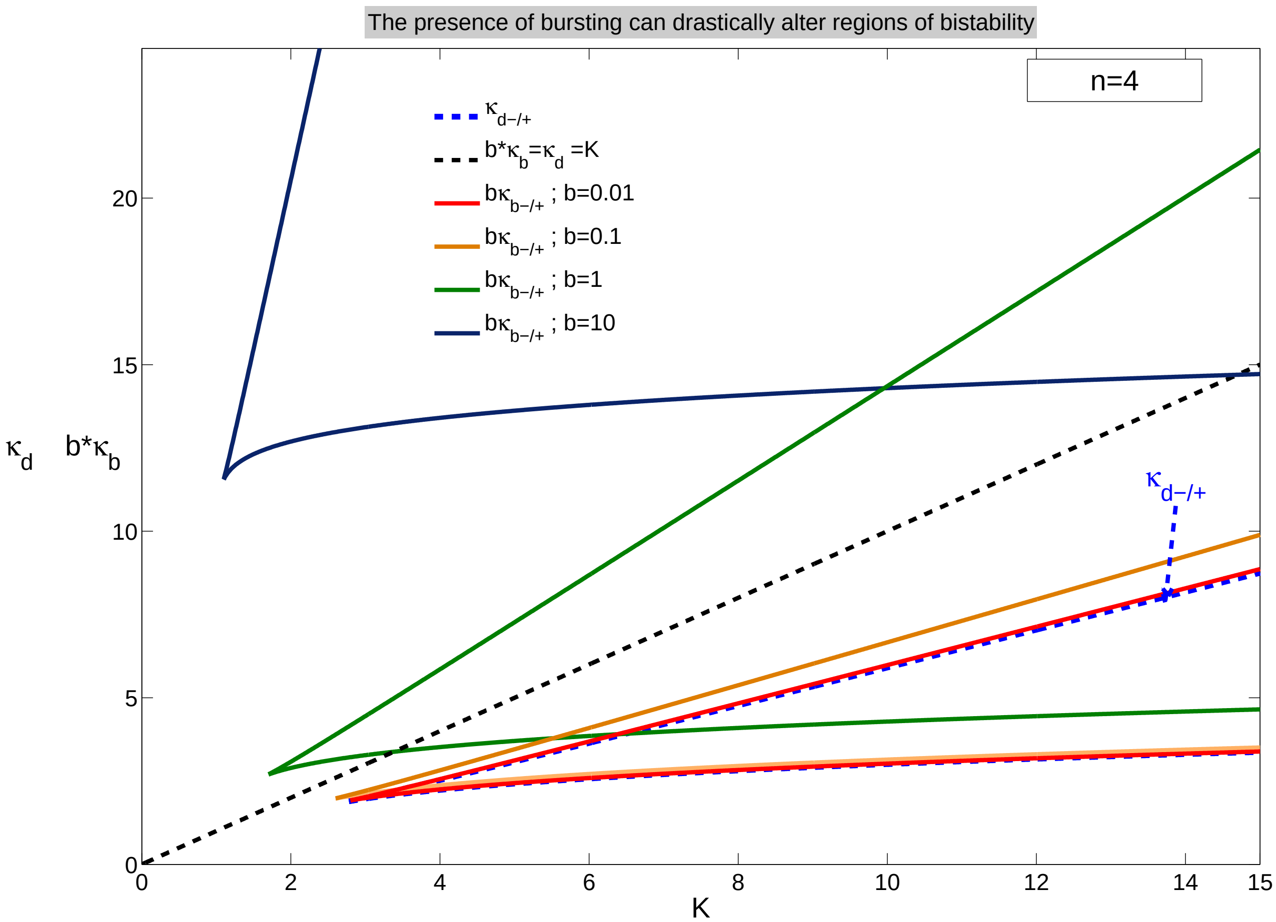
(2) $u_*(x) = \mathcal{C}e^{-x/b}x^{\kappa_b K^{-1}-1}(K+x^n)^\theta, \qquad \theta = \frac{\kappa_b}{n}(1-K^{-1}).$

And every solution $u(t,x)$ is asymptotically stable

Stationary density as a function of κ_b



Effects of bursting



Diffusion (extrinsic noise) in cells

- We consider the fluctuations that appear in the degradation rate γ 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

