

Transporte mediado por motores moleculares e os processos de exclusão assimétricos

Elisa T. Sena

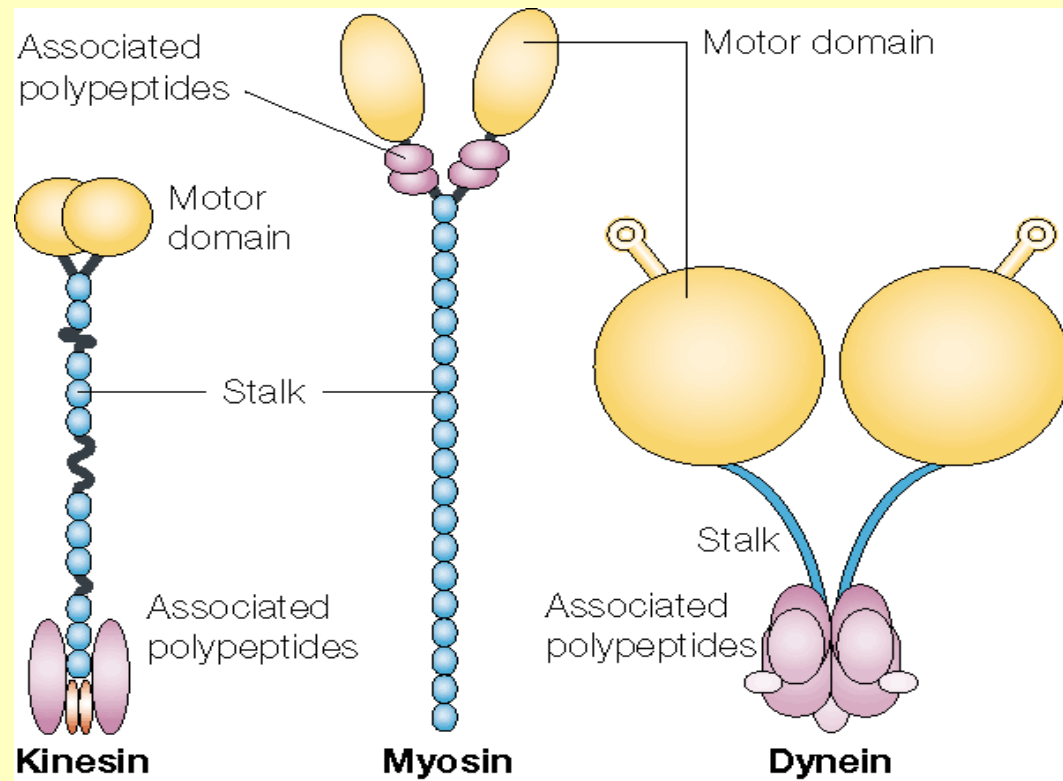
Daniel G. Lichtenthäler

C.G.

