Models of circadian rhythms

Tomáš Vejchodský

Centre for Mathematical Biology
Mathematical Institute

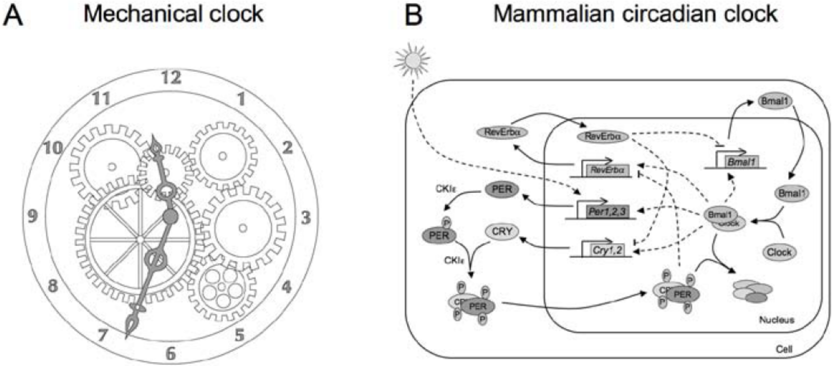
UNIVERSITY OF OXFORD

Summer school, Prague, 6–8 August, 2013

Outline

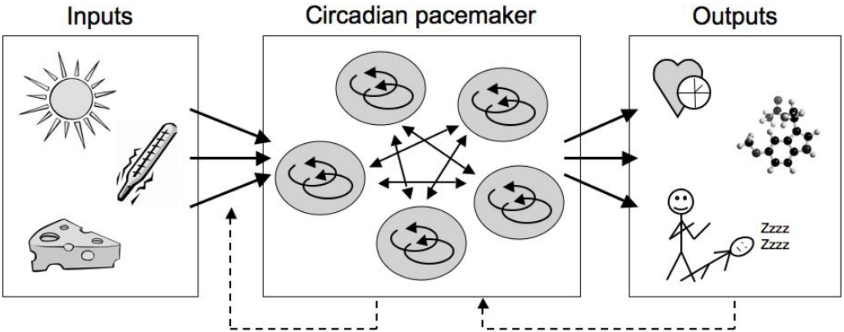
- Motivation
- Theoretical VKBL model
- Model reduction
- Quasi-steady state assumptions (QSSA)
- Delayed quasi-steady state assumptions (D-QSSA)
- Gillespie SSA: deterministic vs. stochastic
- Robustness of oscillations with respect to noise
- Period of stochastic oscillations

Motivation



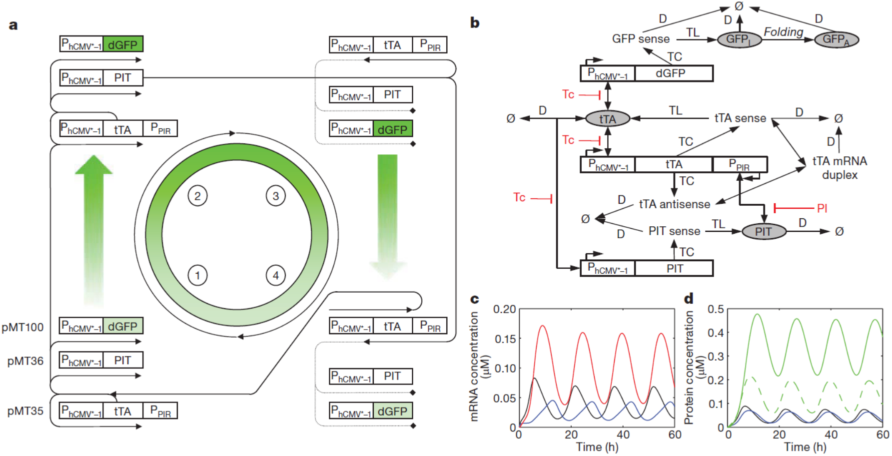
[Gonze 2011]

Motivation



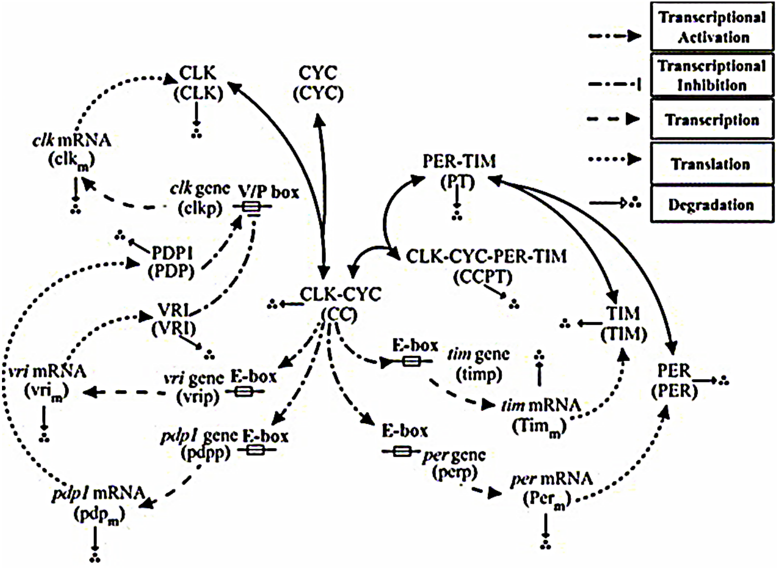
[Gonze 2011]

