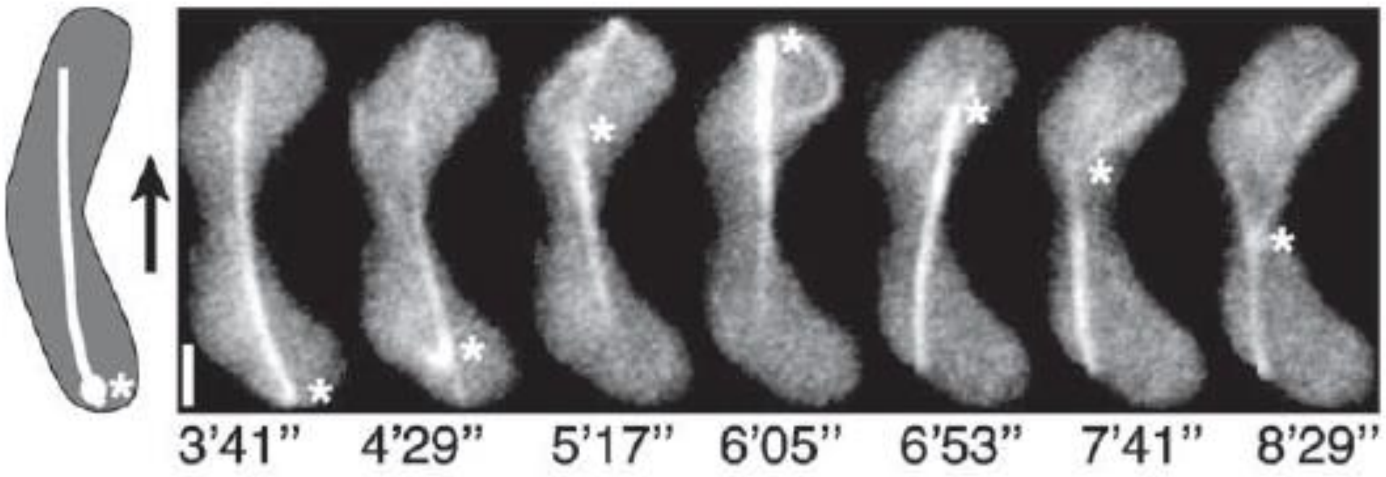
Oscilacije jezgre pokretane dineinima

AGNEZA BOSILJ
MENTOR: IZV. PROF. DR. SC. NENAD PAVIN

Biološka motivacija

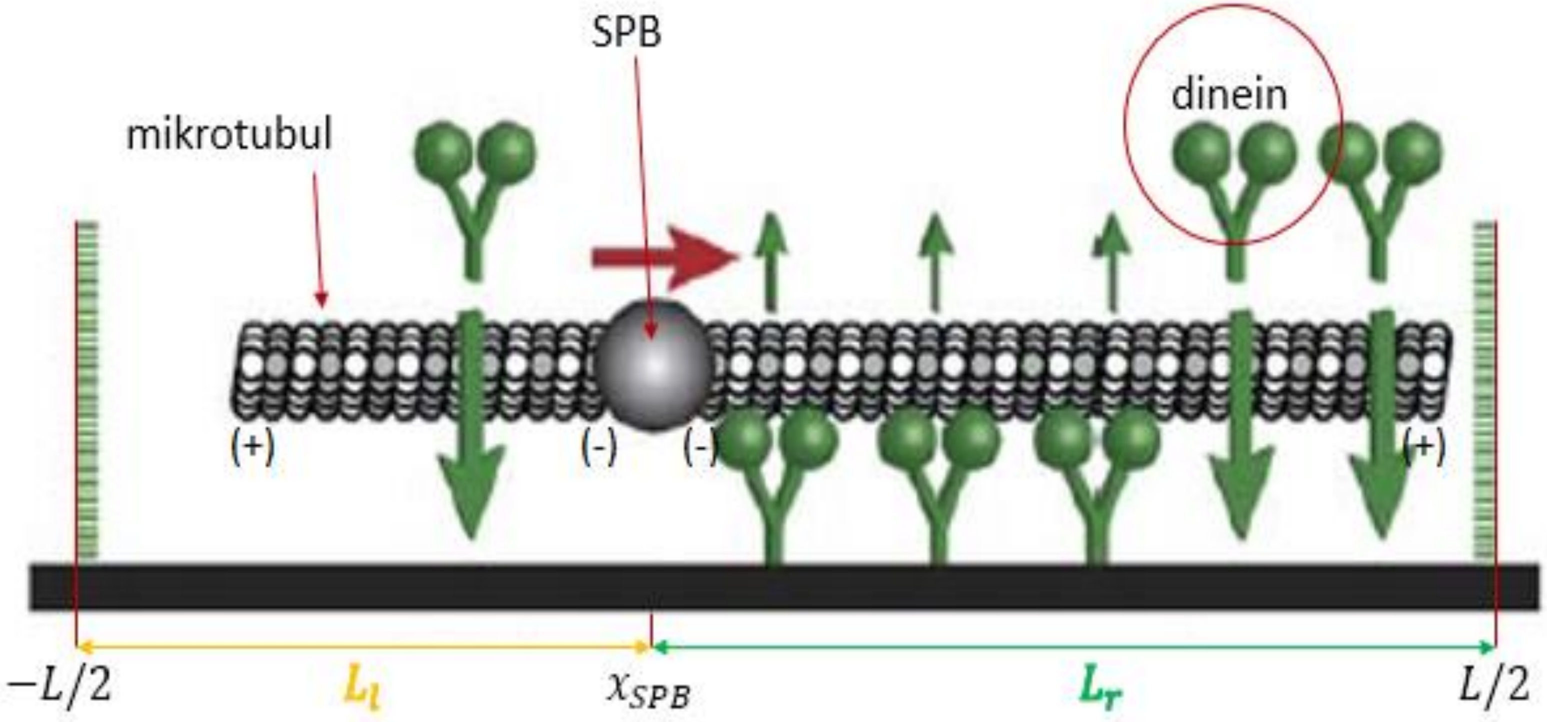
- razmnožavanje bioloških organizama uključuje miješanje genetskog materijala tijekom mejoze
- miješanje i rekombinacija kromosoma zahtijeva koordinirano gibanje stanične jezgre *(kvasac S. pombe)*



Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009) Self-organization of dynein motors generates meiotic nuclear oscillations. PLoS Biol 7(4):e1000087. doi:10.1371/journal.pbio.1000087

Promatrani biološki sustav

- SPB (engl. *spindle pole body*)
- dineini (proteinski motori)
- mikrotubuli



Definicija modela

- dinamika mikrotubula: $$\frac{dL_{l,r}}{dt} = v_{s,g}$$
- dinamika SPB-a u *overdamped* režimu: $$\xi \frac{dx_{SPB}}{dt} = F_l + F_r$$
- sile koje dineini vrše na mikrotubule: $$F_{l,r} = N_{l,r} f_{l,r}$$