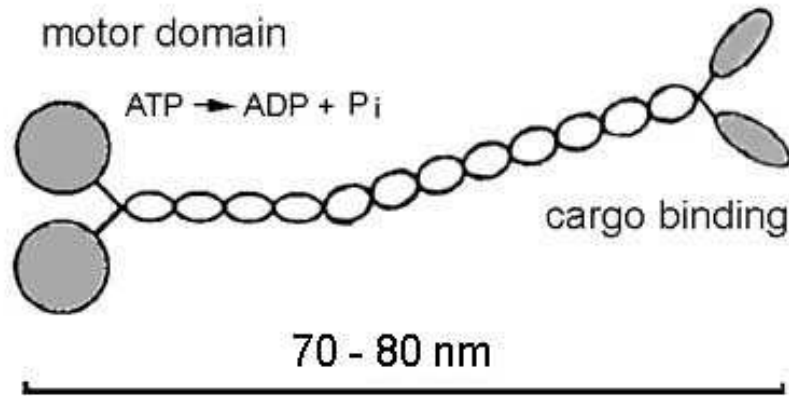
Grupo de Biofísica

IFUSP

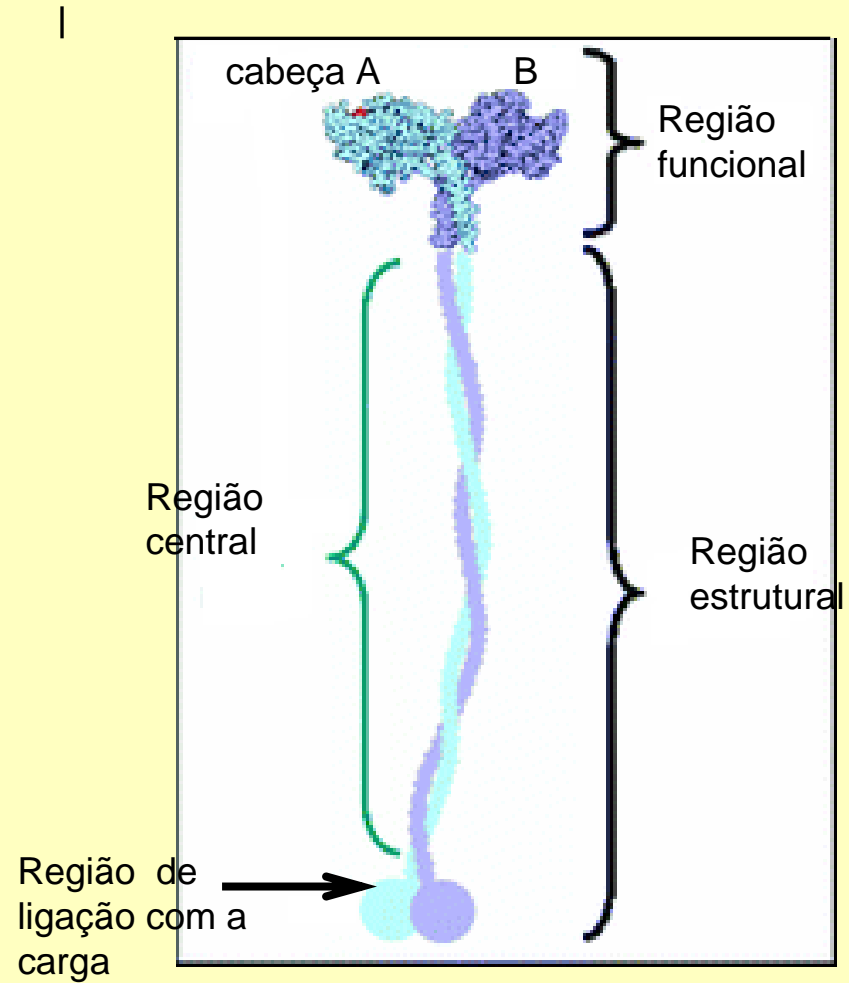
Proteínas motoras



kinesina

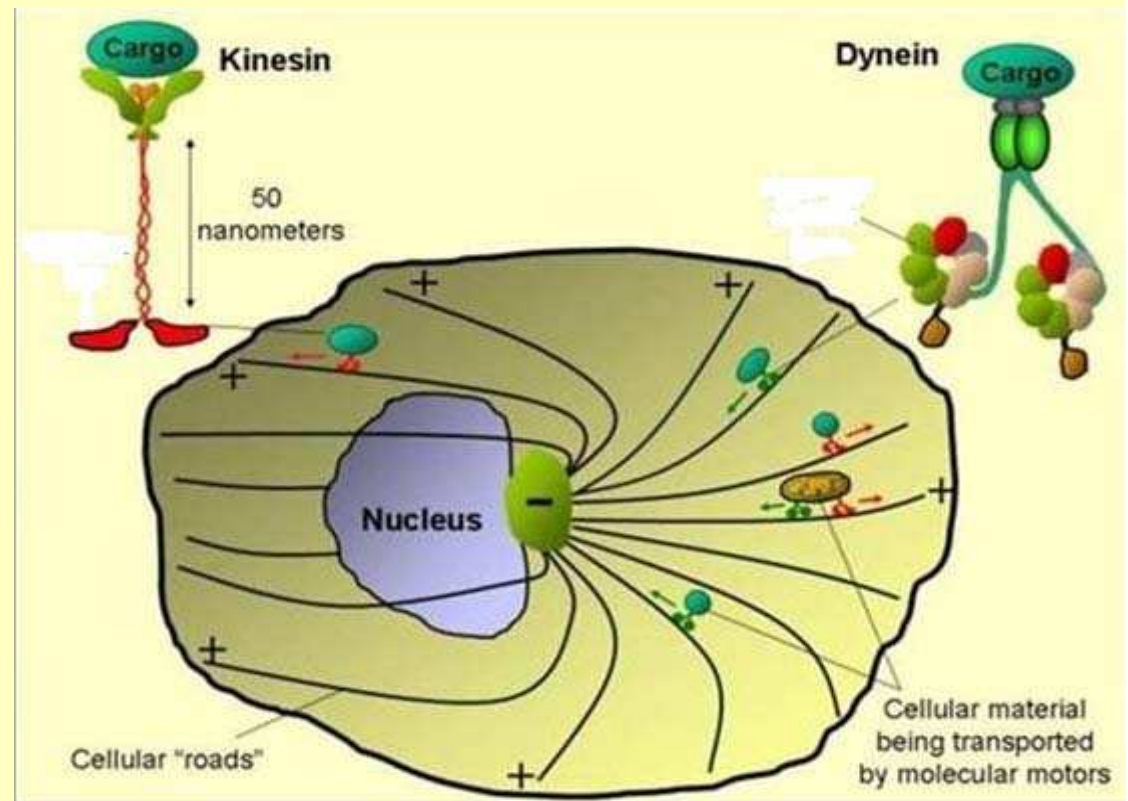


<http://kinesin.kn.lib.bz/>



Kinesina: propriedades / funções

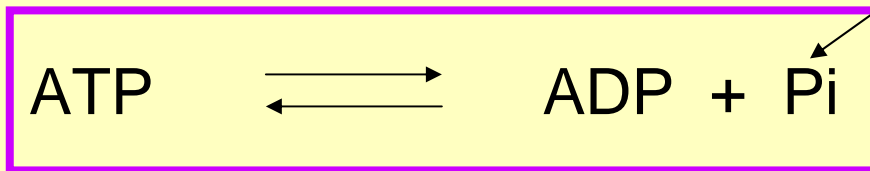
- move-se ao longo de microtubulos no citoesqueleto para **opolo +**
- acumulo de neurotransmissores (aprendizado)(?)
- velocidade típica: 20 nm/s– 2000 nm/s movimento **unidirecional**
- é “flexível”, possui mobilidade interna
- passo ~ 8 nm
- consome 1 ATP/ciclo
- :