Evolution equation for density of x

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

(3) $$\frac{\partial u}{\partial t} = -\frac{\partial\left[(\gamma\kappa_d f(x) - \gamma x)u\right]}{\partial x} + \frac{\sigma^2}{2}\frac{\partial^2 (xu)}{\partial x^2}.$$

Evolution equation for the density of x

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

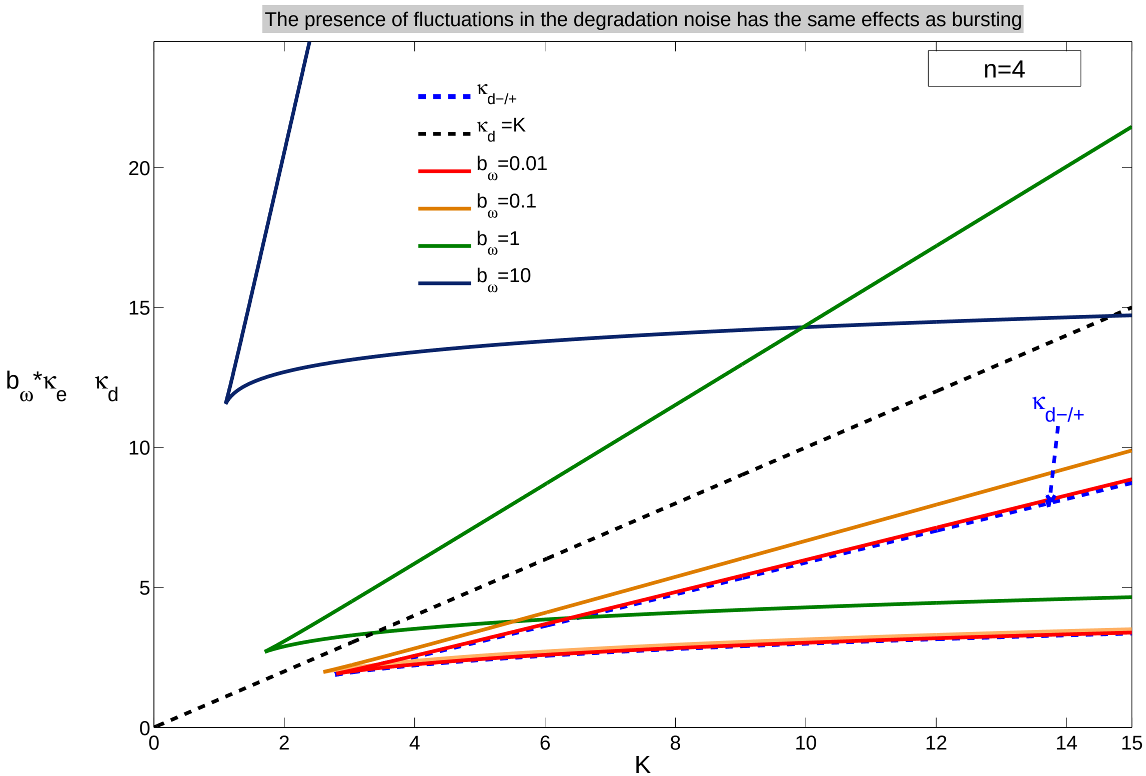
(4) $$\frac{\partial u}{\partial t} 0 = -\frac{d\left[(\gamma\kappa_d f(x) - \gamma x)u^*\right]}{dx} + \frac{\sigma^2}{2}\frac{d^2(xu^*)}{dx^2}.$$

And (Reflecting boundary at $x = 0$)

(5) $$J = \left[(\gamma\kappa_d f(x) - \gamma x)u^*\right] - \frac{\sigma^2}{2}\frac{d(xu^*)}{dx} = 0$$

