A Multiple Spring Model that Predicts Bipedal Locomotion of Crawling Cells

Alex Loosley and Jay X. Tang, Physics Department
Brown University, Providence RI

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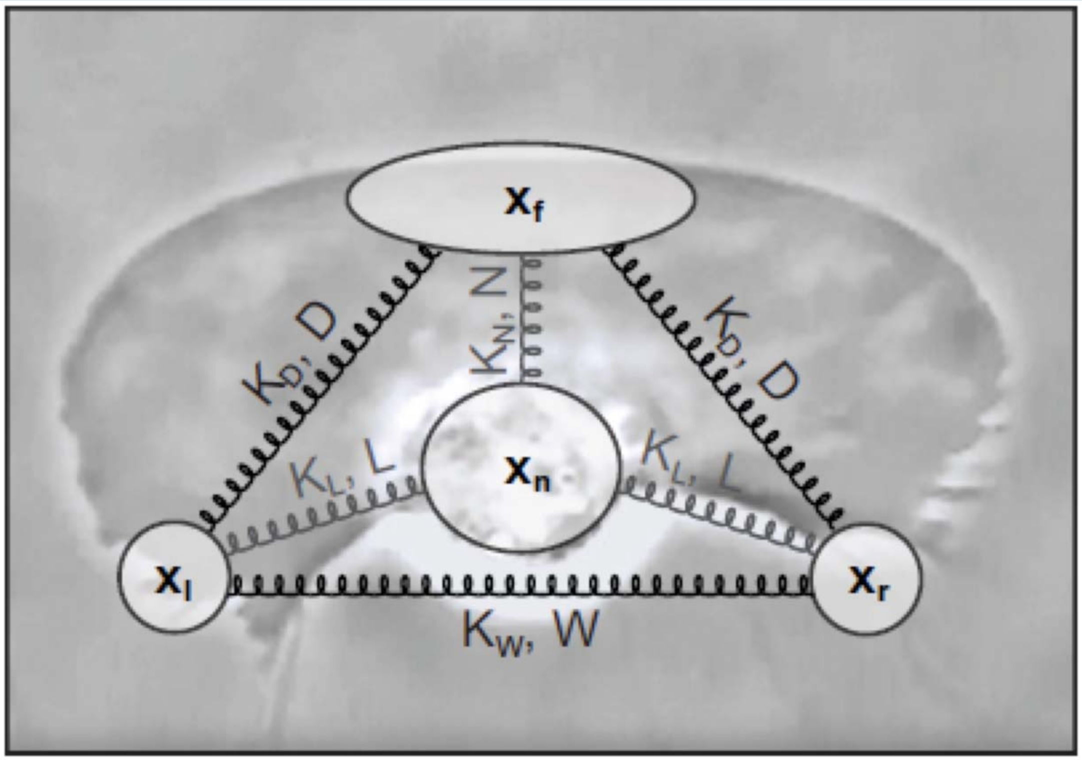
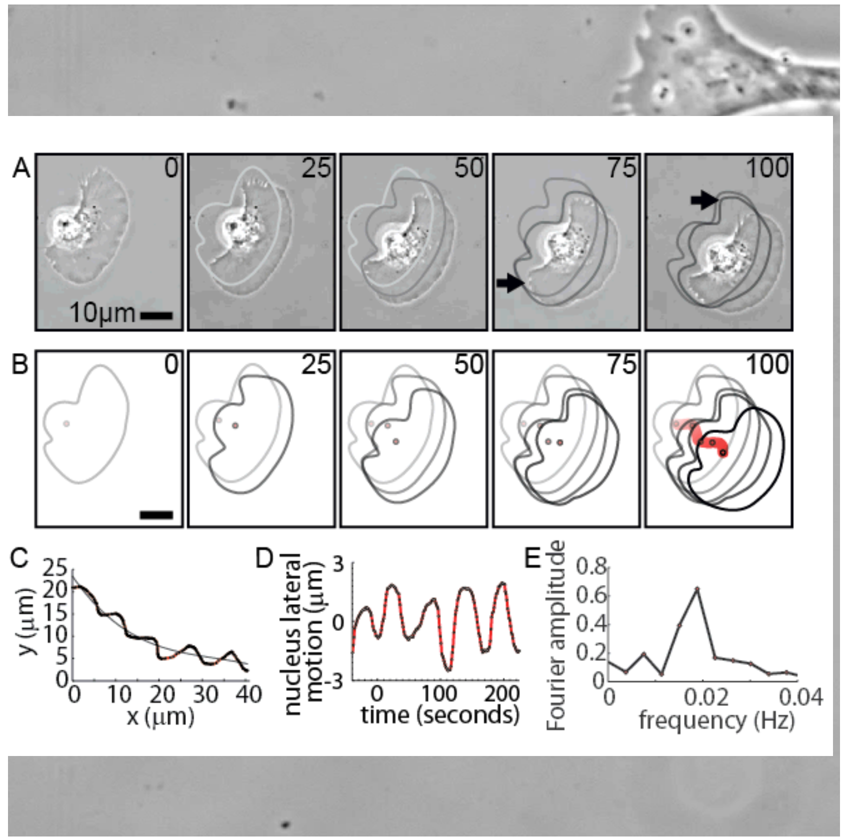