Gross (2004)
Phys. Biol. 1

Fonte de energia: hidrólise de ATP

("adenosina trifosfato")



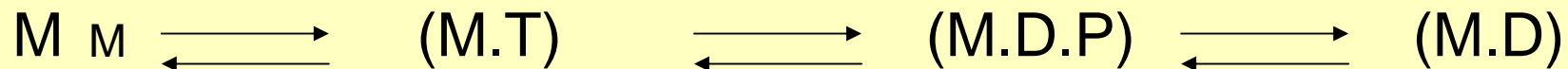
Íon
fosfato

$$\Delta G \approx 50 \cdot 10^{-21} \text{ J}$$

$$10^{-21} \text{ J} = 1 \text{ pN} \cdot (\text{nm})$$

$$1kT \sim 4 \cdot 10^{-21} \text{ J}$$

reação química acoplada :



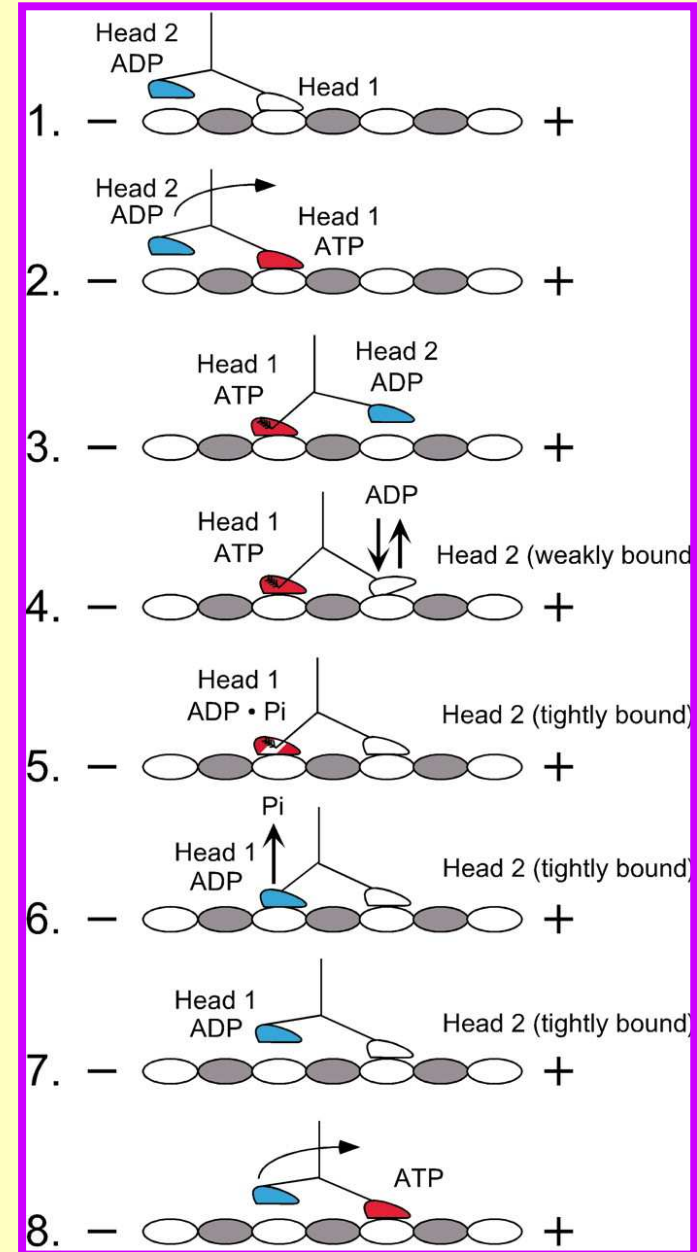
movimento do
motor:

mudança de
conformação em
processo cíclico

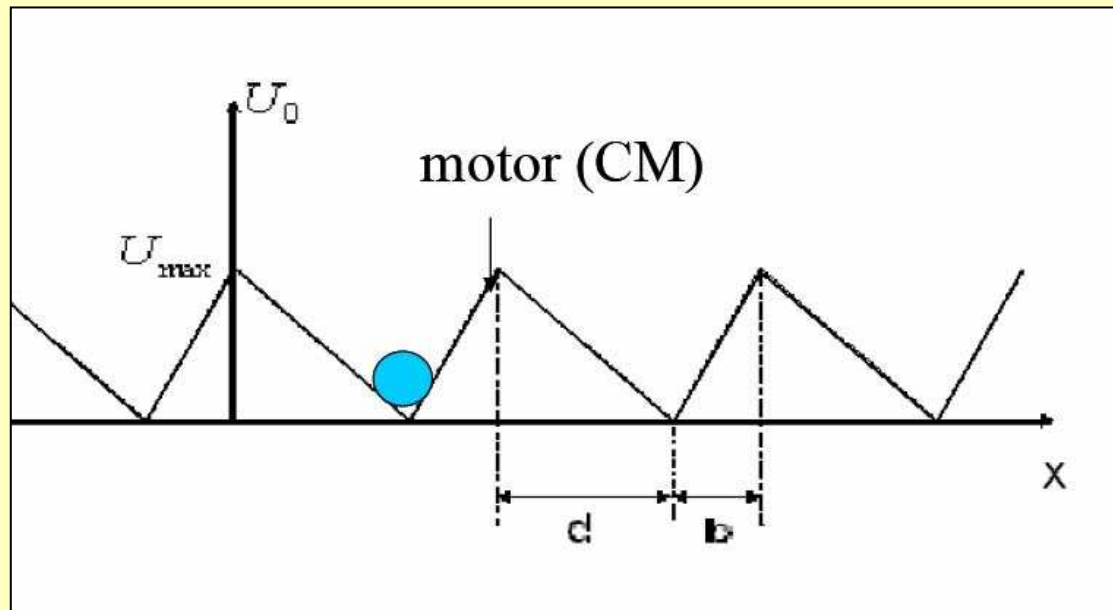
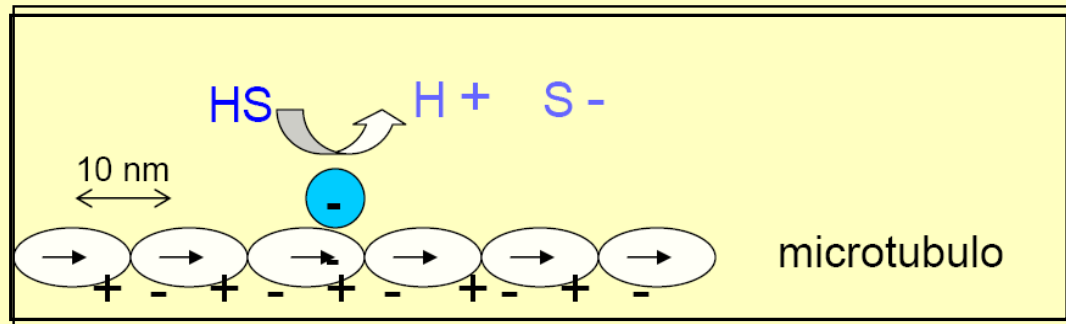
modelo

Exemplo: **kinesina**

Figura: Klumpp L. M. et.al. PNAS 2004;101:3444-3449

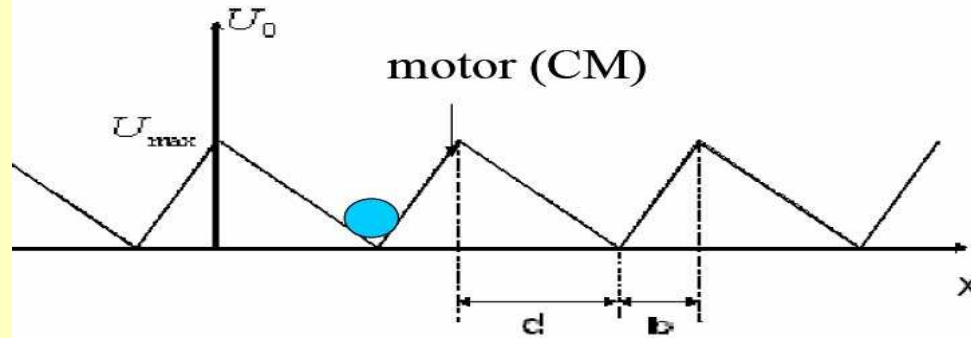


Modelos microscópicos



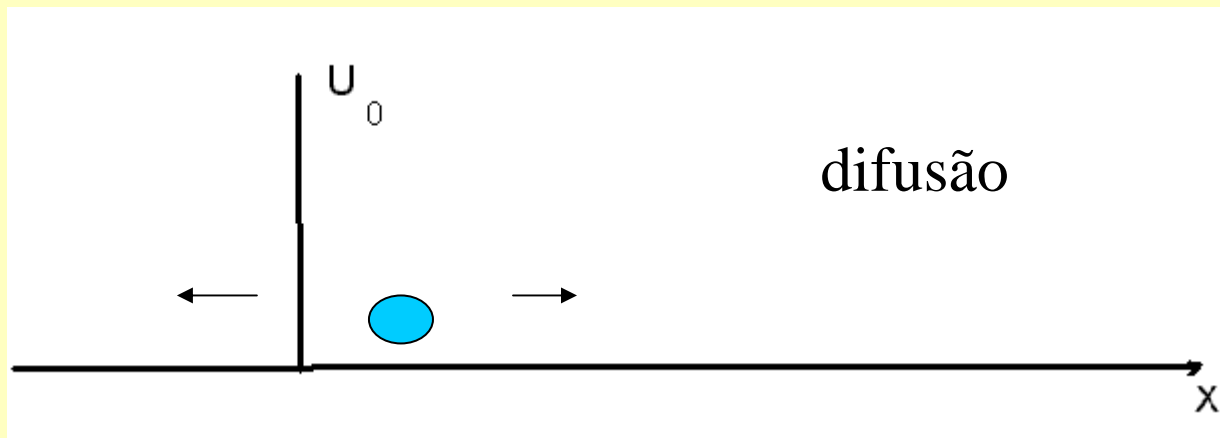
Modelo padrão:
(estocástico) potencial -
assimétrico e -
dependente do tempo -
difusão