Extrinsic noise ∼ intrinsic noise

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



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

Evolution equation for the density of x

The evolution equation for the density $u(t,x) = P_+(t,x) + P_0(t)$ of x is

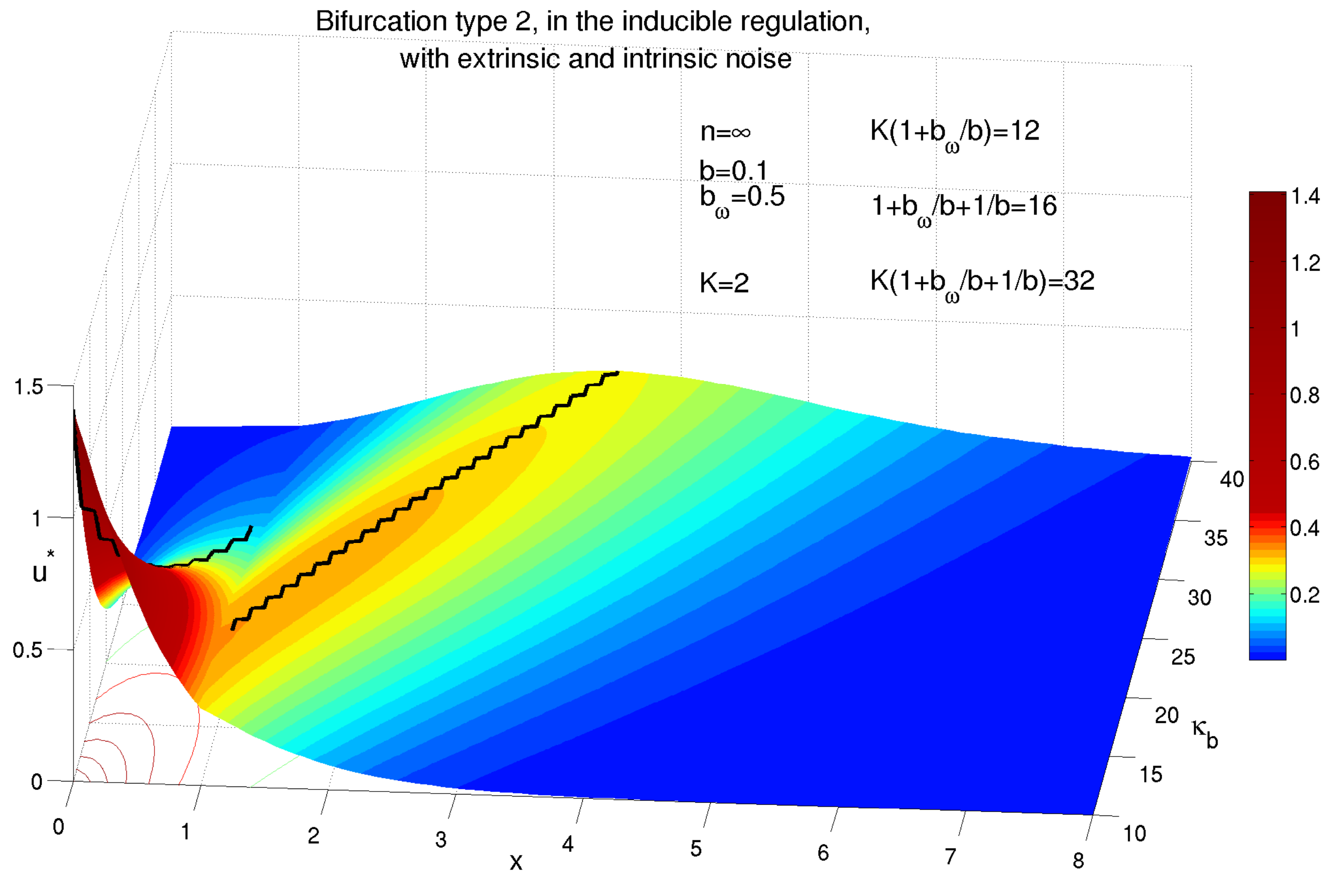
$$\begin{aligned}
\frac{\partial P_+(t,x)}{\partial t} &- \gamma \frac{\partial (x P_+(t,x))}{\partial x} - \frac{\sigma^2}{2} \frac{\partial^2 (x P_+)}{\partial x^2} \\
&= -\gamma \kappa_b f(x) P_+(t,x) + \gamma \kappa_b \int_0^x f(y) P_+(t,y) h(x-y) dy \\
&\quad + \gamma \kappa_b f(0) \frac{1}{b} e^{-x/b} P_0(t), \\
\frac{dP_0(t)}{dt} &= -\gamma \kappa_b f(0) P_0(t) + \left[\gamma x P_+(t,x) + \frac{\sigma^2}{2} \frac{\partial (x P_+)}{\partial x} \right]_{x \to 0} \\
\lim_{x \to 0} (x P_+) &= 0 \\
\lim_{x \to \infty} (x P_+) &= 0
\end{aligned}$$