DINAMIKA MOTORA

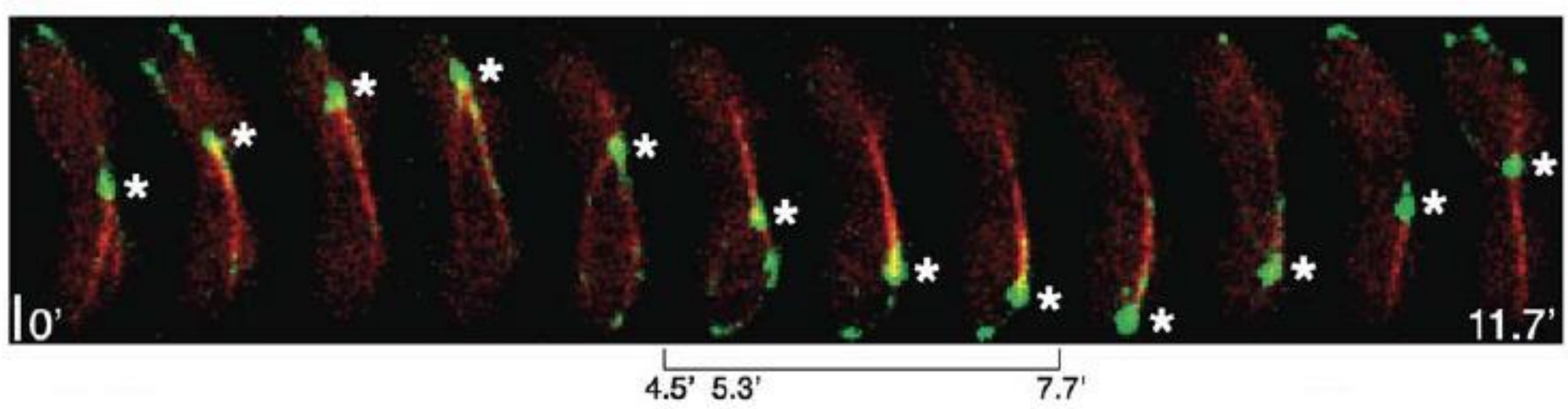
- linearna veza sila-brzina za dineine: $v = v_0(\pm 1 + f_{l,r}/f_0)$

- linearne gustoće dineina spojenih na mikrotubule: $n_{l,r} = N_{l,r}/L_{l,r}$

- kinetičke jednadžbe za linearne gustoće dineina: $\frac{dn_{l,r}}{dt} = k_{on}c - k_{off}(\mp f_{l,r})n_{l,r}$

DINAMIKA MOTORA

- brzina odvajanja dineina ovisna o opterećenju: $k_{off}(f) = k_0 exp(f/f_c)$



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Rješenja modela

$$\frac{dL_{l,r}}{dt} = v_{s,g} \longrightarrow L_{l,r} = L/2 \pm x_{SPB}$$

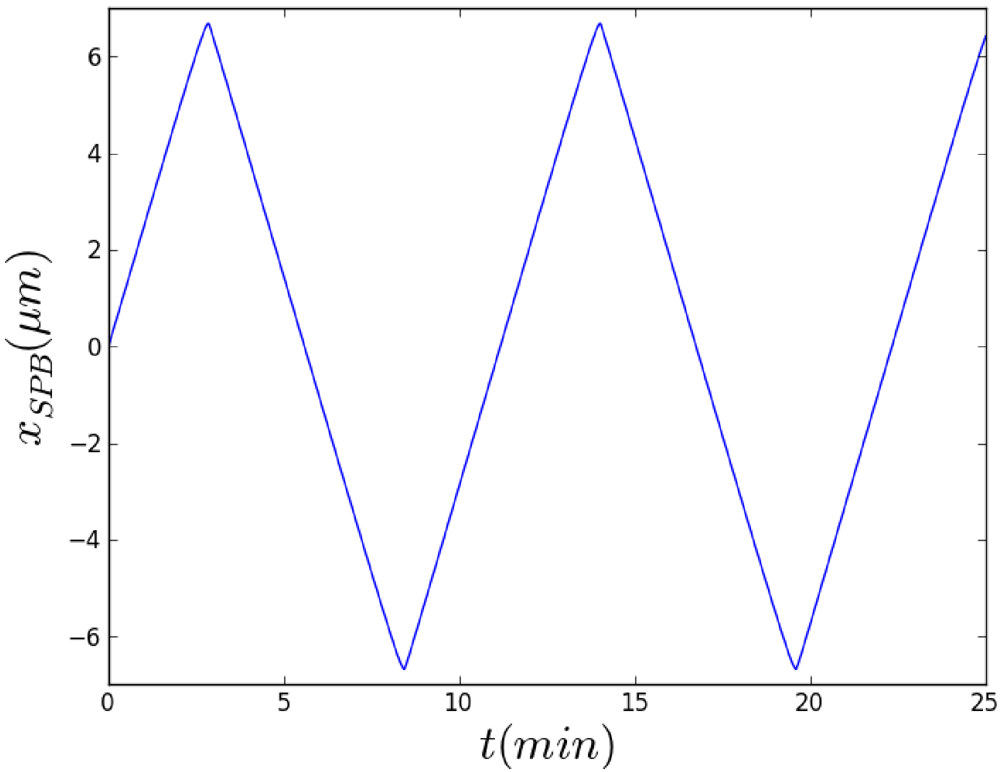
- brzina motora u odnosu na mikrotubule, tj. SPB: $v = -v_{SPB} = -\frac{dx_{SPB}}{dt}$

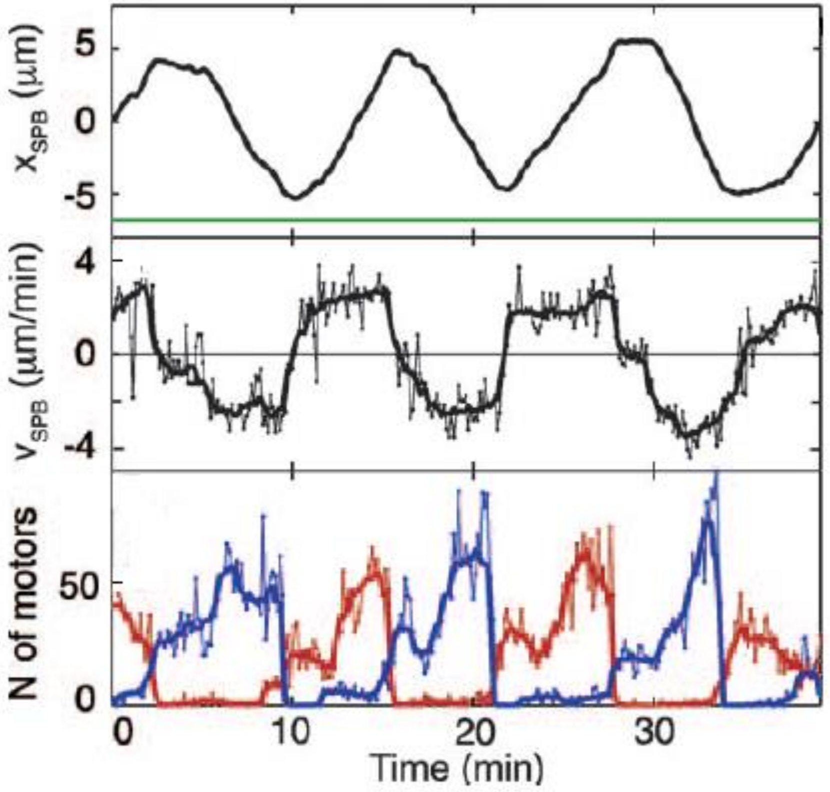
$$\frac{dx_{SPB}}{dt} = \frac{v_0 f_0 \left[n_r \left(\frac{L}{2} - x_{SPB}\right) - n_l \left(\frac{L}{2} + x_{SPB}\right)\right]}{\xi v_0 + f_0 \left[n_r \left(\frac{L}{2} - x_{SPB}\right) + n_l \left(\frac{L}{2} + x_{SPB}\right)\right]}$$