Fish Keratocyte Dynamics

- Front edge extends forward at constant speed (here 0.17 μm/s)
- Cell body contracts in alternate steps from both left and right sides of trailing edge
- Nucleus swings from side to side as the cell crawls forward



E. Barnhart , G. Allen, F. Julicher, J. Theriot, Biophys J, **98**, 933-942 (2010)

Crawling and the 1D Model

1) Actin polymerization occurs at the leading edge of cell to protrude the cell forward
2) Contractile forces generated within cytoskeleton pull the rear forward

Leading Edge: x_1, $\dot{x}_1 = v_f$

Trailing Edge: x_2

Spring represents elastic coupling between elements x_1 and x_2

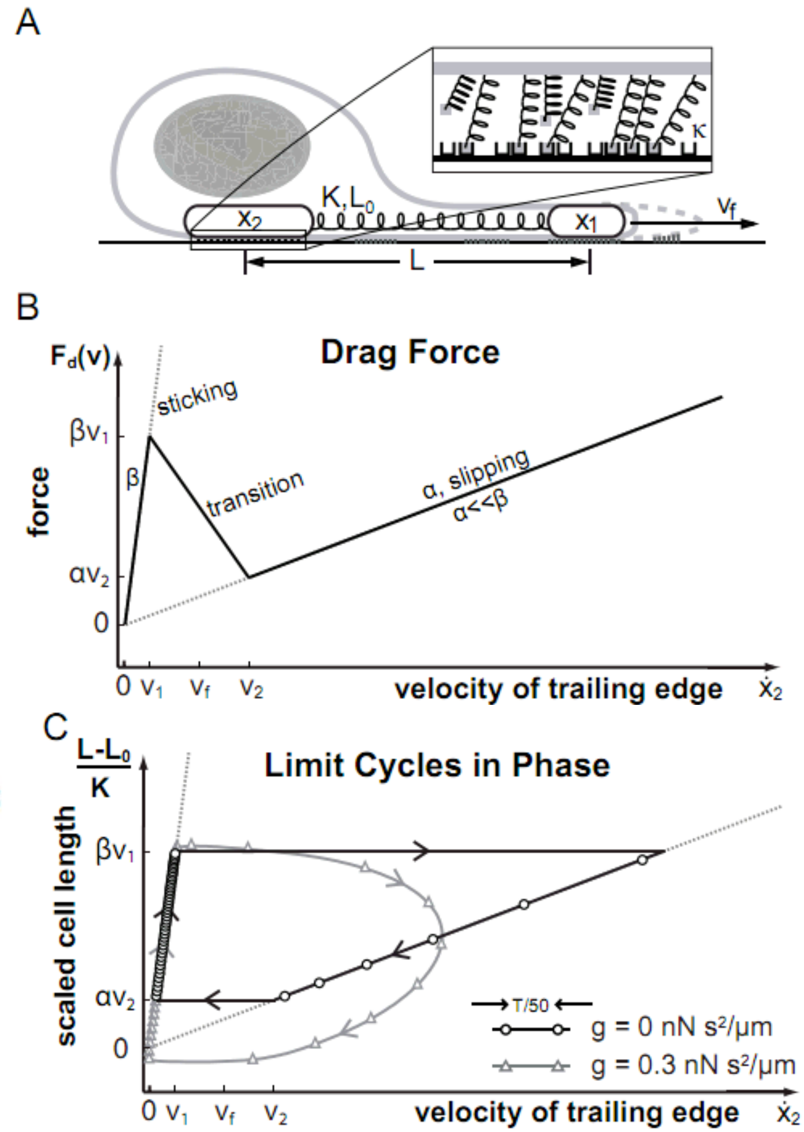
Expression of the Drag Force

$$F_d[\dot{x}_2] = \begin{cases} -\beta \dot{x}_2\,, & \dot{x}_2 < v_1 \\ \frac{v_1 - \dot{x}_2}{v_1 - v_2}(\beta v_1 - \alpha v_2) - \beta v_1\,, & v_1 < \dot{x}_2 < v_2 \\ -\alpha \dot{x}_2\,, & v_2 < \dot{x}_2 \end{cases}$$

Equations of Motion

$$\dot{x}_1 = v_f$$

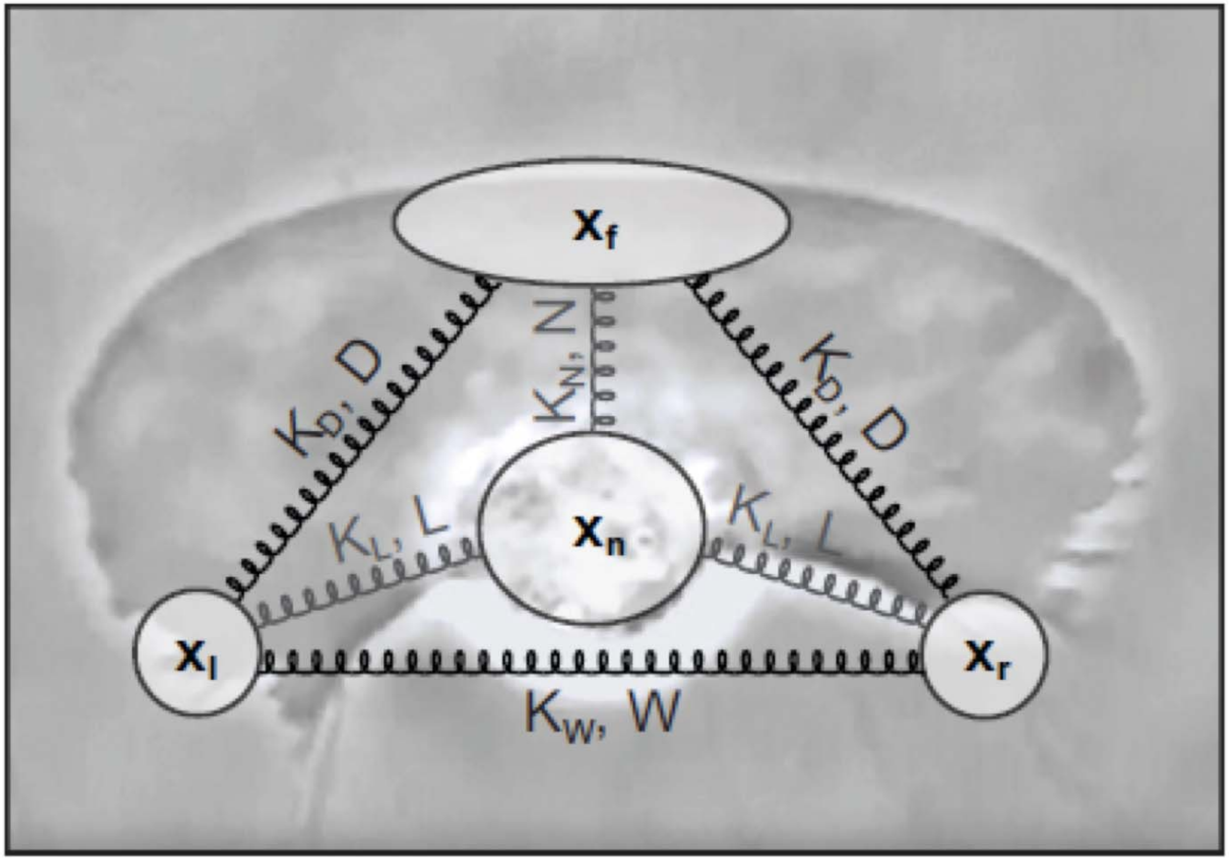
$$g\ddot{x}_2 - F_d[\dot{x}_2] - K(L - L_0) = 0$$