Various models



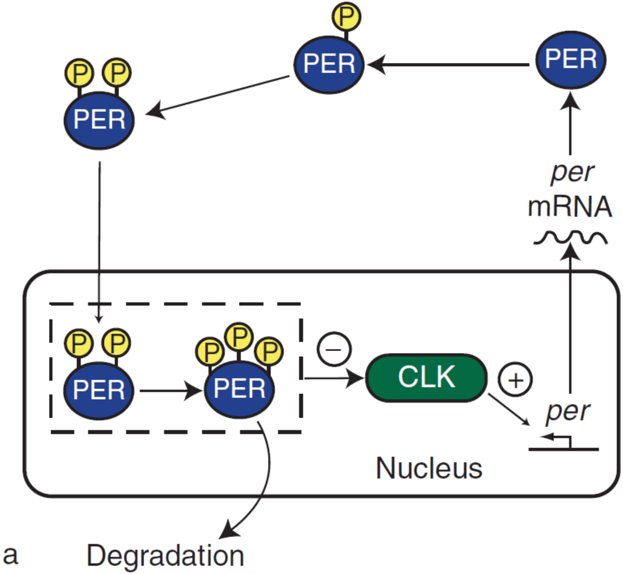
Mammalian oscillator
[Tigges, Marquez-Lago, Stelling, Fussenegger, 2009]

Various models



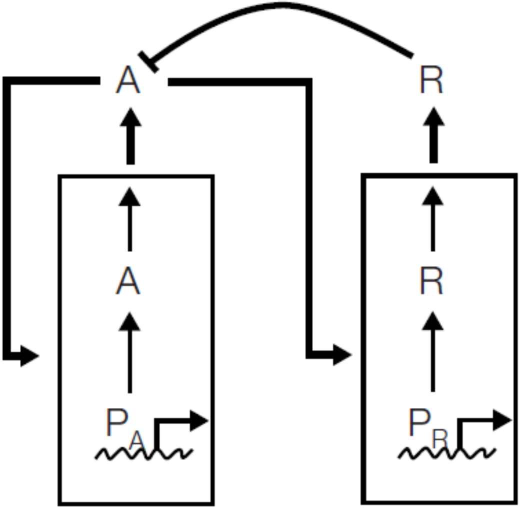
Drosophila [Xie, Kulasiri, 2007]

Various models



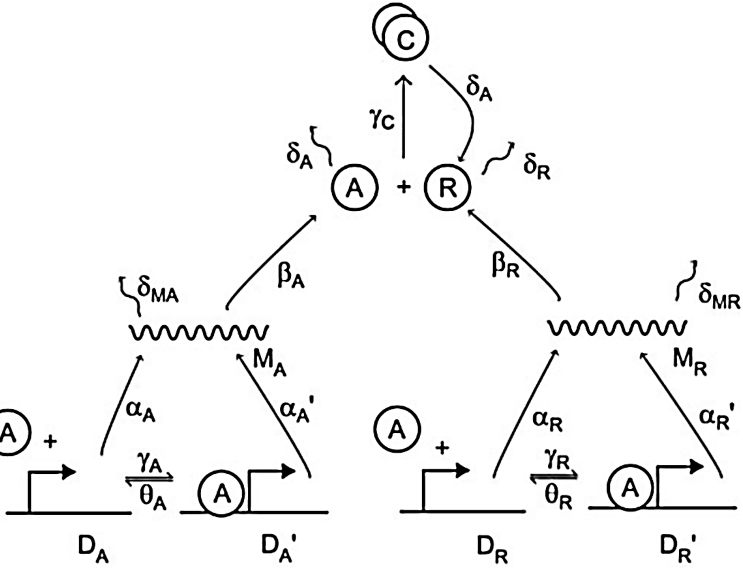
Drosophila [Smoren, Byrne, 2009]

Theoretical model



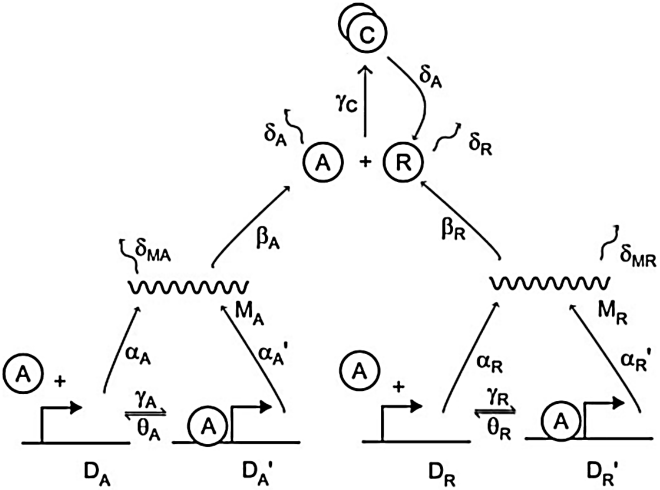
[Barkai, Leibler, 1999]

VKBL model



[Vilar, Kueh, Barkai, Leibler, 2002]

VKBL model – parameters



[Vilar, Kueh, Barkai, Leibler, 2002]

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

VKBL model – law of mass action

UNIVERSITY OF OXFORD

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

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

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

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

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

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

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

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

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

Initial conditions:

$D_A = D_R = 1$ mol

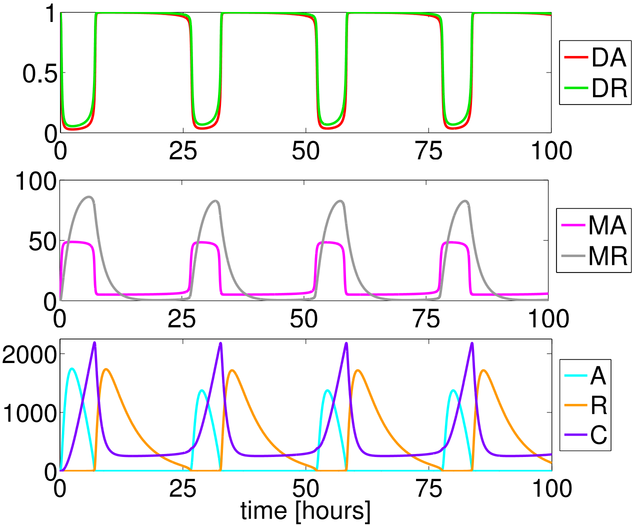
$D'_A = D'_R = M_A = M_R = A = R = C = 0$ mol