$$\frac{dn_r}{dt} = k_{on}c - n_r k_0 exp \left\{ \frac{f_0}{f_c} \left[1 - \frac{f_0 \left(n_r \left(\frac{L}{2} - x_{SPB}\right) - n_l \left(\frac{L}{2} + x_{SPB}\right)\right)}{\xi v_0 + f_0 \left(n_r \left(\frac{L}{2} - x_{SPB}\right) + n_l \left(\frac{L}{2} + x_{SPB}\right)\right)} \right] \right\}$$

$$\frac{dn_l}{dt} = k_{on}c - n_l k_0 exp \left\{ \frac{f_0}{f_c} \left[1 + \frac{f_0 \left(n_r \left(\frac{L}{2} - x_{SPB}\right) - n_l \left(\frac{L}{2} + x_{SPB}\right)\right)}{\xi v_0 + f_0 \left(n_r \left(\frac{L}{2} - x_{SPB}\right) + n_l \left(\frac{L}{2} + x_{SPB}\right)\right)} \right] \right\}$$

Rješenja modela

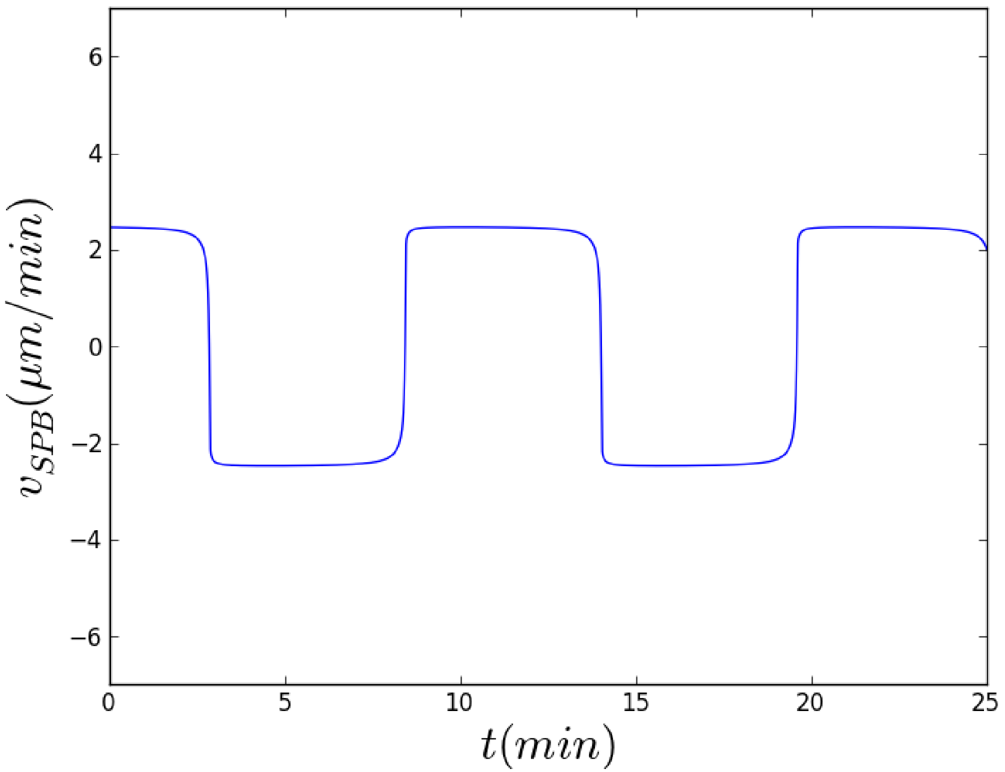


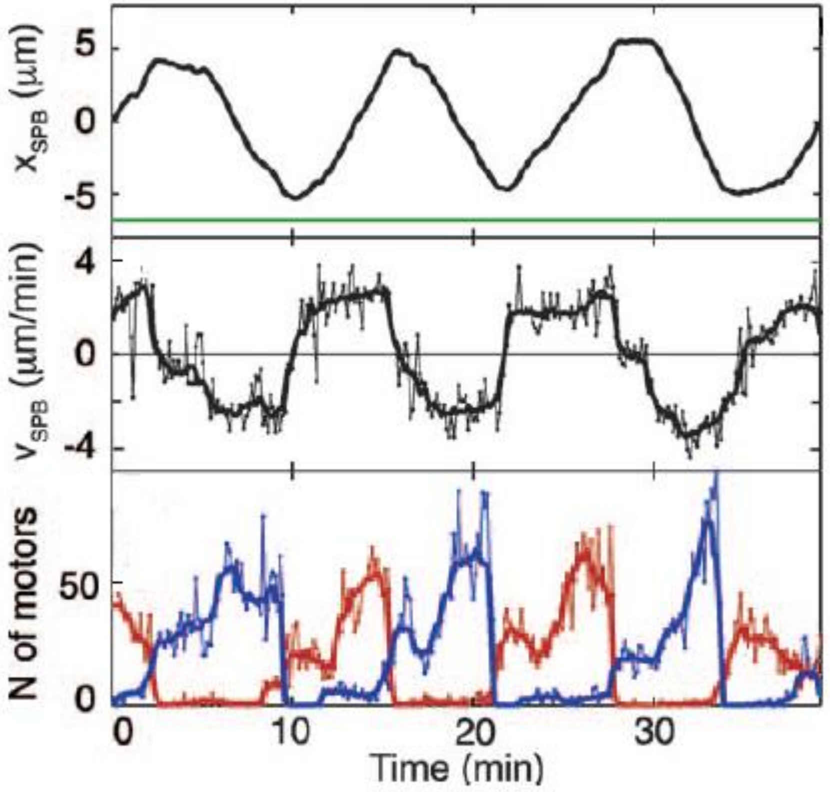


[1]

L	v_0	f_0	$k_{on}c$	k_0	f_c	ξ
$14\mu m$	$2.5\mu m/min$	$7pN$	$0.1\mu m^{-1}s^{-1}$	$0.01s^{-1}$	$2pN$	$100pNs\mu m^{-1}$

