Deterministic and stochastic models of circadian rhythms

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Outline

- VKBL model of circadian rhythms
- Deterministic and stochastic models
  - Comparable behaviour for $\delta_R = 0.2$
  - Qualitatively different behaviour for $\delta_R = 0.05$
- Explanation

VKBL model – parameters

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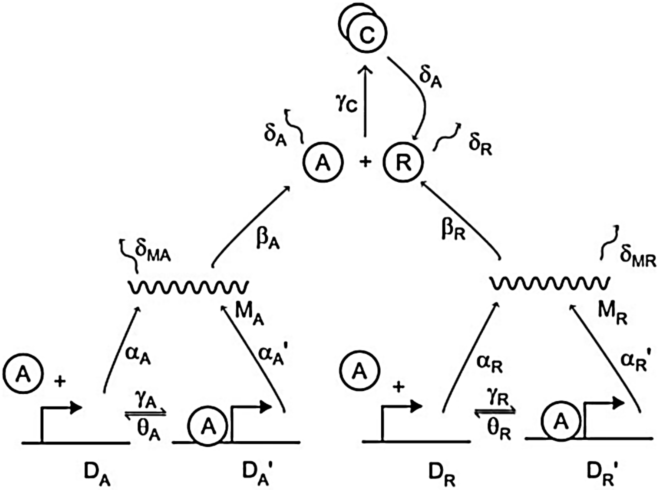

[Vilar, Kueh, Barkai, Leibler, 2002]

$$\alpha_A = 50\,\mathrm{h}^{-1}$$
$$\alpha'_A = 500\,\mathrm{h}^{-1}$$
$$\alpha_R = 0.01\,\mathrm{h}^{-1}$$
$$\alpha'_R = 50\,\mathrm{h}^{-1}$$
$$\beta_A = 50\,\mathrm{h}^{-1}$$
$$\beta_R = 5\,\mathrm{h}^{-1}$$
$$\gamma_A = 1\,\mathrm{mol}^{-1}\ \mathrm{h}^{-1}$$
$$\gamma_R = 1\,\mathrm{mol}^{-1}\ \mathrm{h}^{-1}$$
$$\gamma_C = 2\,\mathrm{mol}^{-1}\ \mathrm{h}^{-1}$$
$$\delta_A = 1\,\mathrm{h}^{-1}$$
$$\delta_R = 0.2\,\mathrm{h}^{-1}$$
$$\delta_{M_A} = 10\,\mathrm{h}^{-1}$$
$$\delta_{M_R} = 0.5\,\mathrm{h}^{-1}$$
$$\theta_A = 50\,\mathrm{h}^{-1}$$
$$\theta_R = 100\,\mathrm{h}^{-1}$$

Deterministic and stochastic modelling

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$$A \xrightarrow{k} \emptyset$$

$A(t)$ ... number of molecules in time t, provided $A(0) = n_0$

Law of mass action:

$$\mathrm{d}A(t)/\mathrm{d}t = -kA(t)$$

Gillespie stochastic simulation algorithm:
$kA(t)\mathrm{d}t$ ... probability that a reaction occurs in $[t, t + \mathrm{d}t)$

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

(b) $\alpha = kA(t), \quad \tau = \dfrac{1}{\alpha} \ln \dfrac{1}{r}$

(c) $A(t + \tau) = A(t) - 1$

(d) $t := t + \tau$, go to (a)

VKBL model – law of mass action

$$\mathrm{d}D_A/\mathrm{d}t = \theta_A D'_A - \gamma_A D_A A$$

$$\mathrm{d}D'_A/\mathrm{d}t = -\theta_A D'_A + \gamma_A D_A A$$

$$\mathrm{d}D_R/\mathrm{d}t = \theta_R D'_R - \gamma_R D_R A$$

$$\mathrm{d}D'_R/\mathrm{d}t = -\theta_R D'_R + \gamma_R D_R A$$

$$\mathrm{d}M_A/\mathrm{d}t = \alpha'_A D'_A + \alpha_A D_A - \delta_{M_A} M_A$$

$$\mathrm{d}M_R/\mathrm{d}t = \alpha'_R D'_R + \alpha_R D_R - \delta_{M_R} M_R$$

$$\mathrm{d}A/\mathrm{d}t = \beta_A M_A + \theta_A D'_A + \theta_R D'_R - A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A)$$

$$\mathrm{d}R/\mathrm{d}t = \beta_R M_R - \gamma_C A R + \delta_A C - \delta_R R$$