Adjari, Prost,
Magnasco, Astumian
(1992 – 1993)

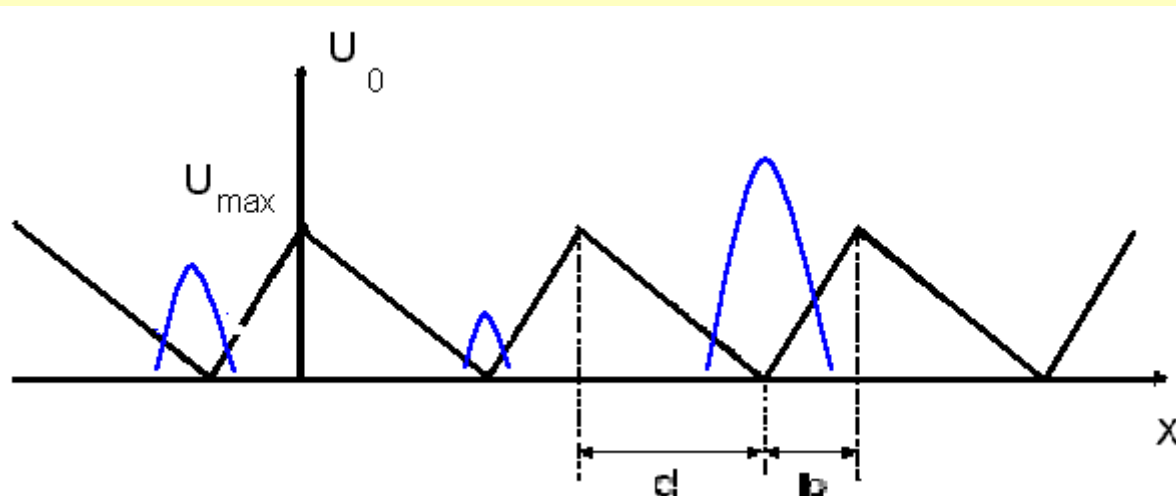


Modelo padrão:
 (estocástico) potencial -
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 (1992 – 1993)



$$t < \tau_1$$



$$t = \tau_1$$

equação de Langevin

$$m \frac{d^2 x(t)}{dt^2} = -\gamma \frac{dx(t)}{dt} - \frac{dU_{\sigma(t)}(x(t))}{dx} + \xi(t) + F(t)$$

soluções aproximadas

A. Adjari, J. Prost, C. R. Acad. Sci. Paris, t315, Sériell, p.1635 (1992)

difusão rápida

$$V_m = \frac{a - b}{2(\tau_1 + \tau_2)} \quad D_m \simeq \frac{D^0 \tau_1}{(\tau_1 + \tau_2)}$$

difusão lenta

$$V_m = \frac{(1 - p)(a + b)}{(\tau_1 + \tau_2)} \quad D_m \simeq \frac{p(1 - p)(a + b)^2}{2(\tau_1 + \tau_2)}$$

$$p = \int_{-b-2a}^{-a} \frac{1}{\sqrt{4\pi D^0 \tau_1}} \exp\left(\frac{-x^2}{4D^0 \tau_1}\right) dx.$$