The 2D Model

General criteria

- Minimal number of components are introduced in the model
- Cell front moves with constant speed
- No asymmetry between left and right is required
-
- Left and right rears can move out of phase
- The nuclear position is shown explicitly



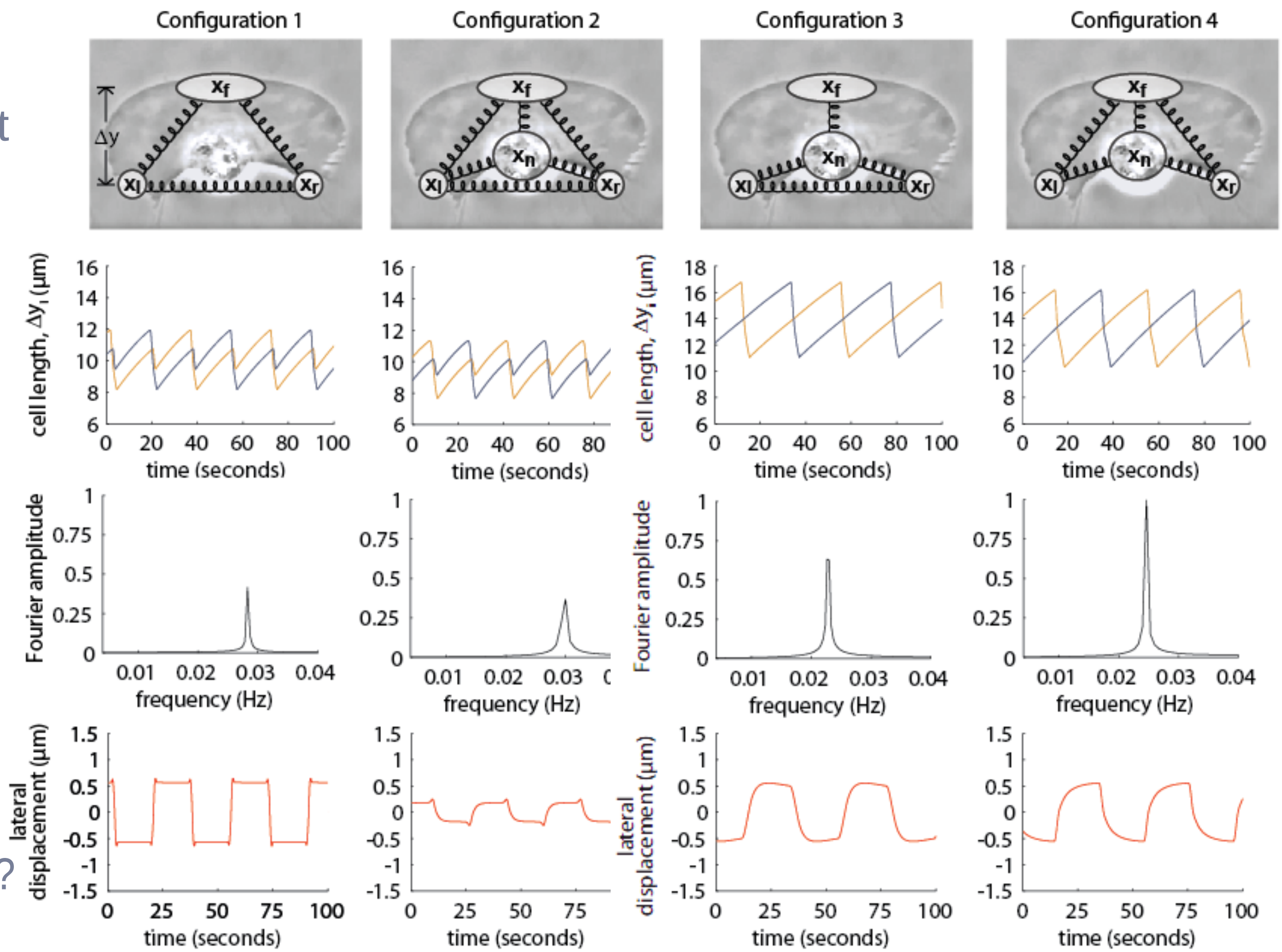
Configurations of the 2D Model

Configuration 1

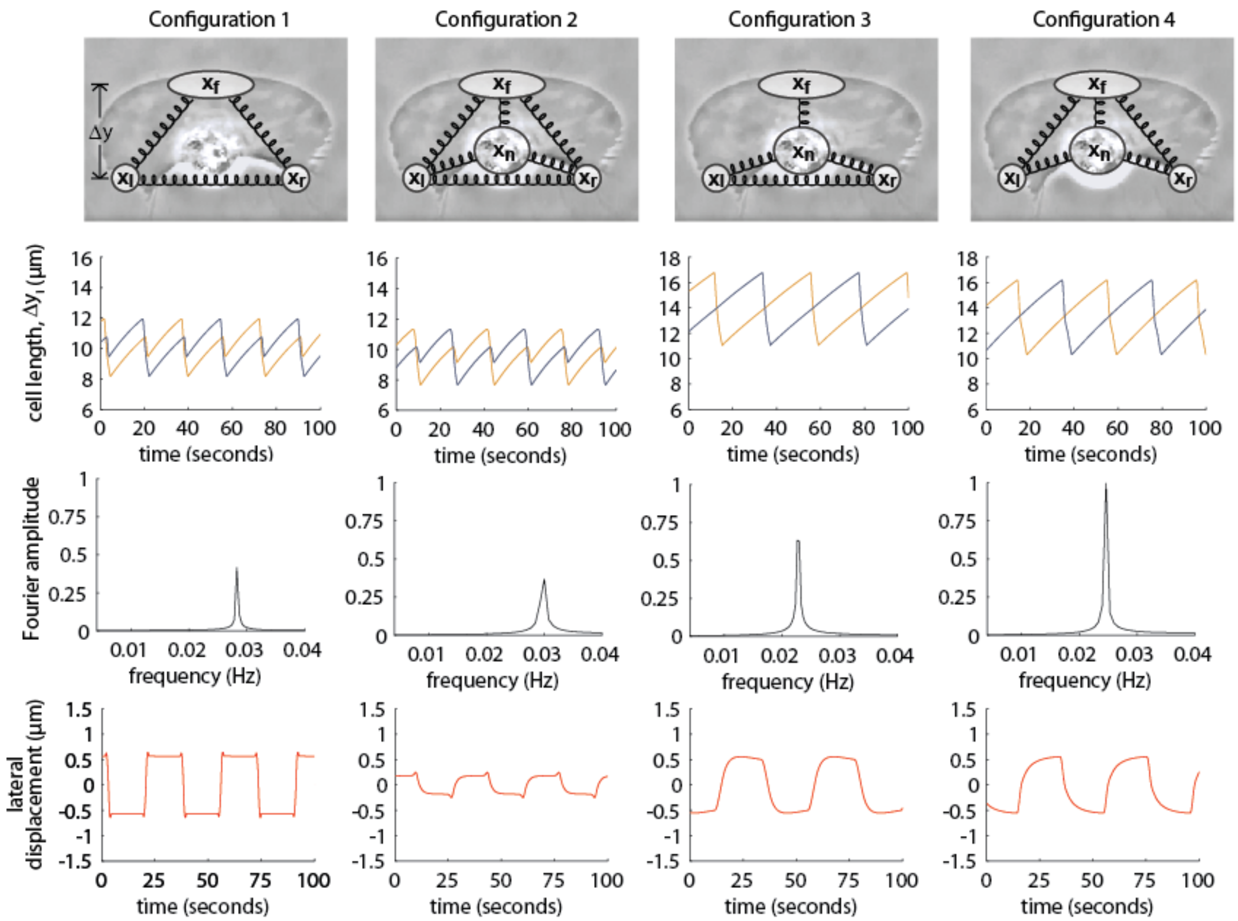
- Simplest configuration that can generate bipedal locomotion
- Problems with cell shape and dynamics