VKBL model – reduction by substitution

UNIVERSITY OF OXFORD

$$
\begin{aligned}
\mathrm{d}D_A/\mathrm{d}t &= \theta_A - (\theta_A + \gamma_A A)D_A \\
D'_A &= 1 - D_A \\
\mathrm{d}D_R/\mathrm{d}t &= \theta_R - (\theta_R + \gamma_R A)D_R \\
D'_R &= 1 - D_R \\
\mathrm{d}M_A/\mathrm{d}t &= \alpha'_A + (\alpha_A - \alpha'_A)D_A - \delta_{M_A} M_A \\
\mathrm{d}M_R/\mathrm{d}t &= \alpha'_R + (\alpha_R - \alpha'_R)D_R - \delta_{M_R} M_R \\
\mathrm{d}A/\mathrm{d}t &= \beta_A M_A + \theta_A(1 - D_A) + \theta_R(1 - D_R) \\
&\quad - A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A) \\
\mathrm{d}R/\mathrm{d}t &= \beta_R M_R - \gamma_C AR + \delta_A C - \delta_R R \\
\mathrm{d}C/\mathrm{d}t &= \gamma_C AR - \delta_A C
\end{aligned}
$$

ODE solution



Quasi-steady state assumptions (QSSA)

$$\mathrm{d}D_A/\mathrm{d}t = \theta_A - (\theta_A + \gamma_A A)D_A$$

$$\mathrm{d}D_R/\mathrm{d}t = \theta_R - (\theta_R + \gamma_R A)D_R$$

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

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

$$\begin{aligned}\mathrm{d}A/\mathrm{d}t &= \beta_A M_A + \theta_A(1 - D_A) + \theta_R(1 - D_R) \\ &\quad - A(\gamma_A D_A + \gamma_R D_R + \gamma_C R + \delta_A)\end{aligned}$$

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

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

$$D'_A = 1 - D_A$$
$$D'_R = 1 - D_R$$

Quasi-steady state assumptions (QSSA)

UNIVERSITY OF OXFORD

$$0 = \theta_A - (\theta_A + \gamma_A A) D_A \quad \Rightarrow \quad D_A = D_A^s = \frac{\theta_A}{\theta_A + \gamma_A A}$$

$$\mathrm{d}D_R/\mathrm{d}t = \theta_R - (\theta_R + \gamma_R A) D_R$$

$$\mathrm{d}M_A/\mathrm{d}t = \alpha'_A + (\alpha_A - \alpha'_A) D_A^s - \delta_{M_A} M_A$$

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

$$\mathrm{d}A/\mathrm{d}t = \beta_A M_A + \theta_A (1 - D_A^s) + \theta_R (1 - D_R) - A(\gamma_A D_A^s + \gamma_R D_R + \gamma_C R + \delta_A)$$

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

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

$$D'_A = 1 - D_A^s$$
$$D'_R = 1 - D_R$$

Quasi-steady state assumptions (QSSA)

UNIVERSITY OF OXFORD

$$0 = \theta_A - (\theta_A + \gamma_A A) D_A \quad \Rightarrow \quad D_A = D_A^s = \frac{\theta_A}{\theta_A + \gamma_A A}$$

$$0 = \theta_R - (\theta_R + \gamma_R A) D_R \quad \Rightarrow \quad D_R = D_R^s = \frac{\theta_R}{\theta_R + \gamma_R A}$$

$$\mathrm{d}M_A/\mathrm{d}t = \alpha'_A + (\alpha_A - \alpha'_A) D_A^s - \delta_{M_A} M_A$$

$$\mathrm{d}M_R/\mathrm{d}t = \alpha'_R + (\alpha_R - \alpha'_R) D_R^s - \delta_{M_R} M_R$$

$$\begin{aligned} \mathrm{d}A/\mathrm{d}t = {} & \beta_A M_A + \theta_A (1 - D_A^s) + \theta_R (1 - D_R^s) \\ & - A(\gamma_A D_A^s + \gamma_R D_R^s + \gamma_C R + \delta_A) \end{aligned}$$

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

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

$$D'_A = 1 - D_A^s$$
$$D'_R = 1 - D_R^s$$

Quasi-steady state assumptions (QSSA)

$$0 = \theta_A - (\theta_A + \gamma_A A) D_A \quad \Rightarrow \quad D_A = D_A^s = \frac{\theta_A}{\theta_A + \gamma_A A}$$

$$0 = \theta_R - (\theta_R + \gamma_R A) D_R \quad \Rightarrow \quad D_R = D_R^s = \frac{\theta_R}{\theta_R + \gamma_R A}$$

$$0 = \alpha'_A + (\alpha_A - \alpha'_A) D_A^s - \delta_{M_A} M_A^s \quad \Rightarrow \quad M_A = M_A^s = \dots$$

$$0 = \alpha'_R + (\alpha_R - \alpha'_R) D_R^s - \delta_{M_R} M_R^s \quad \Rightarrow \quad M_R = M_R^s = \dots$$

$$\begin{aligned} \mathrm{d}A/\mathrm{d}t &= \beta_A M_A^s + \theta_A (1 - D_A^s) + \theta_R (1 - D_R^s) \\ &\quad - A(\gamma_A D_A^s + \gamma_R D_R^s + \gamma_C R + \delta_A) \end{aligned}$$

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

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

$$D'_A = 1 - D_A^s$$
$$D'_R = 1 - D_R^s$$

Quasi-steady state assumptions (QSSA)

$$0 = \theta_A - (\theta_A + \gamma_A A) D_A \quad \Rightarrow \quad D_A = D_A^s = \tfrac{\theta_A}{\theta_A + \gamma_A A^s}$$

$$0 = \theta_R - (\theta_R + \gamma_R A) D_R \quad \Rightarrow \quad D_R = D_R^s = \tfrac{\theta_R}{\theta_R + \gamma_R A^s}$$

$$0 = \alpha'_A + (\alpha_A - \alpha'_A) D_A^s - \delta_{M_A} M_A^s \quad \Rightarrow \quad M_A = M_A^s = \ldots$$

$$0 = \alpha'_R + (\alpha_R - \alpha'_R) D_R^s - \delta_{M_R} M_R^s \quad \Rightarrow \quad M_R = M_R^s = \ldots$$

$$\begin{aligned} 0 = {} & \beta_A M_A^s + \theta_A (1 - D_A^s) + \theta_R (1 - D_R^s) \\ & - A(\gamma_A D_A^s + \gamma_R D_R^s + \gamma_C R + \delta_A) \quad \Rightarrow \quad A = A^s = A^s(R) \end{aligned}$$