Evolution equation for the density of x

The evolution equation for the density $u(t,x) = P^+(t,x) + P_0(t)$ of x is

$$
\begin{aligned}
\frac{\partial P_+(t,x)}{\partial t} \quad &- \quad \gamma \frac{d(xP_+^*)}{dx} - \frac{\sigma^2}{2}\frac{d^2(xP_+^*)}{dx^2} \\
&= \quad -\gamma\kappa_b f(x) P_+^* + \gamma\kappa_b \int_0^x f(y) P_+^* h(x-y)\,dy \\
&\quad\;\; +\gamma\kappa_b f(0) \frac{1}{b} e^{-x/b} P_0^*, \\
\frac{dP_0(t)}{dt} 0 \quad &= \quad -\gamma\kappa_b f(0) P_0^* + \left[\gamma x P_+^* + \frac{\sigma^2}{2}\frac{d(xP_+^*)}{dx}\right]_{x\to 0} \\
\lim_{x\to 0}(xP_+^*) \quad &= \quad 0 \\
\lim_{x\to\infty}(xP_+^*) \quad &= \quad 0
\end{aligned}
$$

Extrinsic and intrinsic noise



Conclusion

- Intrinsic noise and extrinsic noise are indistinguishable from the stationnary density in this model.
- The stationary densities can be much more wider (and asymmmetric) than a poissonian ditribution.
- 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 equilibirum.
- The full three-stage model should be considered with noise.