Configuration 2

- Element representing the nucleus added
- System over-constrained by too many springs?



Configurations of the 2D Model



Configuration 3

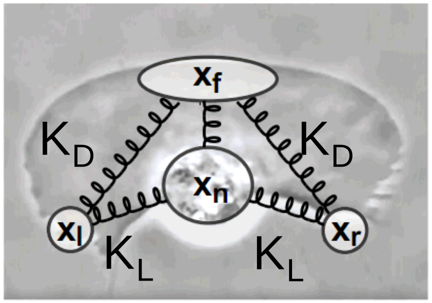
- Configuration proposed by Barnhart *et al.*
- The addition of spring K_{nf} gives realistic cell length

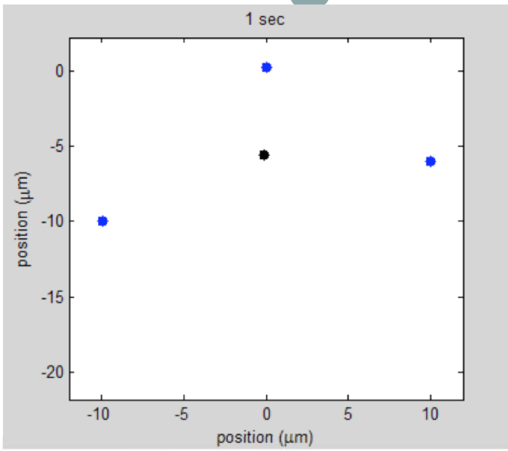
Configuration 4

- An alternative spring configuration based on assumptions of cell symmetry and element localization