Rješenja modela





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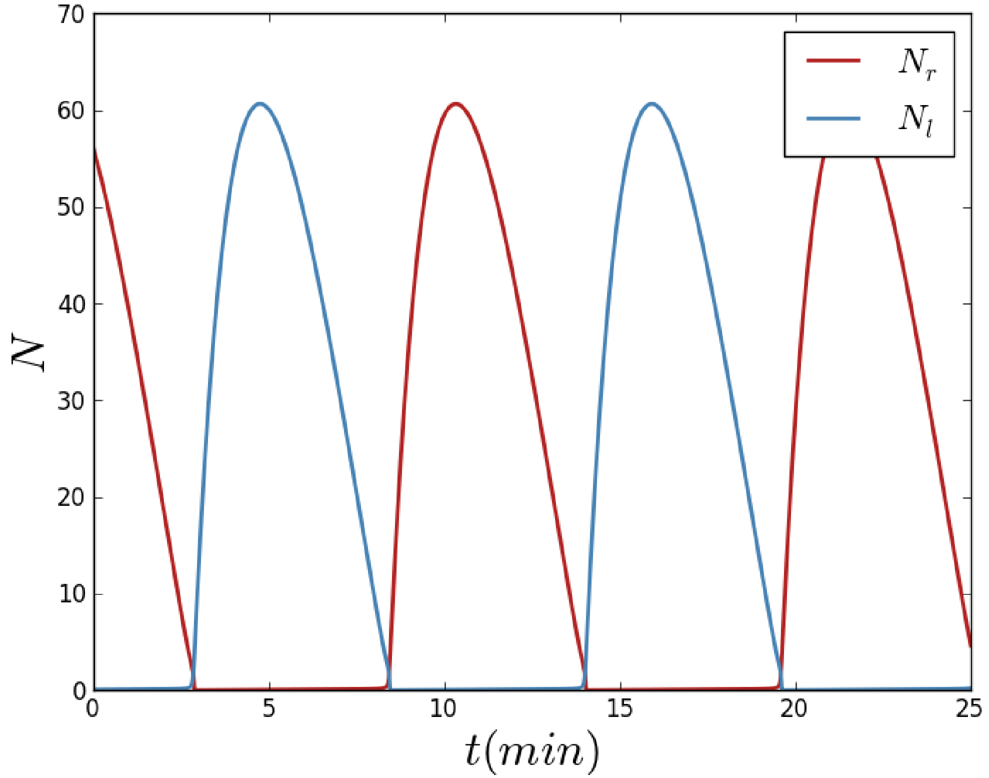

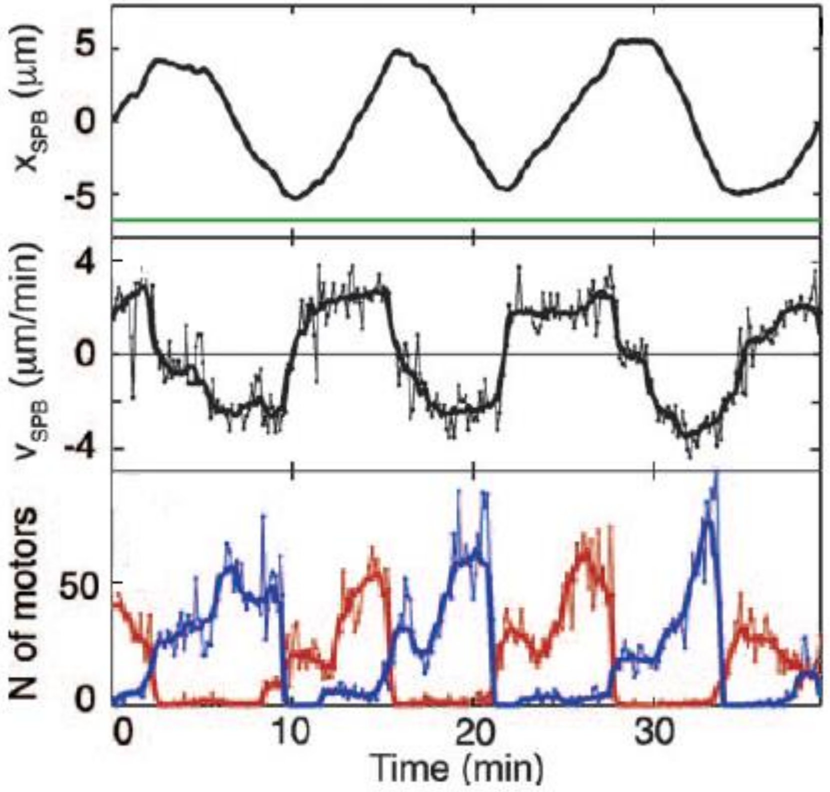

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Parametarski prostor

- nelinearni dinamički sustavi koji ovise o parametrima mogu pokazivati vrlo složena ponašanja u slučaju promjene nekog parametra
- analizom linearne stabilnosti dobivamo više informacija o ponašanju sustava u slučaju variranja parametara

Analiza linearne stabilnosti

- za sistem dan sa:

$$\dot{x} = f_1(x, y, z)$$
$$\dot{y} = f_2(x, y, z)$$
$$\dot{z} = f_3(x, y, z)$$

- potrebno je pronaći fiksnu točku: $(\dot{x} = 0, \dot{y} = 0, \dot{z} = 0) \longrightarrow (x^*, y^*, z^*)$

- uvodimo male perturbacije:

$$x(t) = x^* + \hat{x}(t)$$
$$y(t) = y^* + \hat{y}(t)$$
$$z(t) = z^* + \hat{z}(t)$$

- Taylorovim razvojem novih diferencijalnih jednadžbi oko fiksne točke do 1. reda dobivamo:

$$\frac{d}{dt}\begin{pmatrix}\hat{x}(t)\\ \hat{y}(t)\\ \hat{z}(t)\end{pmatrix} = \begin{pmatrix}\frac{\partial f_1}{\partial x} & \frac{\partial f_1}{\partial y} & \frac{\partial f_1}{\partial z}\\ \frac{\partial f_2}{\partial x} & \frac{\partial f_2}{\partial y} & \frac{\partial f_2}{\partial z}\\ \frac{\partial f_3}{\partial x} & \frac{\partial f_3}{\partial y} & \frac{\partial f_3}{\partial z}\end{pmatrix}\Bigg|_{F.P.} \begin{pmatrix}\hat{x}(t)\\ \hat{y}(t)\\ \hat{z}(t)\end{pmatrix}$$

- općenito rješenje linearnog sustava diferencijalnih jednadžbi dano je oblikom:

$$\begin{pmatrix} \hat{x}(t) \\ \hat{y}(t) \\ \hat{z}(t) \end{pmatrix} = \begin{pmatrix} \hat{x}^{(1)} \\ \hat{y}^{(1)} \\ \hat{z}^{(1)} \end{pmatrix} e^{\lambda_1 t} + \begin{pmatrix} \hat{x}^{(2)} \\ \hat{y}^{(2)} \\ \hat{z}^{(2)} \end{pmatrix} e^{\lambda_2 t} + \begin{pmatrix} \hat{x}^{(3)} \\ \hat{y}^{(3)} \\ \hat{z}^{(3)} \end{pmatrix} e^{\lambda_3 t}$$

Hopfova bifurkacija

(Poincaré–Andronov–Hopf bifurcation [2])