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

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

$$\begin{aligned} D'_A &= 1 - D_A^s \\ D'_R &= 1 - D_R^s \end{aligned}$$

Case 1: QSSA on D_A, D_R, M_A, M_R

$$
\begin{aligned}
\mathrm{d}A/\mathrm{d}t &= \beta_A M_A^s(A) + \theta_A(1 - D_A^s(A)) + \theta_R(1 - D_R^s(A)) \\
&\qquad - A(\gamma_A D_A^s(A) + \gamma_R D_R^s(A) + \gamma_C R + \delta_A) \\
\mathrm{d}R/\mathrm{d}t &= \beta_R M_R^s(A) - \gamma_C AR + \delta_A C - \delta_R R \\
\mathrm{d}C/\mathrm{d}t &= \gamma_C AR - \delta_A C
\end{aligned}
$$

$$
\begin{aligned}
D_A(t) &\approx D_A^s(A(t)) = \tfrac{\theta_A}{\theta_A + \gamma_A A(t)} \\
D_R(t) &\approx D_R^s(A(t)) = \tfrac{\theta_R}{\theta_R + \gamma_R A(t)} \\
M_A(t) &\approx M_A^s(A(t)) = \tfrac{\alpha'_A + (\alpha_A - \alpha'_A) D_A^s(A(t))}{\delta_{M_A}} = \tfrac{\alpha'_A}{\delta_{M_A}} + \tfrac{\theta_A(\alpha_A - \alpha'_A)}{\delta_{M_A}(\theta_A + \gamma_A A(t))} \\
M_R(t) &\approx M_R^s(A(t)) = \tfrac{\alpha'_R + (\alpha_R - \alpha'_R) D_R^s(A(t))}{\delta_{M_R}} = \tfrac{\alpha'_R}{\delta_{M_R}} + \tfrac{\theta_R(\alpha_R - \alpha'_R)}{\delta_{M_R}(\theta_R + \gamma_R A(t))}
\end{aligned}
$$

Case 2: QSSA on D_A, D_R, M_A, M_R, A

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

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

$$A(t) \approx \widetilde{A}^s(R(t)) = \frac{1}{2}(\alpha'_A \rho(R(t)) - K_d) + \frac{1}{2}\sqrt{(\alpha'_A \rho(R(t)) - K_d)^2 + 4\alpha_A \rho(R(t)) K_d}$$

$$\rho(R(t)) = \frac{\beta_A}{\delta_{MA}} \frac{1}{\gamma_C R(t) + \delta_A}, \quad K_d = \frac{\theta_A}{\gamma_A}$$

$$D_A(t) \approx \widetilde{D}_A^s(R(t)) = \frac{\theta_A}{\theta_A + \gamma_A \widetilde{A}^s(R(t))}$$

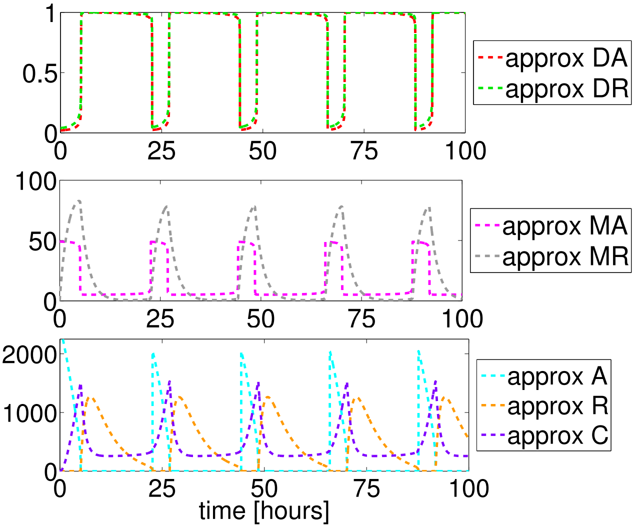
$$D_R(t) \approx \widetilde{D}_R^s(R(t)) = \frac{\theta_R}{\theta_R + \gamma_R \widetilde{A}^s(R(t))}$$

$$M_A(t) \approx \widetilde{M}_A^s(R(t)) = = \frac{\alpha'_A}{\delta_{M_A}} + \frac{\theta_A(\alpha_A - \alpha'_A)}{\delta_{M_A}(\theta_A + \gamma_A \widetilde{A}^s(R(t)))}$$

$$M_R(t) \approx \widetilde{M}_R^s(R(t)) = = \frac{\alpha'_R}{\delta_{M_R}} + \frac{\theta_R(\alpha_R - \alpha'_R)}{\delta_{M_R}(\theta_R + \gamma_R \widetilde{A}^s(R(t)))}$$

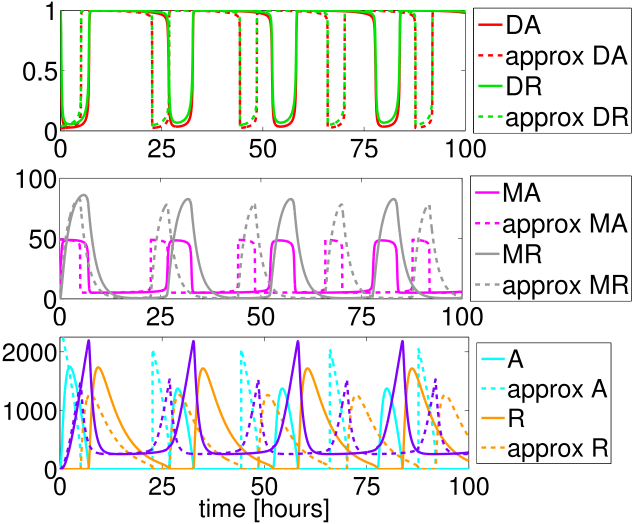
Case 1 (three ODEs)