A detailed analysis of Configuration 4

Configuration 4





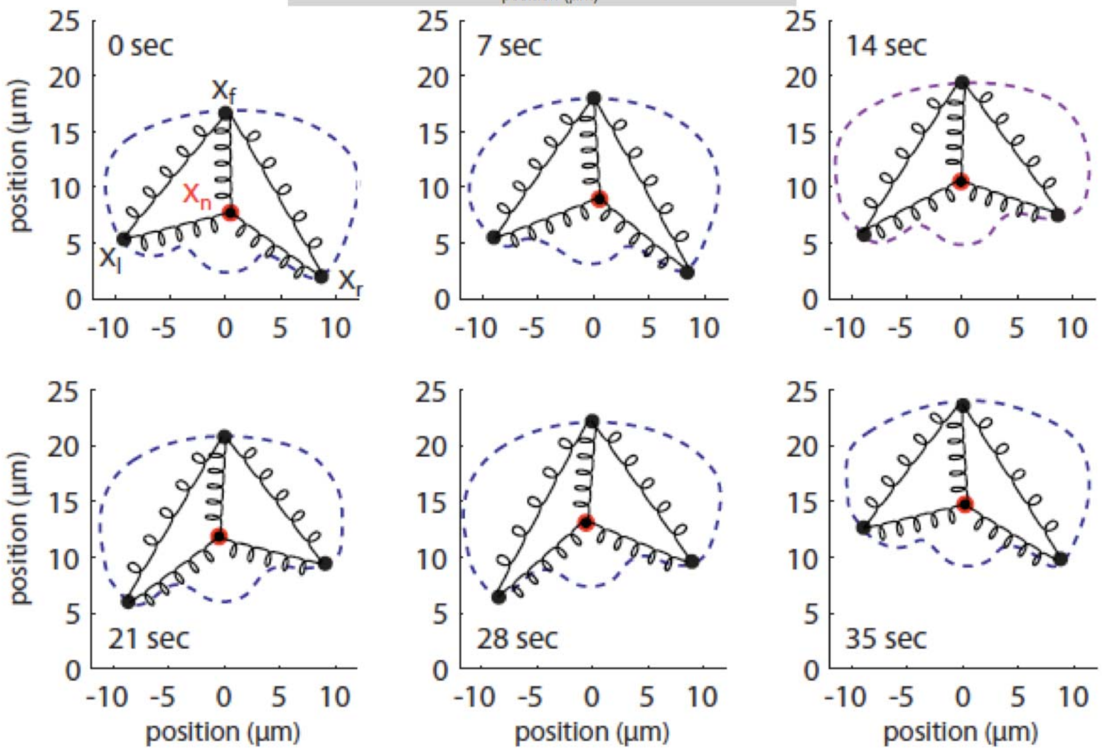
Equations of Motion:

$$\dot{\mathbf{x}}_f = v_f \hat{y}$$

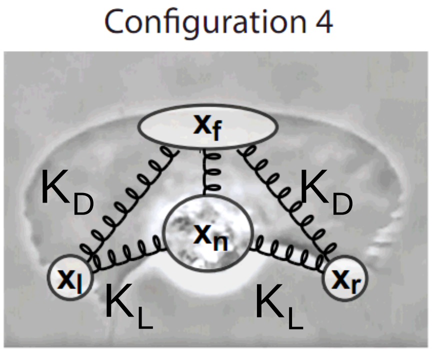
$$\gamma \dot{\mathbf{x}}_n - \sum_{i=f,l,r} K_{in}(|\mathbf{x}_n - \mathbf{x}_i| - L_{in,0}) \frac{\mathbf{x}_n - \mathbf{x}_i}{|\mathbf{x}_n - \mathbf{x}_i|} = 0$$