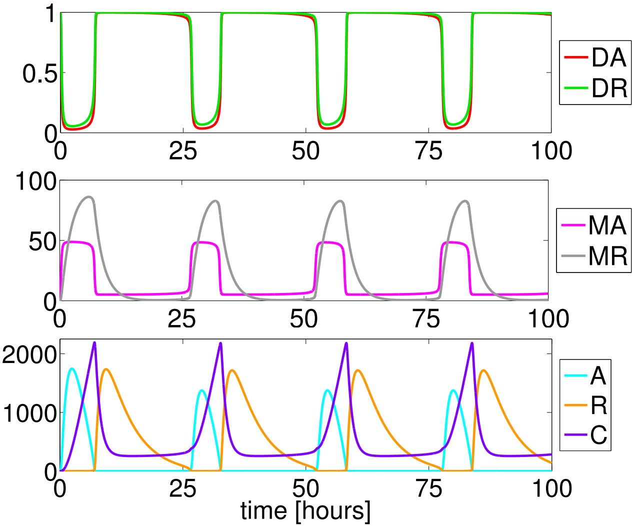
$$\mathrm{d}C/\mathrm{d}t = \gamma_C A R - \delta_A C$$

Initial conditions:

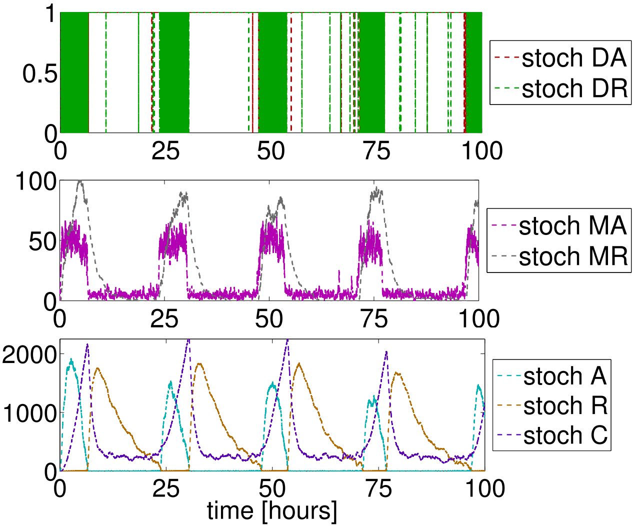
$D_A = D_R = 1$ mol

$D'_A = D'_R = M_A = M_R = A = R = C = 0$ mol

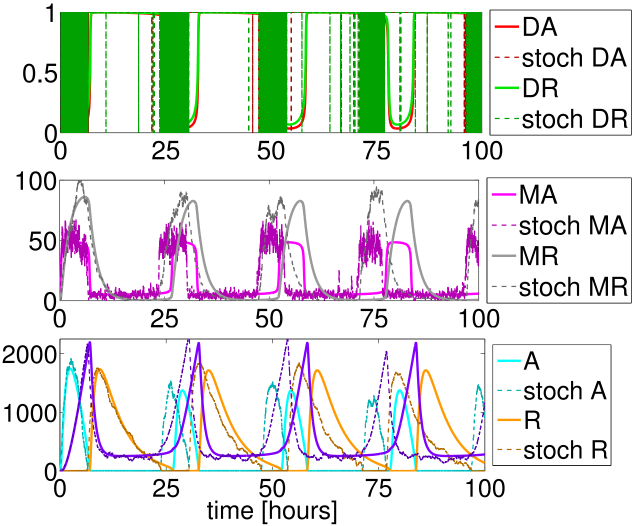