“modelo padrão”: conclusões

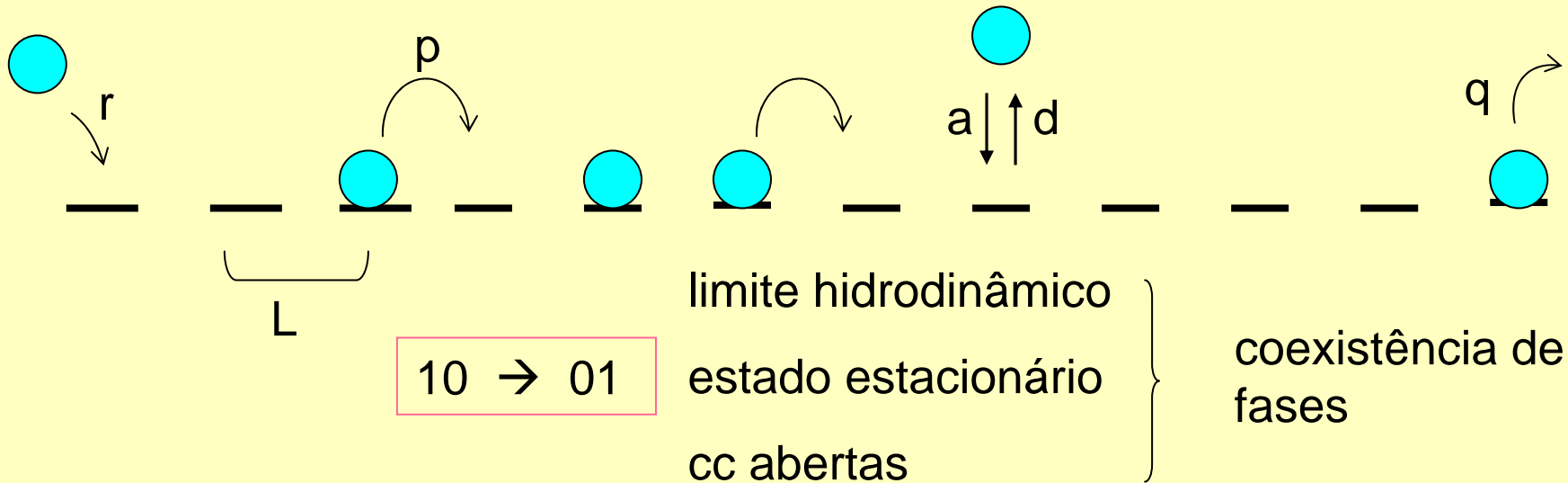
- inclui flutuações térmicas e outras não-térmicas
- Feynmann (Lectures in Physics): *ratchet and paw*
- *drift* dos motores: calor \rightarrow trabalho mecânico
- ok com a 2a - lei da Termodinâmica

questão do tráfego: efeitos coletivos

TASEP +
Langmuir



A Parmeggiani, T Franosh, E.
Frey, PRL (2003)



$$\frac{L}{N} \partial_x^2 \rho + K(2\rho - 1) \partial_x \rho + A(1 - \rho) - D\rho = 0$$

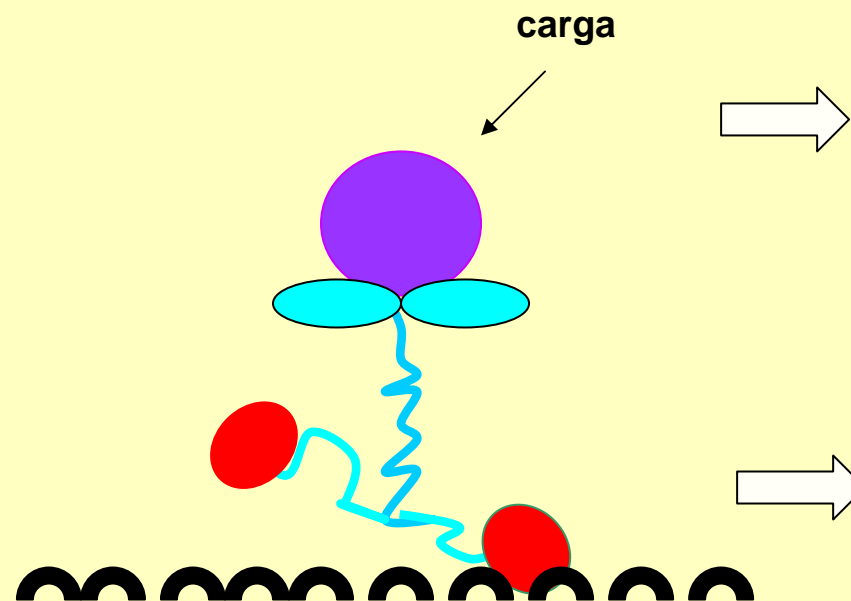
transporte



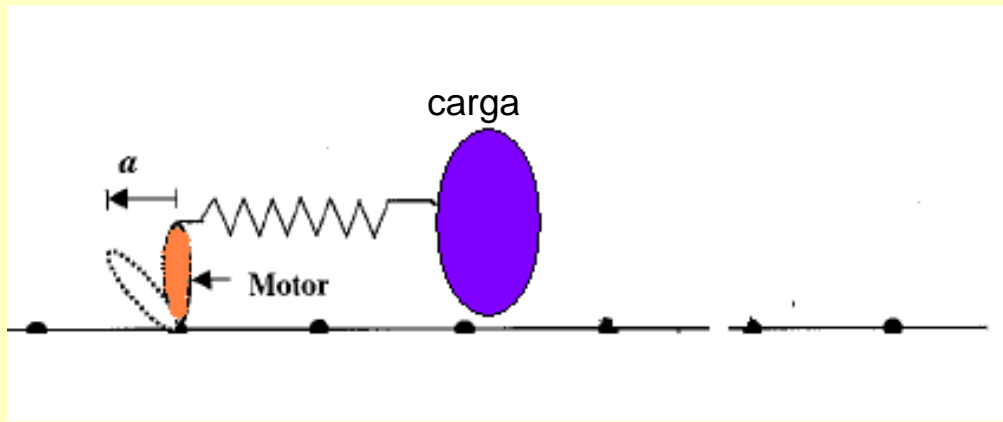
Imagem capturada por microscopia de contraste diferencial mostra uma bolinha de vidro ($d \sim 1 \text{ um}$) sendo carregada por kinesina(s) ao longo de microtubulos de tubulina

modelos (1)

movimento do **complexo** carga/motor



modelos (2)