QSS assumptions on D_A, D_R, M_A, M_R



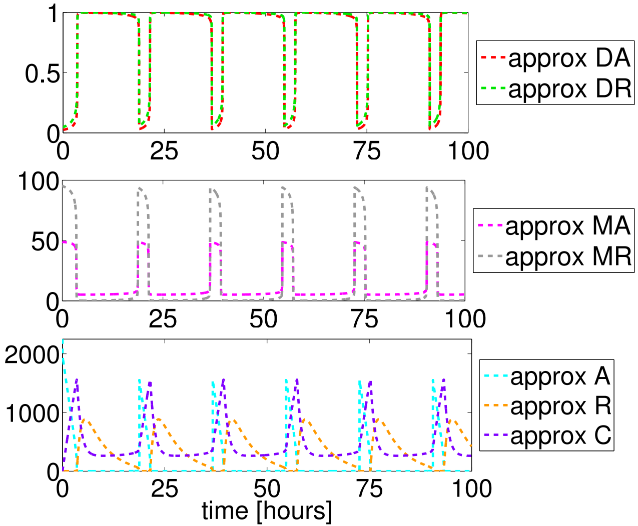
Case 1 (three ODEs)

QSS assumptions on D_A, D_R, M_A, M_R



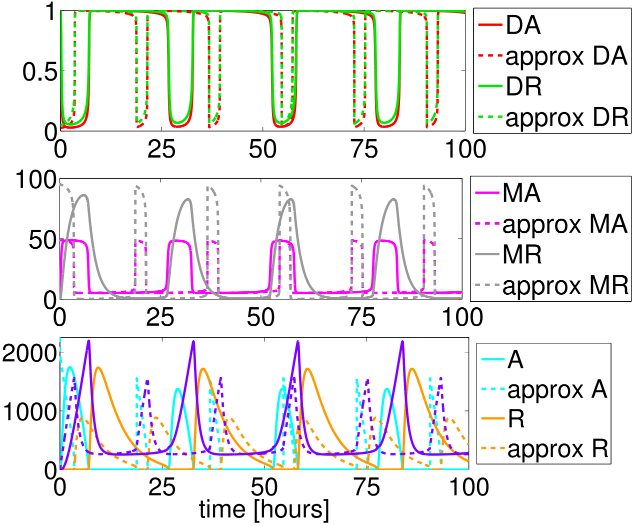
Case 2 (two ODEs)

QSS assumptions on D_A, D_R, M_A, M_R, A



Case 2 (two ODEs)

QSS assumptions on D_A, D_R, M_A, M_R, A



Delayed quasi-steady state assumptions

Case 1:

$$
\begin{aligned}
\mathrm{d}A/\mathrm{d}t &= \beta_A M_A^\tau(t) + \theta_A(1 - D_A^\tau(t)) + \theta_R(1 - D_R^\tau(t)) \\
&\quad - A(\gamma_A D_A^\tau(t) + \gamma_R D_R^\tau(t) + \gamma_C R + \delta_A) \\
\mathrm{d}R/\mathrm{d}t &= \beta_R M_R^\tau(t) - \gamma_C AR + \delta_A C - \delta_R R \\
\mathrm{d}C/\mathrm{d}t &= \gamma_C AR - \delta_A C
\end{aligned}
$$

$$
\begin{aligned}
\tau_{DA}(t) &= [\theta_A + \gamma_A A(t)]^{-1} & D_A^\tau(t) &= D_A^s(A(t - \tau_{DA}(t))) \\
\tau_{DR}(t) &= [\theta_R + \gamma_R A(t)]^{-1} & D_R^\tau(t) &= D_R^s(A(t - \tau_{DR}(t))) \\
\tau_{MA}(t) &= \delta_{MA}^{-1} & M_A^\tau(t) &= M_A^s(A(t - \tau_{MA})) \\
\tau_{MR}(t) &= \delta_{MR}^{-1} & M_R^\tau(t) &= M_R^s(A(t - \tau_{MR}))
\end{aligned}
$$

Delayed quasi-steady state assumptions

UNIVERSITY OF OXFORD

Case 2:

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

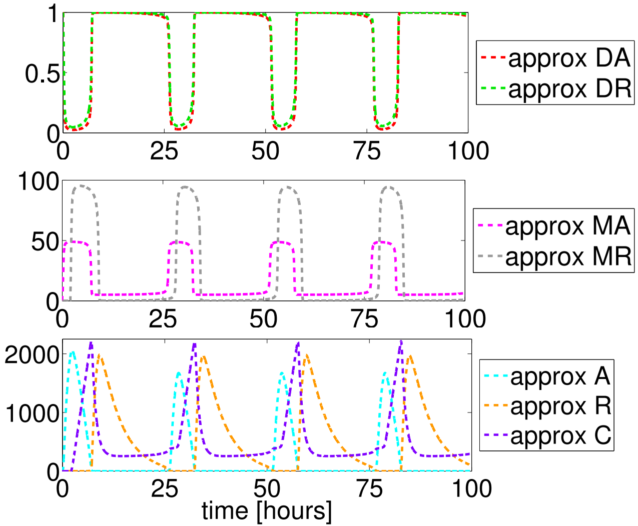
$$\tau_{DA}(t) = \left[\theta_A + \gamma_A \widetilde{A}^s(R(t))\right]^{-1}, \quad D_A^\tau(t) = D_A^s(A^\tau(t - \tau_{DA}(t)))$$
$$\tau_{DR}(t) = \left[\theta_R + \gamma_R \widetilde{A}^s(R(t))\right]^{-1}, \quad D_R^\tau(t) = D_R^s(A^\tau(t - \tau_{DR}(t)))$$
$$\tau_{MA}(t) = \delta_{MA}^{-1}, \quad M_A^\tau(t) = M_A^s(A^\tau(t - \tau_{MA}))$$
$$\tau_{MR}(t) = \delta_{MR}^{-1}, \quad M_R^\tau(t) = M_R^s(A^\tau(t - \tau_{MR}))$$

$$\tau_A(t) = [\gamma_A D_A(t) + \gamma_R D_R(t) + \gamma_C R(t) + \delta_A]^{-1}, \quad A^\tau(t) = A^s(t - \tau_A)$$

$$A^s(t) = \frac{\beta_A M_A^\tau(t) + \theta_A(1 - D_A^\tau(t)) + \theta_R(1 - D_R^\tau(t))}{\gamma_A D_A^\tau(t) + \gamma_R D_R^\tau(t) + \gamma_C R + \delta_A}$$