Full system – solution of ODE



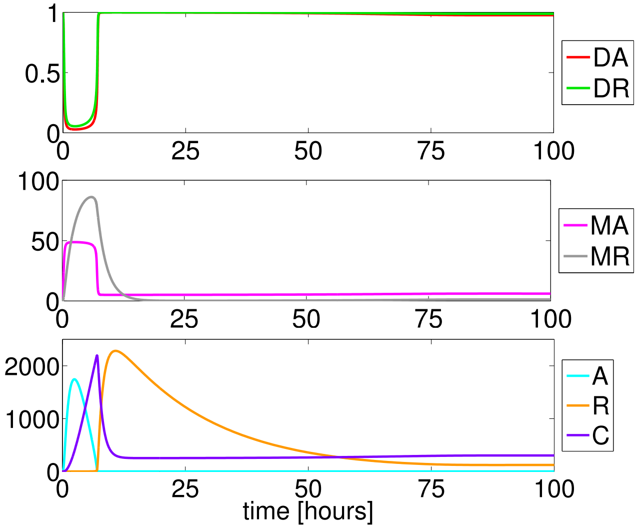
Full system – Gillespie SSA



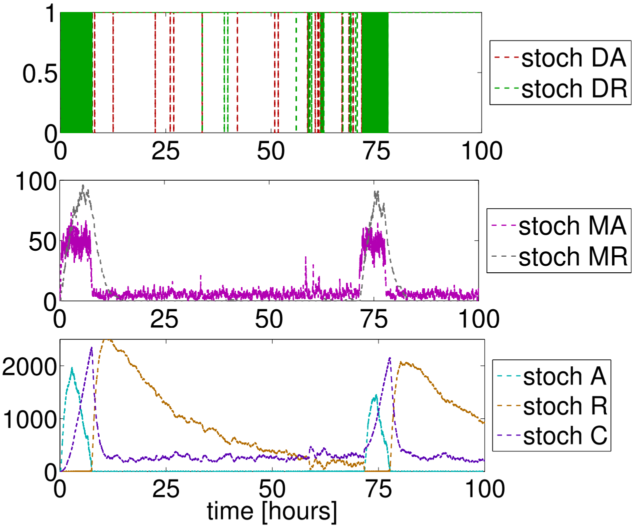
Full system – comparison



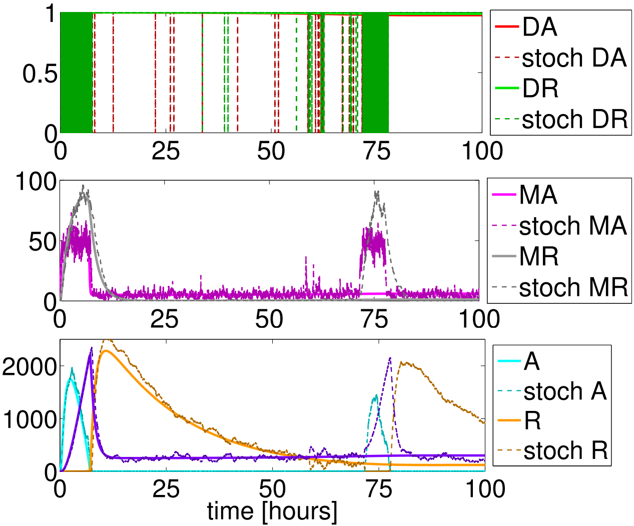
Full system – $\delta_R = 0.05$ – solution of ODE