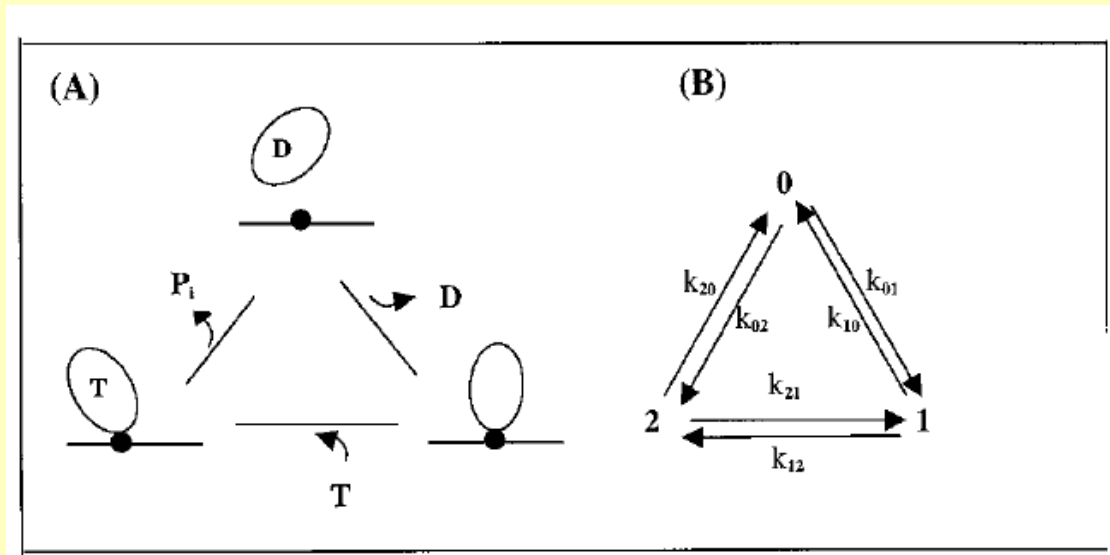


1- Elston, Peskin, SIAM J. Appl. Math (2000)

2- Y Chen Biophys. J. (2000)

3- Zeldovich, Joanny, **Prost**, Eur. Phys. J. E (2005)

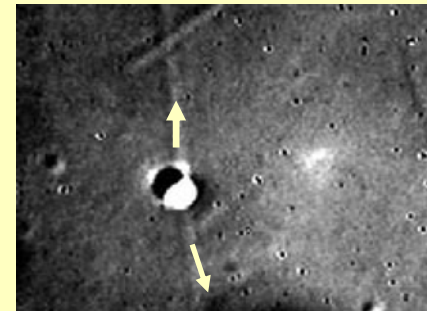
reação-difusão



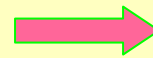
movimento bidirecional

Microscopia confocal +
fluorescência + tempo de
aquisição menor

- mudanças de sentido
- não-difusivo
- observado no movimento da “carga”



Ref. revisão: Gross 04, Welte 04

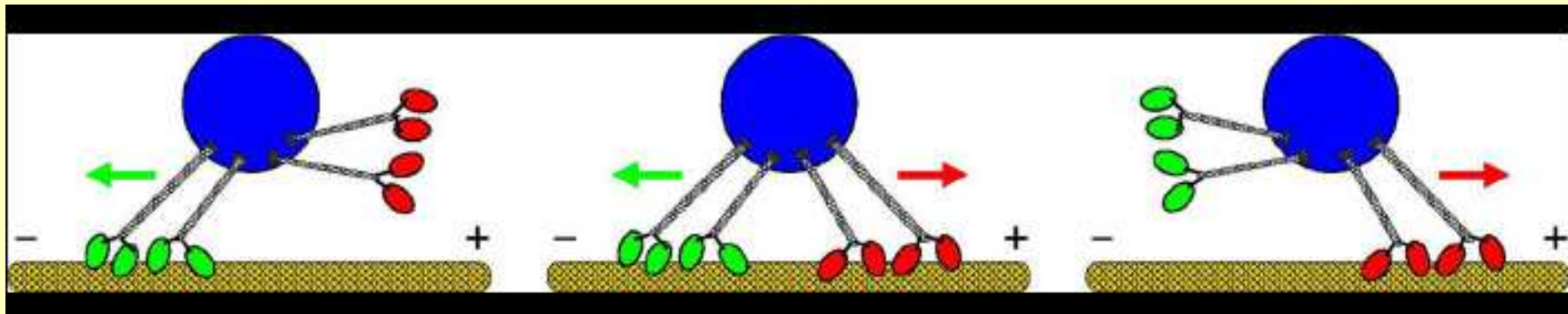


efeitos coletivos

modelos (3)

-coordenação
entre tipos
diferentes

(Gross,
Welte,...2003 -04)