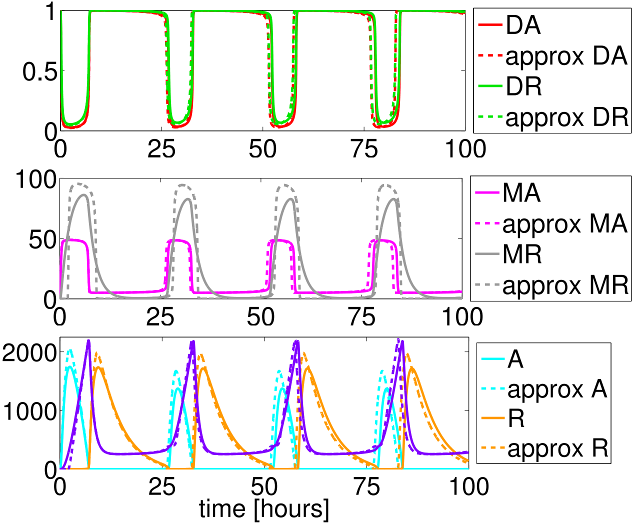
Case 1 (three ODEs)

D-QSS assumptions on D_A, D_R, M_A, M_R



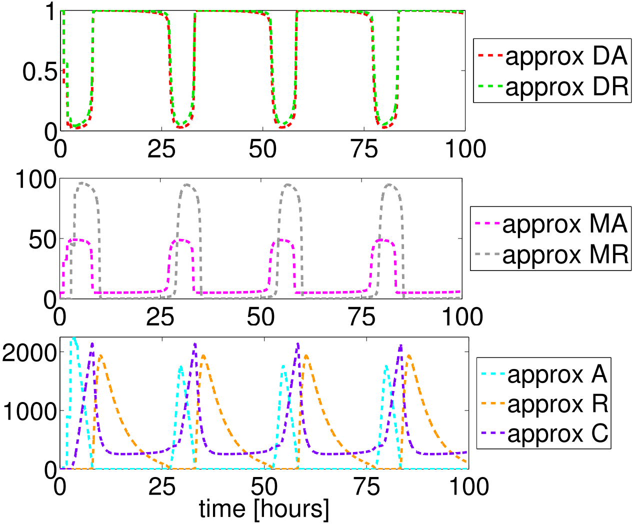
Case 1 (three ODEs)

D-QSS assumptions on D_A, D_R, M_A, M_R



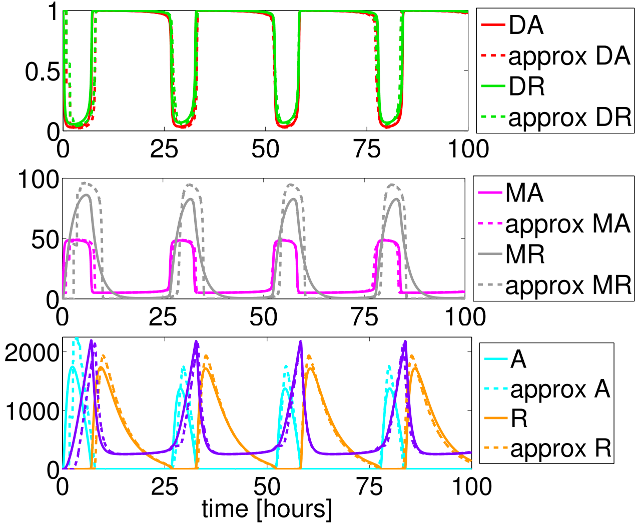
Case 2 (two ODEs)

D-QSS assumptions on D_A, D_R, M_A, M_R, A



Case 2 (two ODEs)

D-QSS assumptions on D_A, D_R, M_A, M_R, A

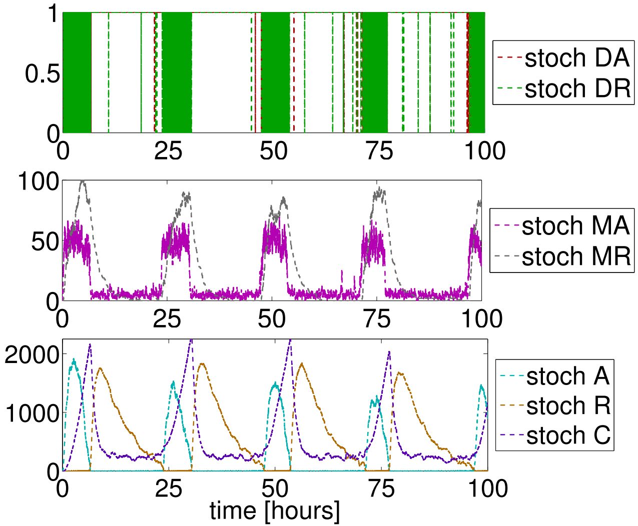


Comparison of QSS and D-QSS

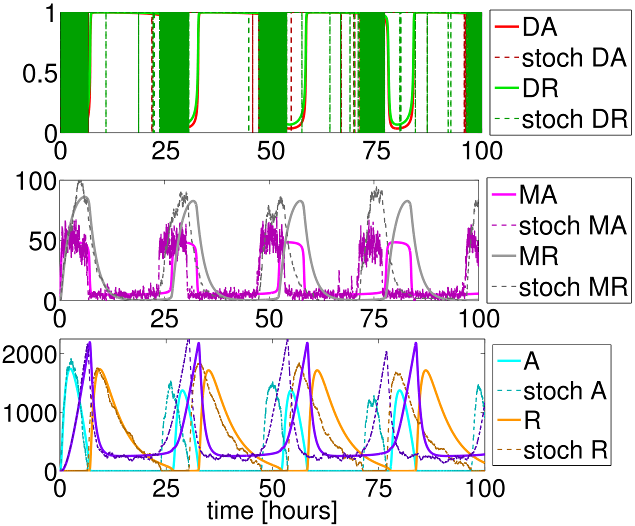
Period of the original system: 25.56 h

method	Rel Err Per	Rel Err L^2
Case 1 QSS	16.3 %	26 %
Case 2 QSS	29.8 %	93 %
Case 1 D-QSS	1.3 %	16 %
Case 2 D-QSS	1.7 %	19 %