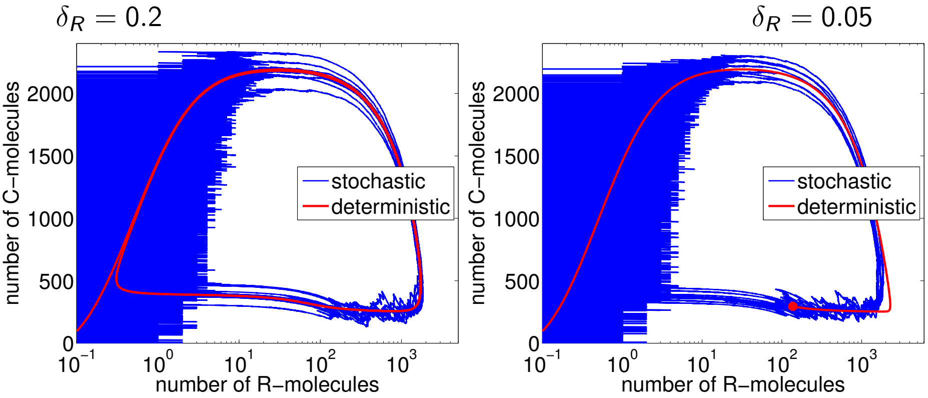
Full system – $\delta_R = 0.05$ – Gillespie SSA



Full system – $\delta_R = 0.05$ – comparison



Full system – phase diagram



Simplified system

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Quasi-steady state assumptions:

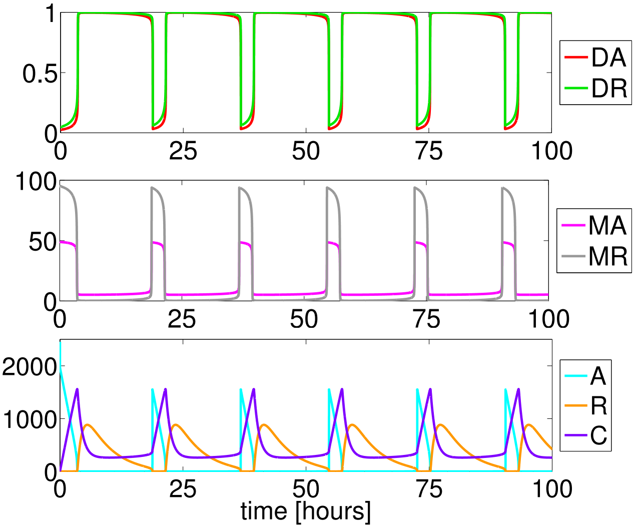
$$\mathrm{d}R/\mathrm{d}t = \beta_R \widetilde{M}_R^s(R) - \gamma_C \widetilde{A}^s(R)R + \delta_A C - \delta_R R$$
$$\mathrm{d}C/\mathrm{d}t = \gamma_C \widetilde{A}^s(R)R - \delta_A C$$

$$\widetilde{A}^s(R) = \tfrac{1}{2}(\alpha'_A \rho(R) - K_d) + \tfrac{1}{2}\sqrt{(\alpha'_A \rho(R) - K_d)^2 + 4\alpha_A \rho(R) K_d}$$
$$\rho(R) = \frac{\beta_A}{\delta_{M_A}} \frac{1}{\gamma_C R + \delta_A}, \quad K_d = \frac{\theta_A}{\gamma_A}$$
$$\widetilde{M}_R^s(R) = \frac{\alpha'_R}{\delta_{M_R}} + \frac{\theta_R(\alpha_R - \alpha'_R)}{\delta_{M_R}(\theta_R + \gamma_R \widetilde{A}^s(R))}$$

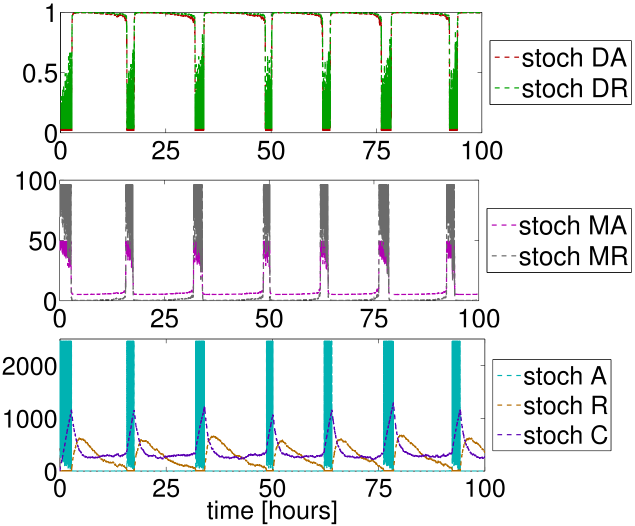
Simplified chemical system:

$$\emptyset \underset{\delta_R}{\overset{k_1}{\rightleftharpoons}} R \underset{\delta_A}{\overset{k_2}{\rightleftharpoons}} C, \quad k_1 = \beta_R \widetilde{M}_R^s(R), \quad k_2 = \gamma_C \widetilde{A}^s(R)$$