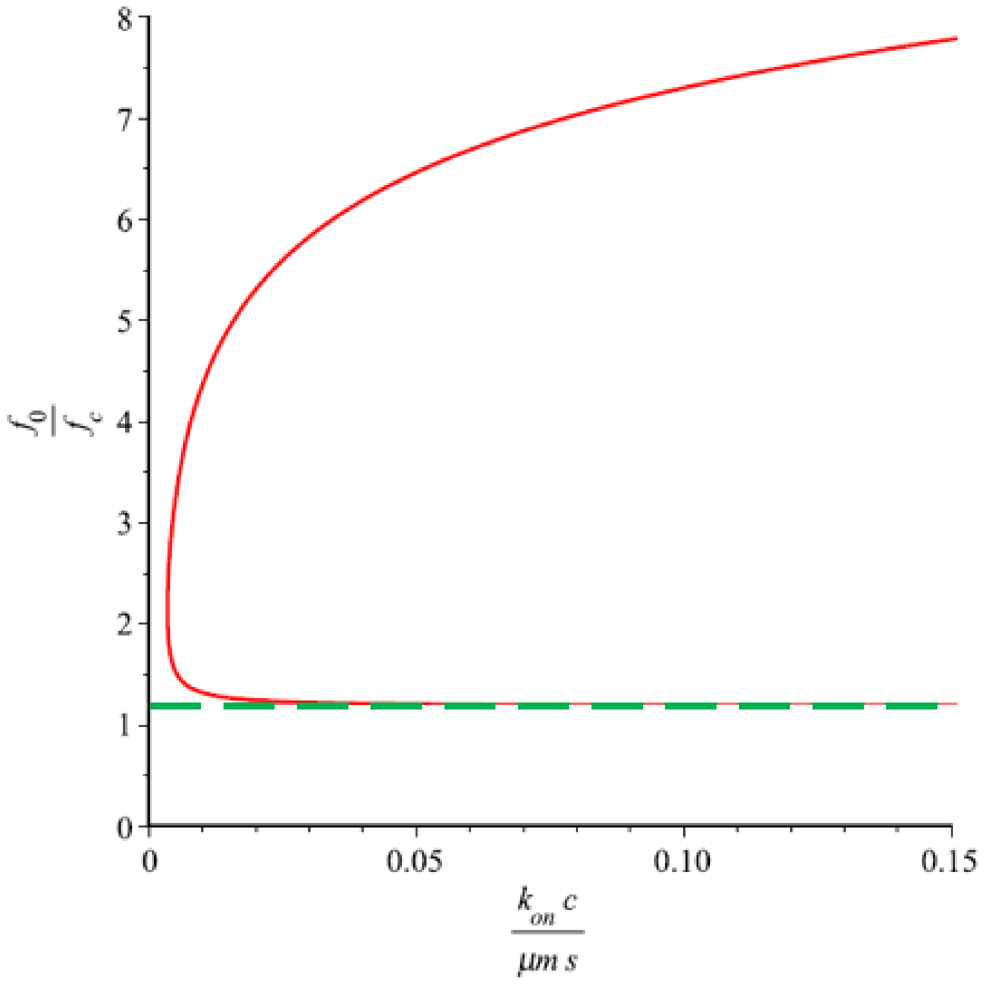
- pojavu ili nestajanje periodične orbite tijekom lokalne promjene u svojstvima stabilnosti fiksne točke nazivamo Hopfovom bifurkacijom

- za pojavu Hopfove bifurkacije nužno je da sve svojstvene vrijednosti imaju negativni realni dio osim para čisto kompleksno konjugiranih svojstvenih vrijednosti

$$\lambda_1 \to -\alpha \quad \lambda_{2,3} \to \pm i\beta$$

PARAMETAR	OPIS	IZNOS	IZVOR
L	duljina stanice	$14\mu m$	mjereno
v_0	brzina u odsutnosti sile	$2.5\mu m/min$	mjereno
f_0	sila otpora	$7pN$	[1]
$k_{on}c$	brzina prijanjanja po jedinici duljine	$0.1\mu m^{-1}s^{-1}$ $(0.08 - 10)$	varijabilno
k_0	brzina odvajanja u odsutnosti opterećenja	$0.01s^{-1}$ $(0.001 - 0.1)$	varijabilno
f_c	karakteristična sila	$2pN$	varijabilno
ξ	koeficijent trenja	$100pNs\mu m^{-1}$	[1]

Rezultati analize



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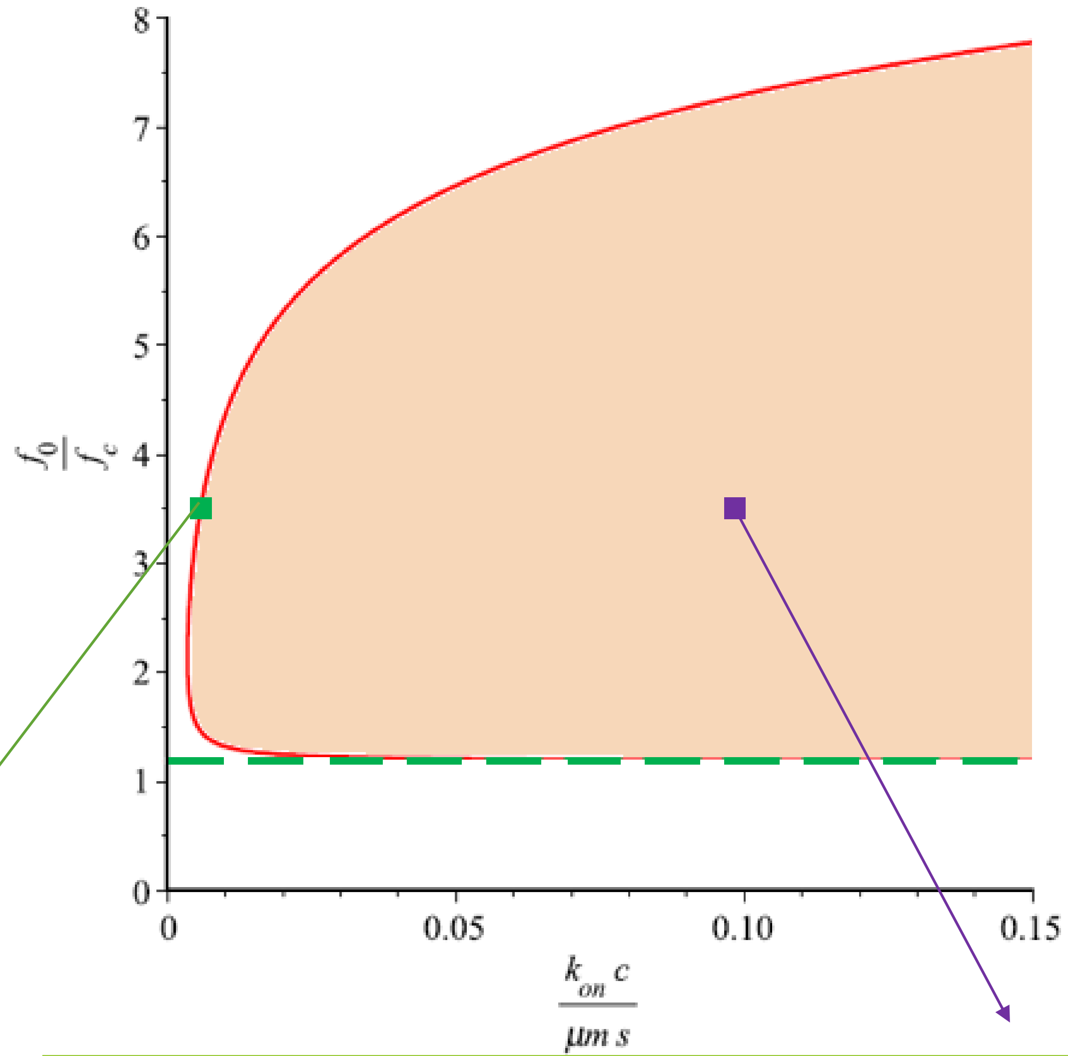
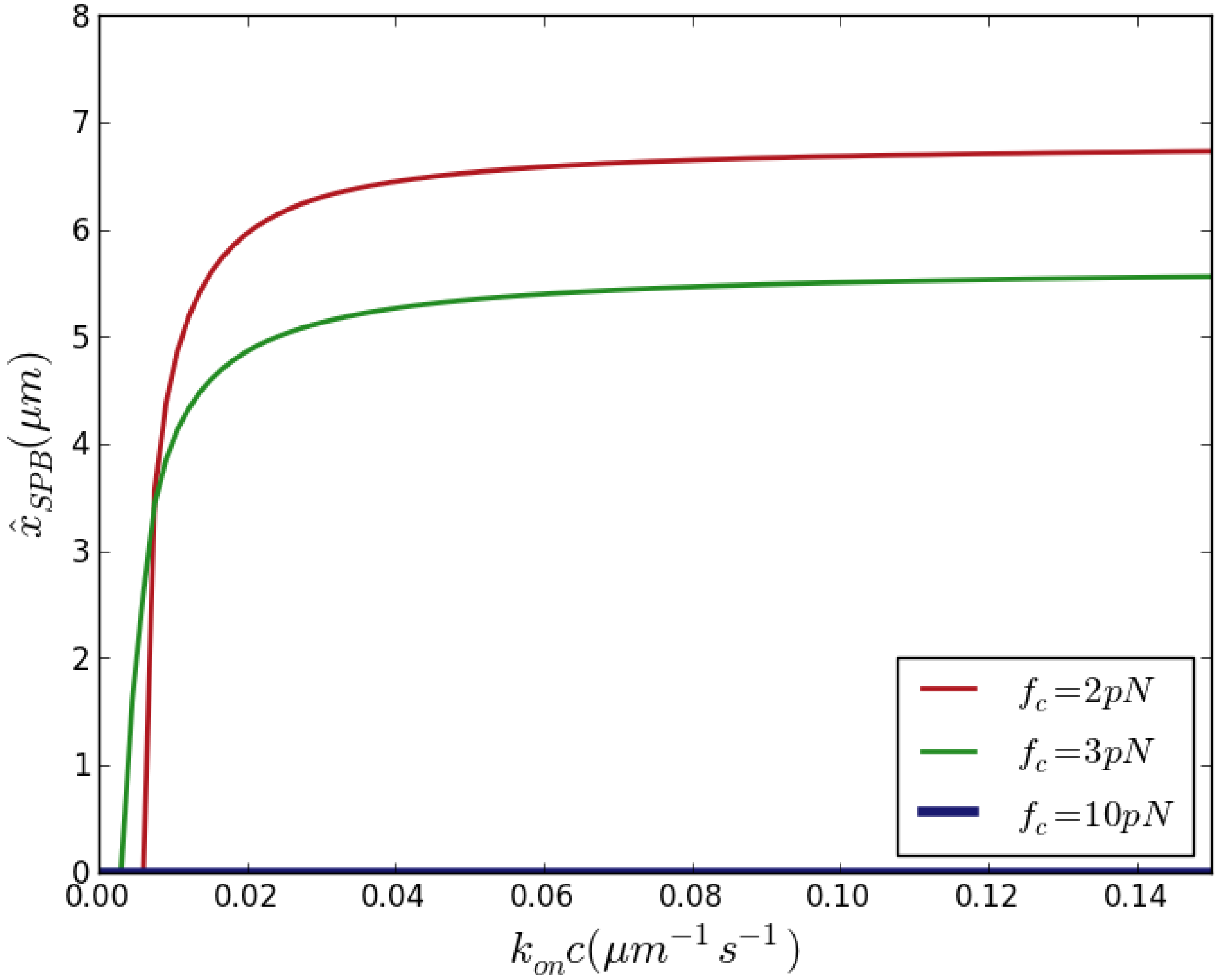