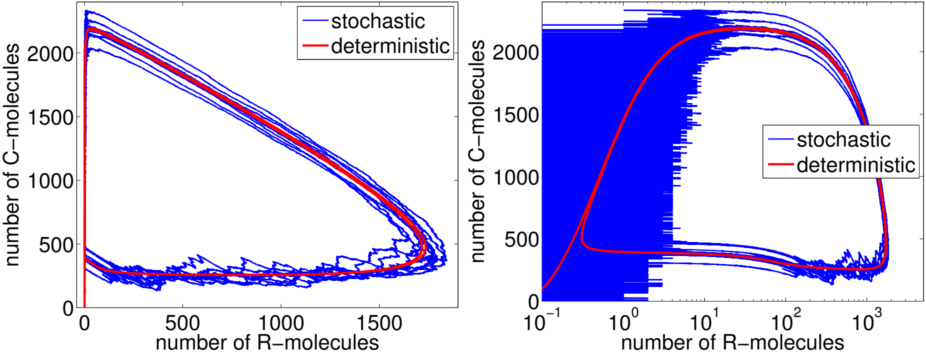
Gillespie SSA – full system



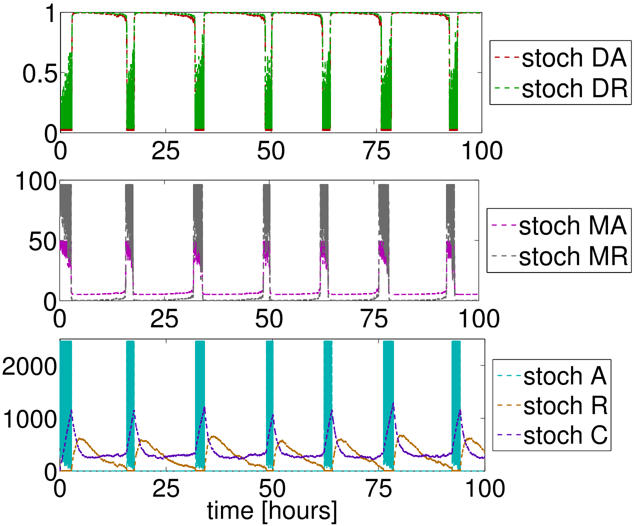
Gillespie SSA – full system



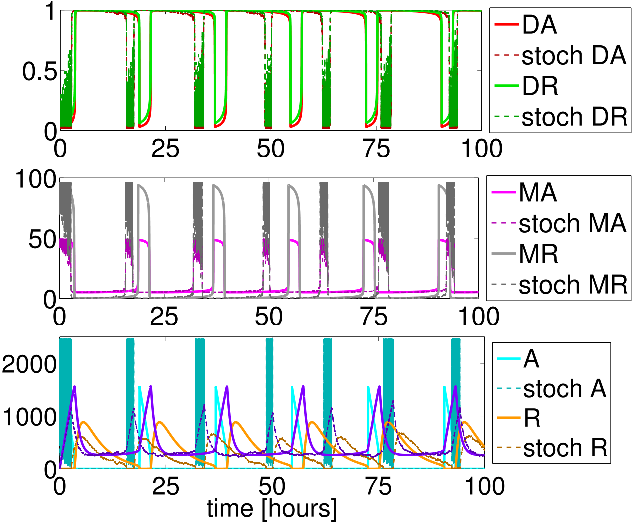
Gillespie SSA – full system



Gillespie SSA – QSSA, Case 2

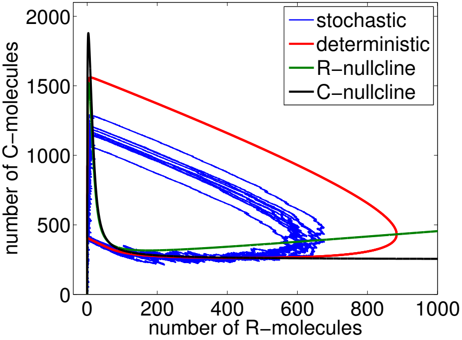


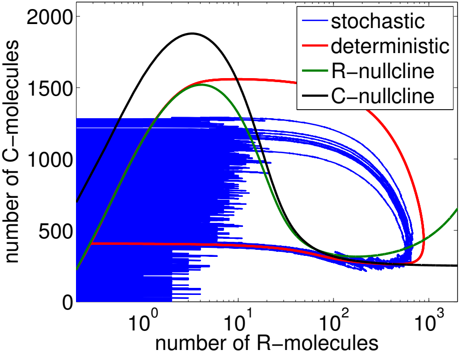
Gillespie SSA – QSSA, Case 2



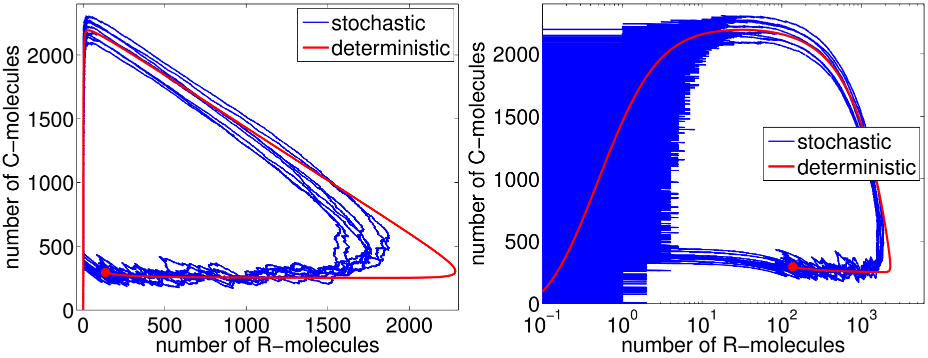
Gillespie SSA – QSSA, Case 2

Robustness with respect to noise





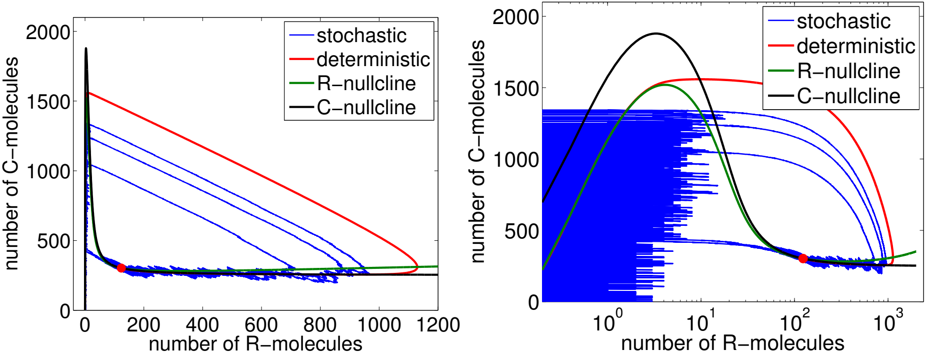
Gillespie SSA – full system, $\delta_R = 0.05$



Gillespie SSA – QSSA, Case 2, $\delta_R = 0.05$

UNIVERSITY OF OXFORD

Robustness with respect to noise



Period of stochastic oscillations (Case 2)

UNIVERSITY OF OXFORD

Stationary chemical Fokker-Planck equation:

$p_s(r,c)$ ... probability that $R(t) = r$ and $C(t) = c$ for $t \to \infty$

$$\frac{\partial^2}{\partial r^2}(\mathcal{A}_{RR} p_s) + 2\frac{\partial^2}{\partial r \partial c}(\mathcal{A}_{RC} p_s) + \frac{\partial^2}{\partial c^2}(\mathcal{A}_{CC} p_s) - \frac{\partial}{\partial r}(f_R p_s) - \frac{\partial}{\partial c}(f_C p_s) = 0$$

Boundary conditions: no flux

τ-equation:

$\tau(r,c)$ ... average time to leave domain S provided $R(0) = r$, $R(0) = c$

$$\mathcal{A}_{RR}\frac{\partial^2 \tau}{\partial r^2} + 2\mathcal{A}_{RC}\frac{\partial^2 \tau}{\partial r \partial c} + \mathcal{A}_{CC}\frac{\partial^2 \tau}{\partial c^2} + f_R \frac{\partial \tau}{\partial r} + f_C \frac{\partial \tau}{\partial c} = -1, \quad \text{in } S$$

Boundary conditions: no flux, if $r = 0$ or $c = 0$ and $\tau = 0$ elsewhere

Notation: $\mathcal{A}_{RR} = (\alpha_1(r) + \alpha_2(r) + \alpha_3(r) + \alpha_4(c))/2$,
$\mathcal{A}_{CC} = (\alpha_2(r) + \alpha_4(c))/2$, $\mathcal{A}_{RC} = -\mathcal{A}_{CC}$

Period of stochastic oscillations (Case 2)