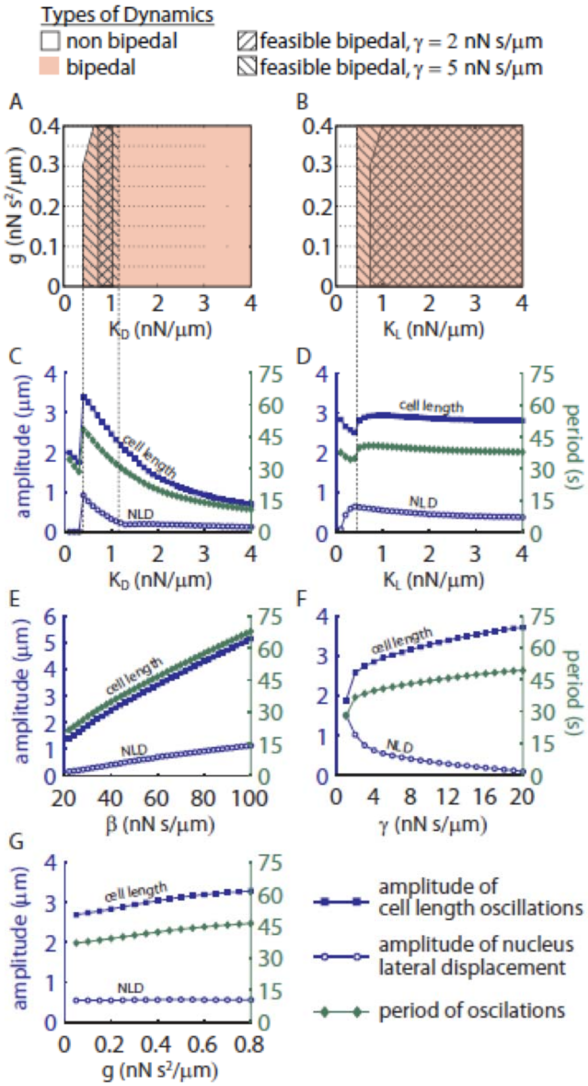
$$g\ddot{\mathbf{x}}_l - F_d(|\dot{\mathbf{x}}_l|)\frac{\dot{\mathbf{x}}_l}{|\dot{\mathbf{x}}_l|} - \sum_{i=f,n,r} K_{il}(|\mathbf{x}_l - \mathbf{x}_i| - L_{il,0}) \frac{\mathbf{x}_l - \mathbf{x}_i}{|\mathbf{x}_l - \mathbf{x}_i|} = 0$$

$$g\ddot{\mathbf{x}}_r - F_d(|\dot{\mathbf{x}}_r|)\frac{\dot{\mathbf{x}}_r}{|\dot{\mathbf{x}}_r|} - \sum_{i=f,n,l} K_{ir}(|\mathbf{x}_r - \mathbf{x}_i| - L_{ir,0}) \frac{\mathbf{x}_r - \mathbf{x}_i}{|\mathbf{x}_r - \mathbf{x}_i|} = 0$$



Model predictions of Configuration 4





parameter	meaning	range investigated	units
α	slipping drag coefficient (viscous shear)	0.15 - 0.5	$nN\ s/\mu m$
β	sticking drag coefficient (adhesion at trailing edge)	20 - 100	$nN\ s/\mu m$
γ	nuclear drag coefficient (adhesion at cell nucleus)	1 - 20	$nN\ s/\mu m$
g	inertial term (sets the time-scale of switching between stick and slip dynamics)	0 - 0.8	$nN s^2/\mu m$
v_1	critical sticking velocity (upper limit of the sticking domain)	0.08	$\mu m/s$
v_2	critical slipping velocity (lower limit of the slipping domain)	1	$\mu m/s$
v_f	leading edge velocity ($v_f > v_1$ required for stick-slip dynamics)	0.2	$\mu m/s$
K_N	spring constant	0.1 - 10	$nN/\mu m$
K_D	spring constant	0.1 - 10	$nN/\mu m$
K_L	spring constant	0.1 - 10	$nN/\mu m$
K_W	spring constant	0.1 - 10	$nN/\mu m$
N	spring length	conforms to cell shape	μm
D	spring length	conforms to cell shape	μm
L	spring length	conforms to cell shape	μm
W	spring length	conforms to cell shape	μm

Advantage of Configuration 4

It recapitulates the correct:

- Timescale
  (period ~ 40 sec)
- Amplitudes
  (bipedal ~2.5 μm)
  (lateral disp. ~ 0.5 μm)
- Smooth lateral motion of nucleus

This configuration robustly generates bipedal locomotion and appropriate lateral displacement of the nucleus over realistic variation of parameters.

Summary

- Two 4 element configurations with centralized mechanical coupling produce the realistic length and timescales of bipedal locomotion
- Both configurations robustly generate bipedal locomotion over a range of realistic parameter variations
- The new configuration we propose explicitly couples the nucleus with the cytoskeletal elements, thus the model reproduces the nuclear lateral motion observed experimentally

Acknowledgements

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