$k_{on}c = 0.00567\mu m^{-1}s^{-1}$

L	v_0	f_0	$k_{on}c$	k_0	f_c	ξ
$14\mu m$	$2.5\mu m/min$	$7pN$	$0.1\mu m^{-1}s^{-1}$	$0.01s^{-1}$	$2pN$	$100pNs\mu m^{-1}$

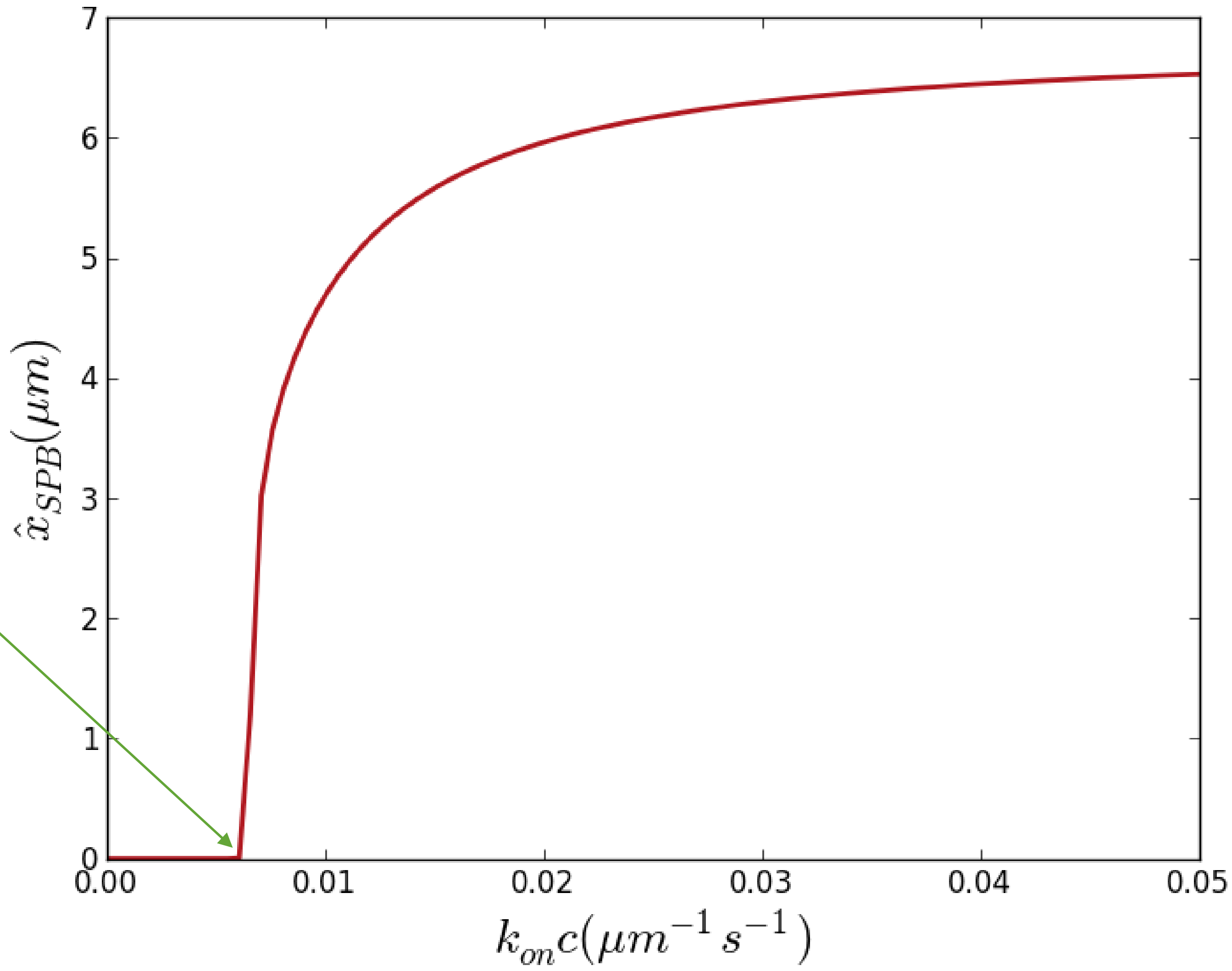
Ovisnost amplitude oscilacija $\hat{x}_{SPB}$ o promjeni parametra $k_{on}c$ za odabrane vrijednosti parametra f_c:



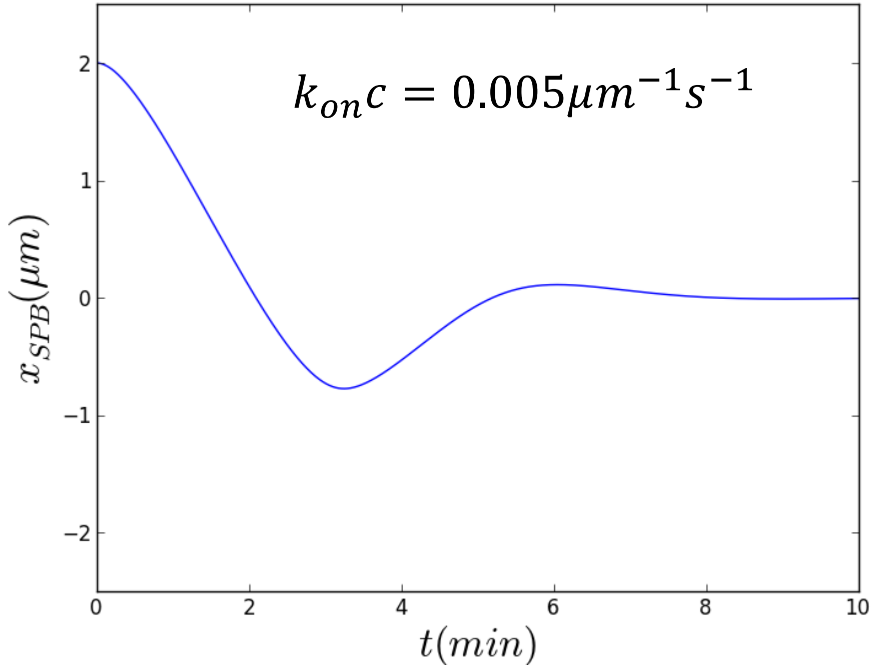
L	v_0	f_0	k_0	f_c	ξ
$14\mu m$	$2.5\mu/min$	$7pN$	$0.01s^{-1}$	$2pN$	$100pNs\mu m^{-1}$

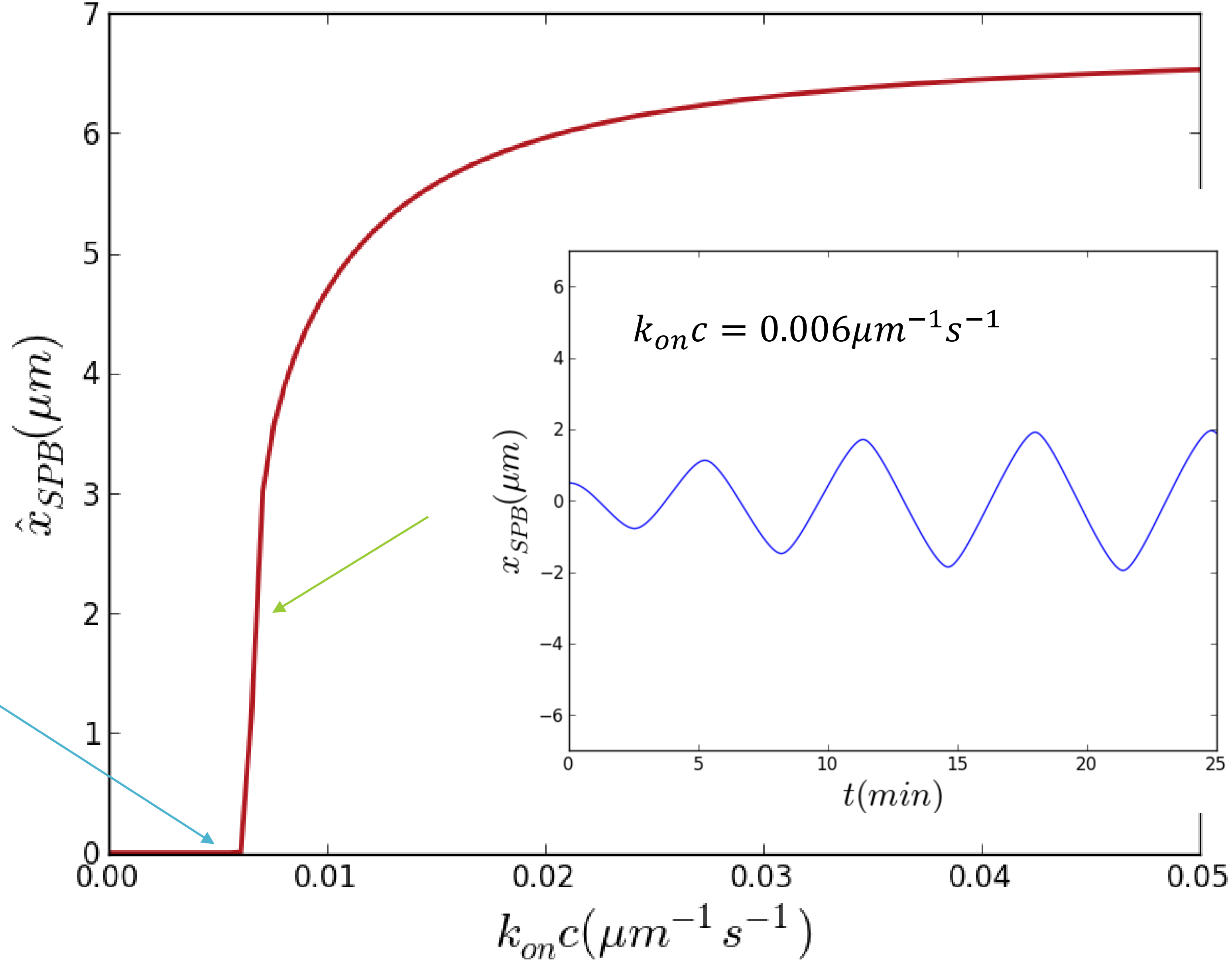
Bifurkacijska vrijednost:

$k_{on}c = 0.00567\mu m^{-1}s^{-1}$

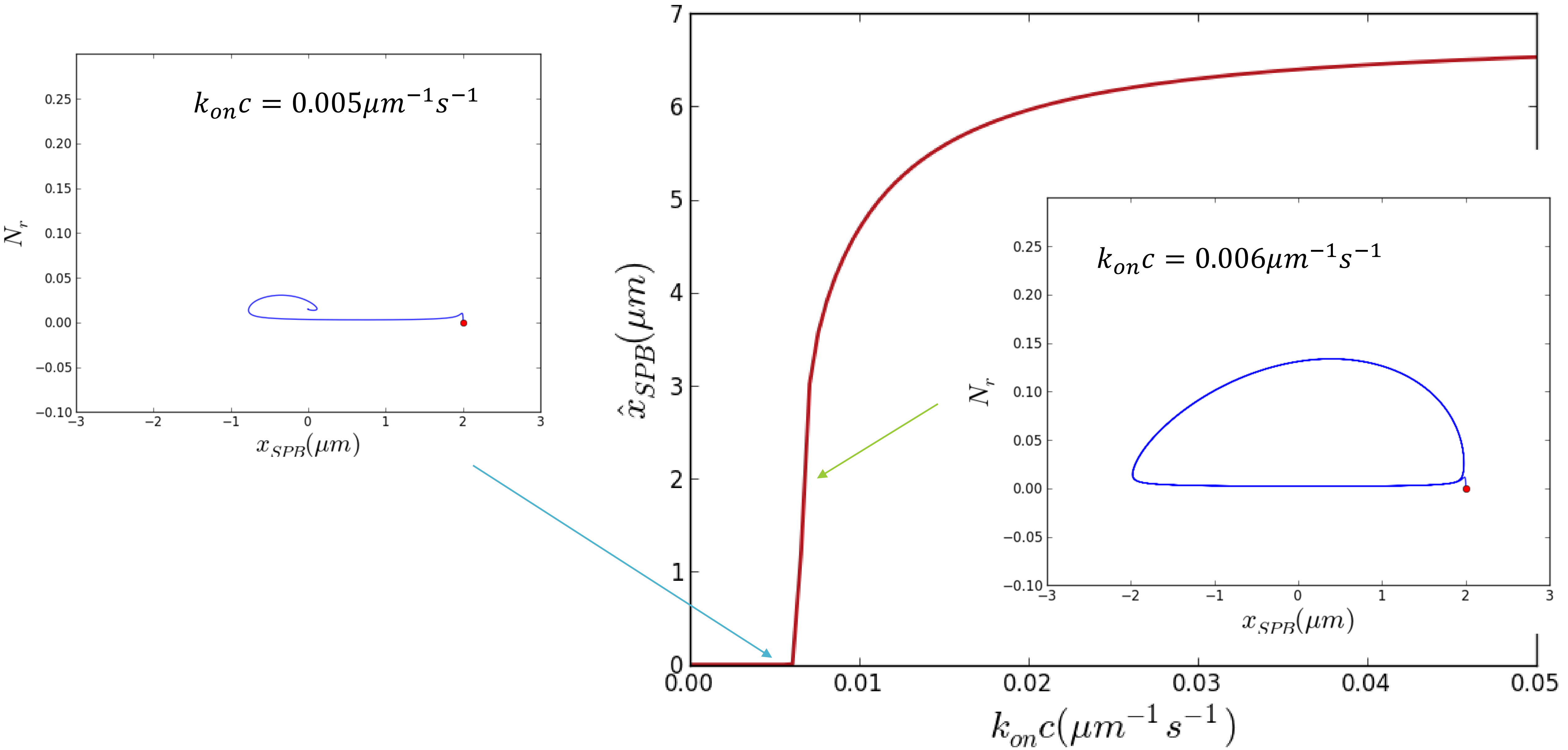


Promjena režima oscilacija s prelaskom preko bifurkacijske vrijednosti



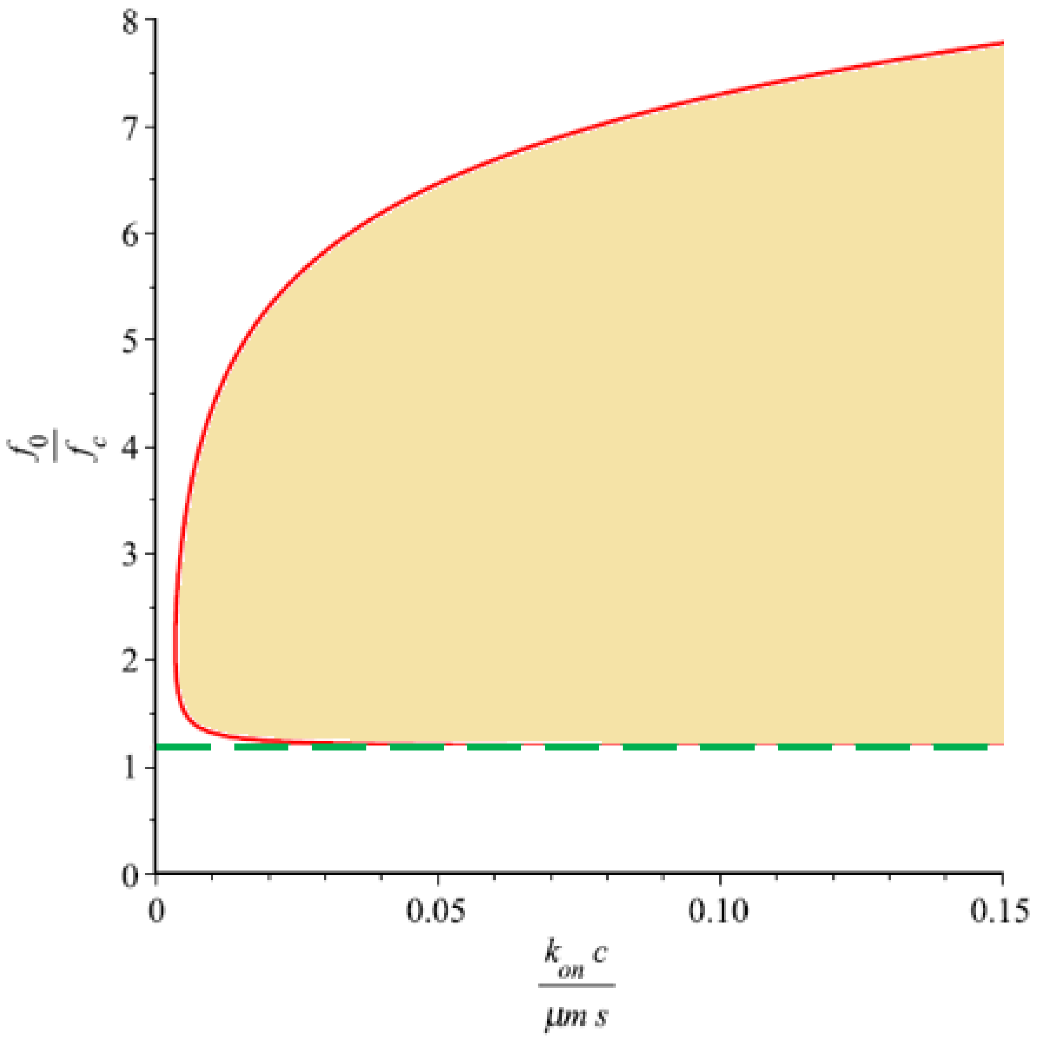


Razvoj *limit cyclea* s prelaskom preko bifurkacijske vrijednosti



Zaključak

- linearnom analizom stabilnosti dobivene su teorijske vrijednosti parametara $k_{on}c$ i f_c koje uvrštene u model daju stabilna periodička rješenja



Literatura

[1] Vogel SK, Pavin N, Maghelli N, Jülicher F, Tolić-Nørrelykke IM (2009) Self-organization

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doi:10.1371/journal.pbio.1000087

[2] Marsden JE, McCracken M (1976) The Hopf bifurcation and its applications. Springer-Verlag New York Inc.

Zahvala!

Zahvaljujem mentoru izv. prof. dr. sc. Nenadu Pavinu za svu pomoć pri izradi ovog rada!