UNIVERSITY OF OXFORD

Stationary chemical Fokker-Planck equation:

$p_s(r,c)$ ... probability that $R(t) = r$ and $C(t) = c$ for $t \to \infty$

$$\frac{\partial^2}{\partial r^2}(\mathcal{A}_{RR} p_s) + 2\frac{\partial^2}{\partial r \partial c}(\mathcal{A}_{RC} p_s) + \frac{\partial^2}{\partial c^2}(\mathcal{A}_{CC} p_s) - \frac{\partial}{\partial r}(f_R p_s) - \frac{\partial}{\partial c}(f_C p_s) = 0$$

Boundary conditions: no flux

τ-equation:

$\tau(r,c)$ ... average time to leave domain S provided $R(0) = r$, $R(0) = c$

$$\mathcal{A}_{RR}\frac{\partial^2 \tau}{\partial r^2} + 2\mathcal{A}_{RC}\frac{\partial^2 \tau}{\partial r \partial c} + \mathcal{A}_{CC}\frac{\partial^2 \tau}{\partial c^2} + f_R \frac{\partial \tau}{\partial r} + f_C \frac{\partial \tau}{\partial c} = -1, \quad \text{in } S$$

Boundary conditions: no flux, if $r = 0$ or $c = 0$ and $\tau = 0$ elsewhere

Approximation of the period: $T(\gamma) = \dfrac{\int_\gamma \tau(r,c) p_s(r,c) \mathrm{d}r\mathrm{d}c}{\int_\gamma p_s(r,c)\mathrm{d}r\mathrm{d}c}$

γ ... a suitable subdomain of S (e.g. a line)

Summary

- Theoretical model of circadian rhythms (VKLB)
- Model reduction
- Quasi steady state assumptions
- Delayed quasi steady state assumptions
- Robustness of oscillations with respect to noise
- Period of stochastic oscillations

Acknowledgement

I am thankful to Radek Erban and Philip K. Maini for their support and fruitful discussions about the topics presented during this summer school.

Marie Curie Fellowship, StochDetBioModel

The research leading to these results has received funding from the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement no. 328008.

Thank you for your attention

Tomáš Vejchodský

Centre for Mathematical Biology
Mathematical Institute

UNIVERSITY OF OXFORD

Summer school, Prague, 6–8 August, 2013