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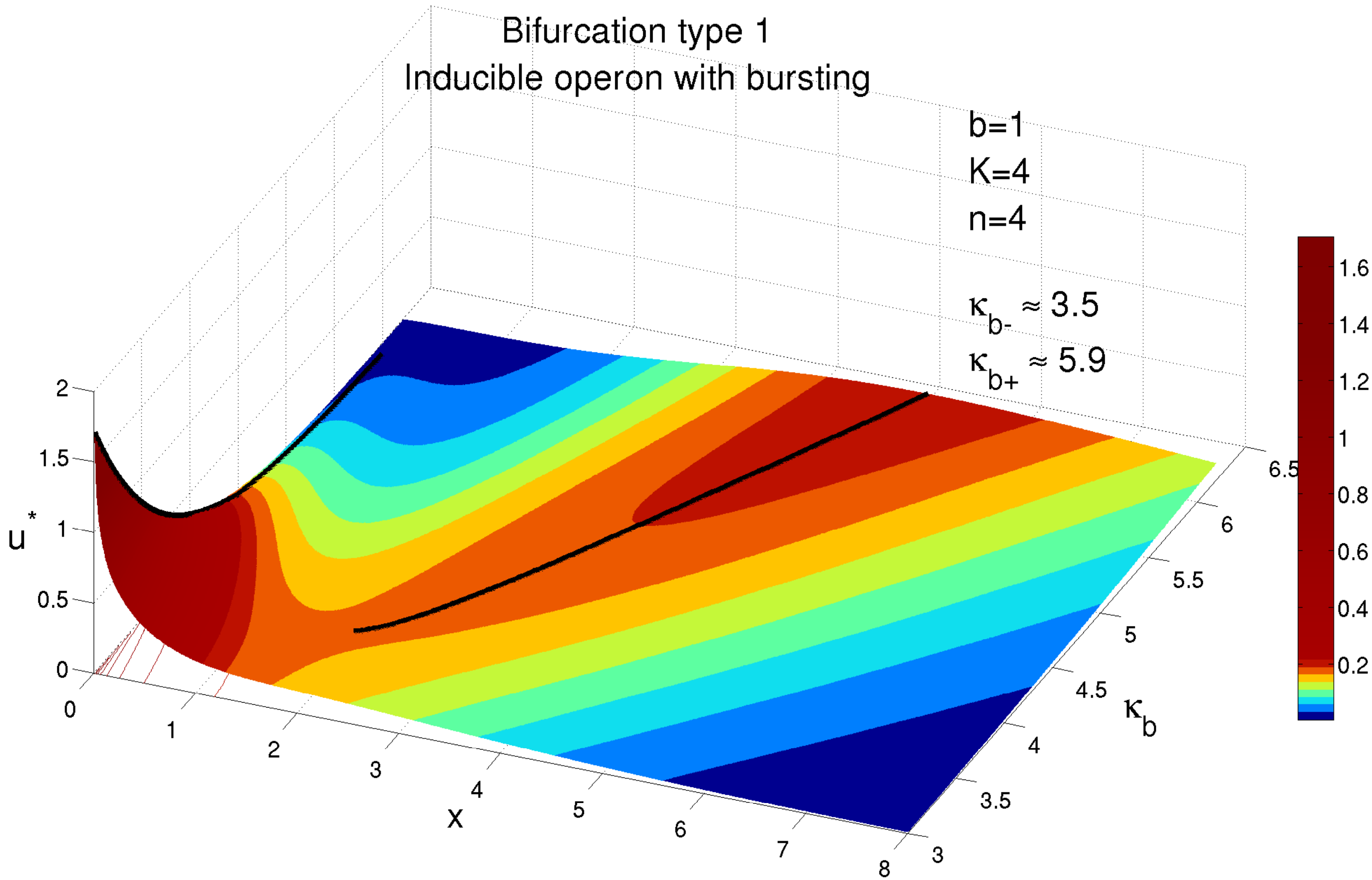
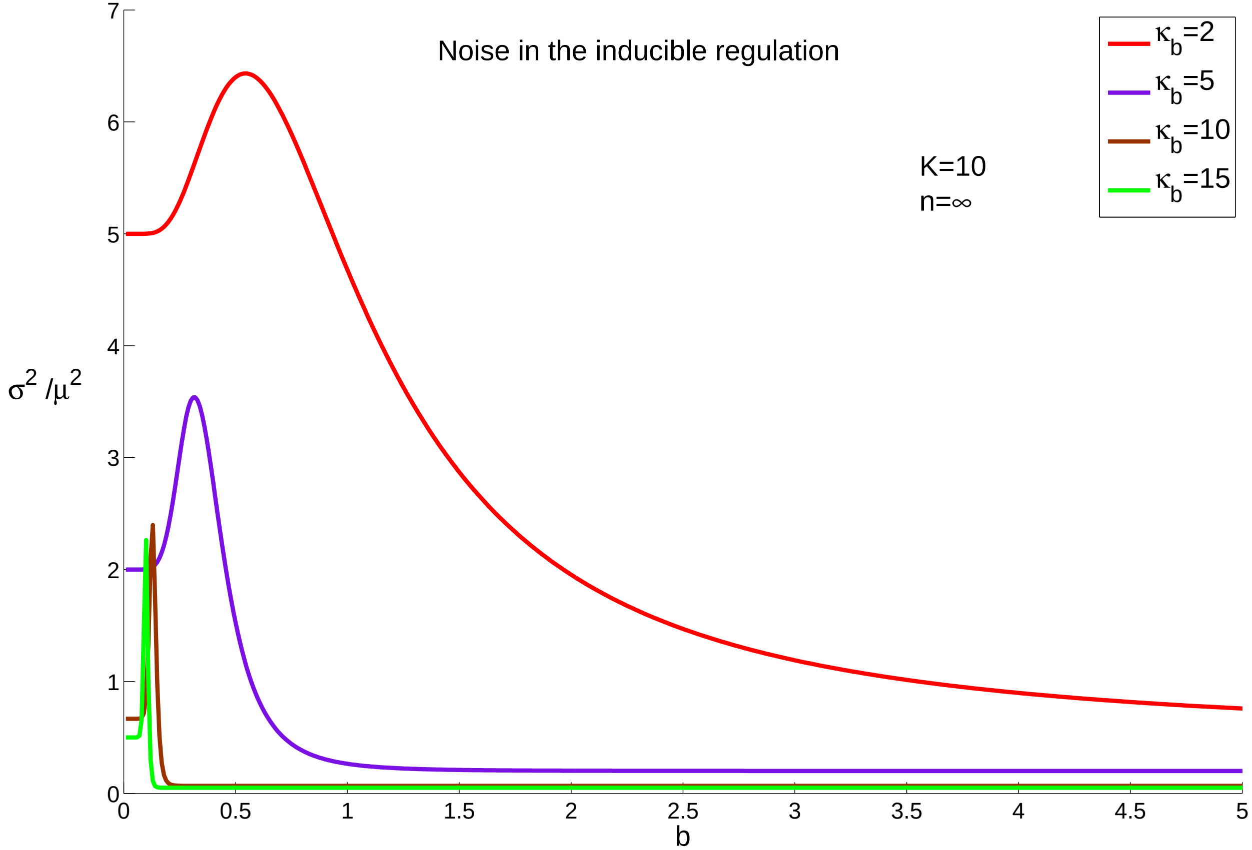
and Michael C. Mackey

THANK YOU!