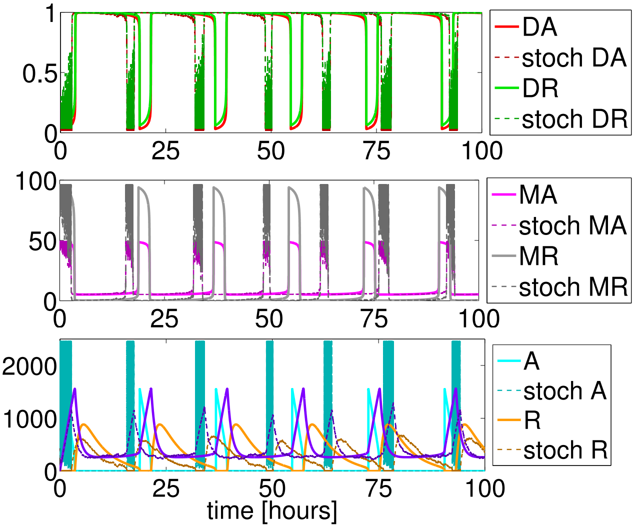
Simplified system – $\delta_R = 0.2$ – two ODE



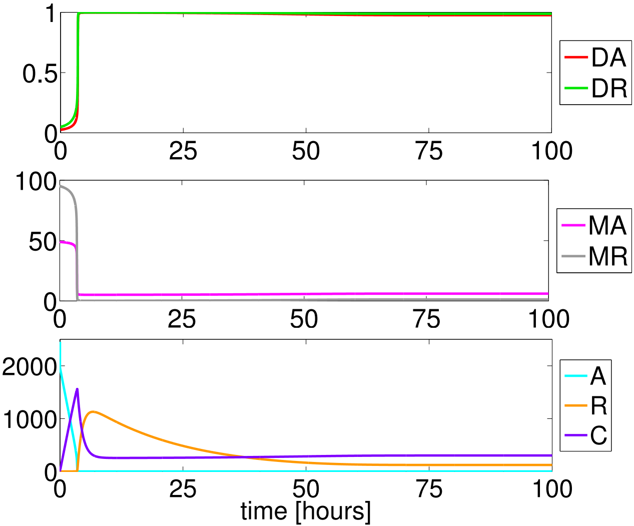
Simplified system – $\delta_R = 0.2$ – Gillespie SSA



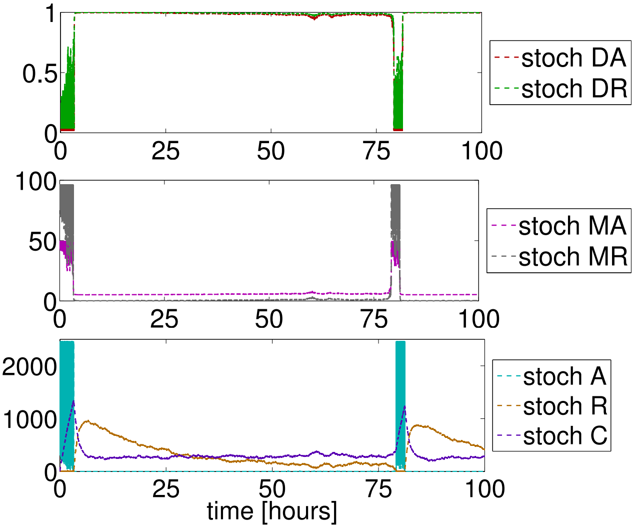
Simplified system – $\delta_R = 0.2$ – comparison