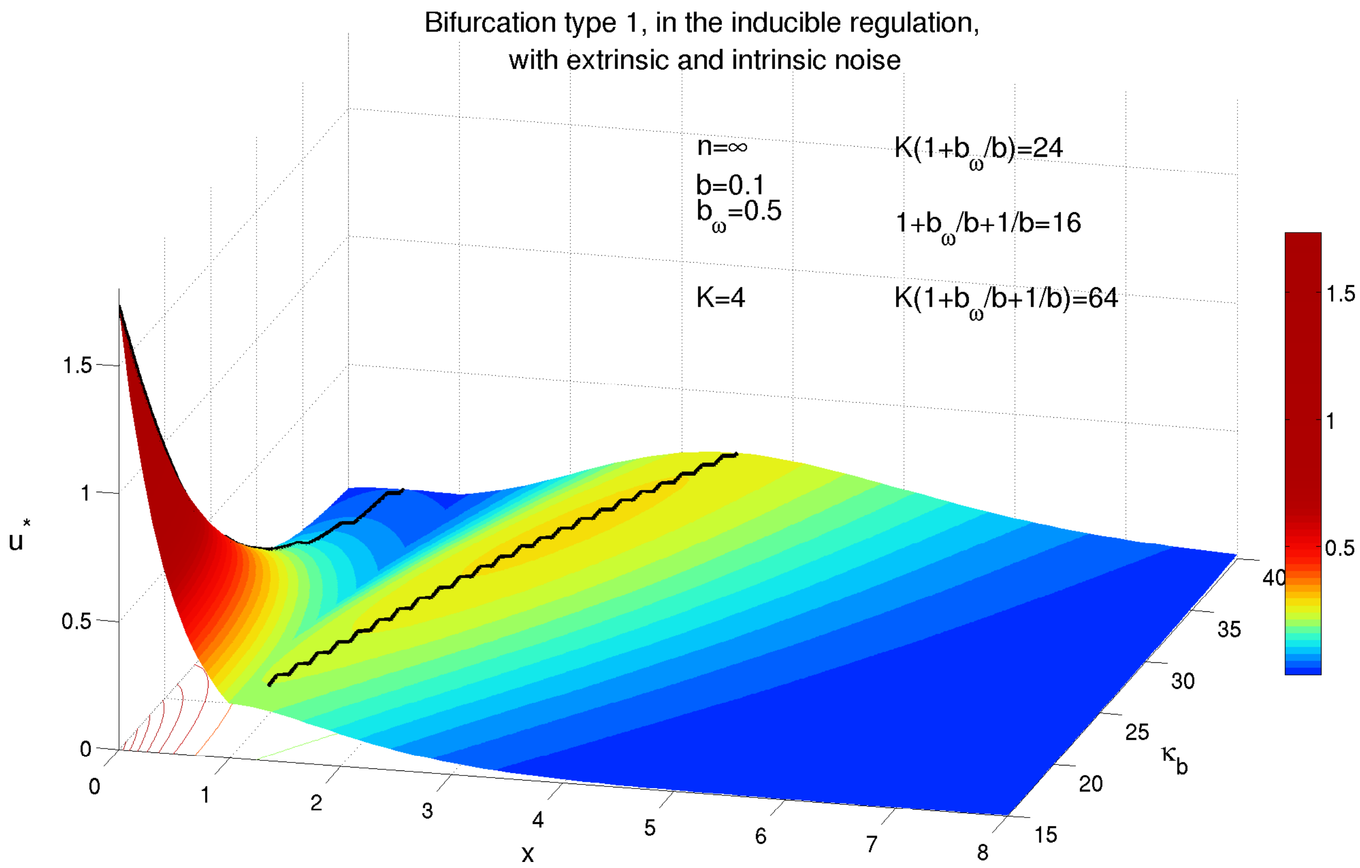
Stationary density as a function of κ_b



Noise induced by bursting



Extrinsic and intrinsic noise



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