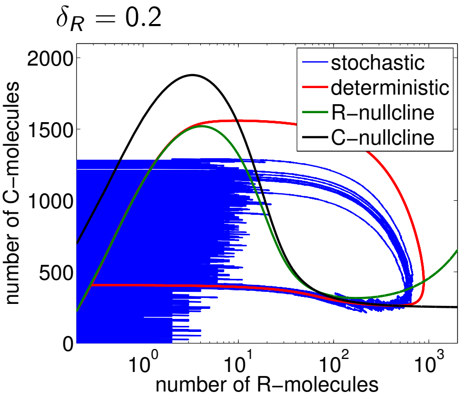
Simplified system – $\delta_R = 0.05$ – two ODE

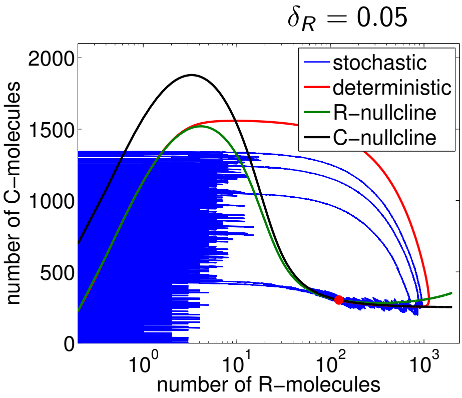


Simplified system – $\delta_R = 0.05$ – Gillespie SSA

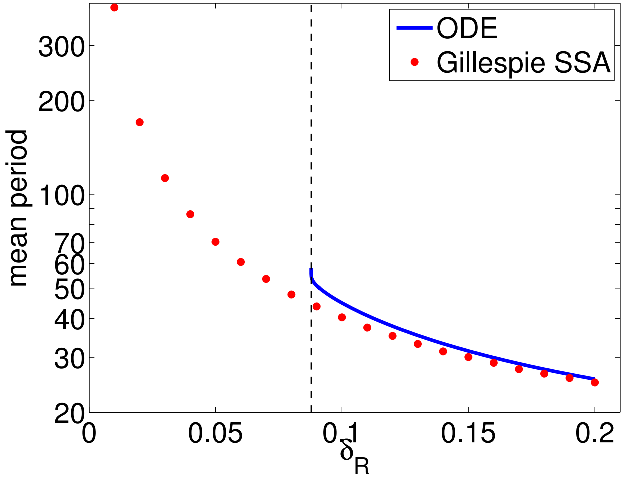


Simplified system – phase diagram

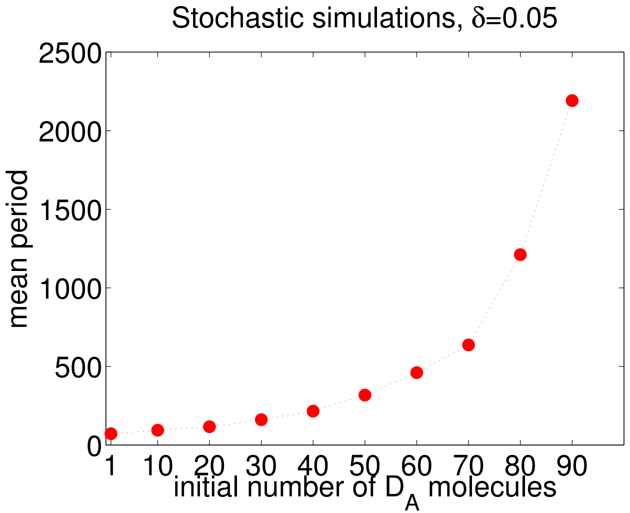




Mean period vs. δ_R



Mean period – $\delta_R = 0.05$



Period of deterministic system is infinite.

Conclusion

- Qualitatively different behaviour appears close to a bifurcation point
- Bifurcation point of stochastic system seems to be around $\delta_R = 0.001$
- Low copy numbers of a chemical species $\Longrightarrow$ stochastic effects
- High copy numbers $\Longrightarrow$ stochastic and deterministic models agree

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Thank you for your attention

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