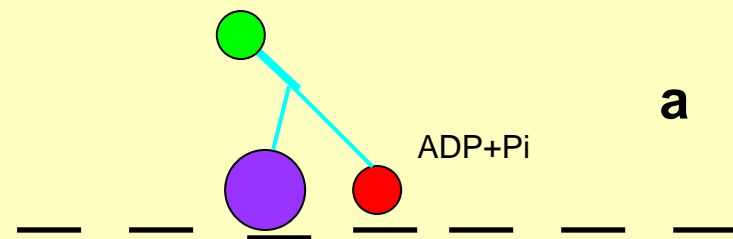


? coordenador

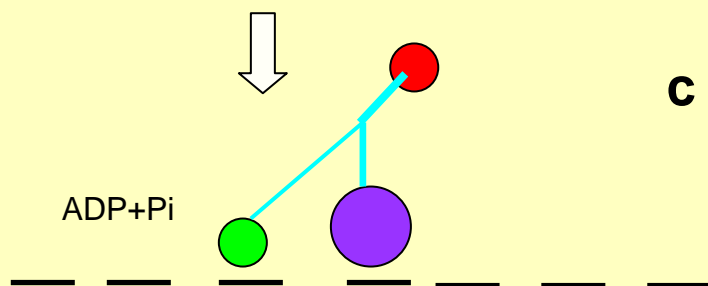
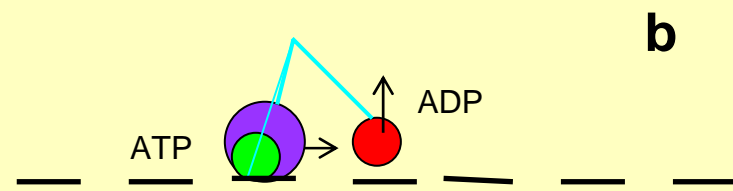


R. Lipowsky PNAS (2008)

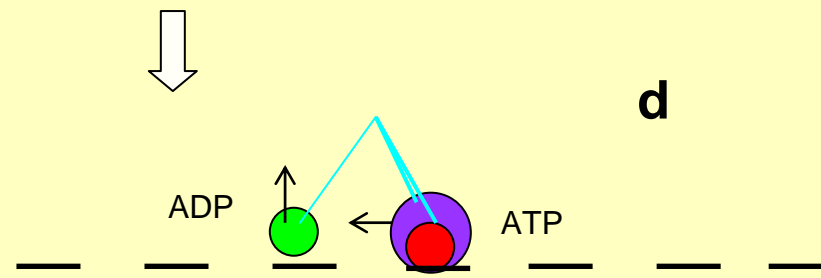
modelos (4)



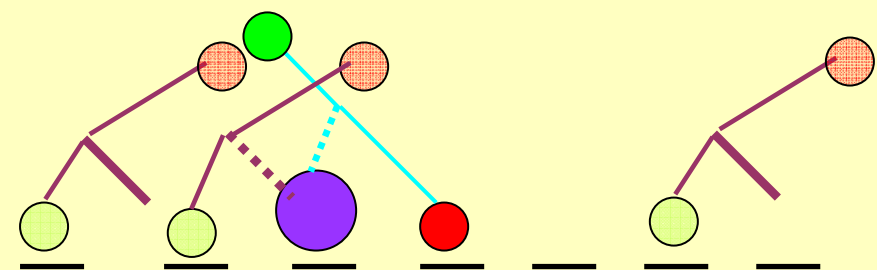
2 1



1 2



2 1



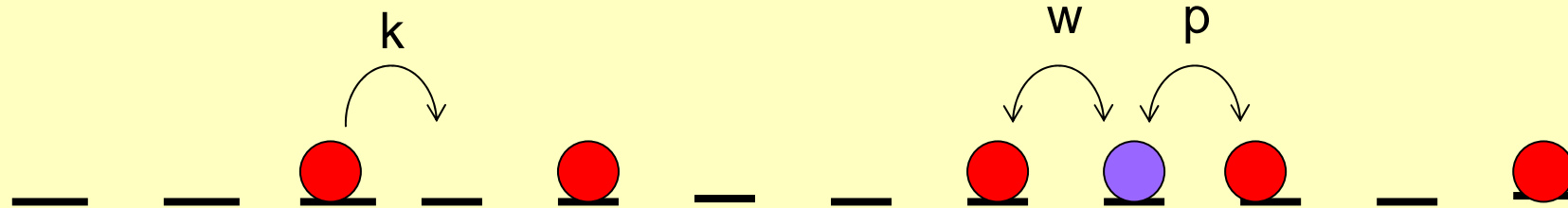
1 1 2 1 0 1 0

f

processo de exclusão assimétrico para o transporte de “carga” (ASEP)

- motor → partícula 1
- carga → partícula 2

E. Sena, C. G. (2008)



carga {

- 10 → 01 taxa k
- 12 → 21 taxa w
- 21 → 12 taxa p

- estado estacionário
 - cc periódicas

2a classe {

- 10 → 01
- 12 → 21
- 20 → 02

N sítios, **M** motores, **K** cargas \rightarrow **N - M - K > 0** buracos

ansatz das matrizes [Derrida, J. Phys.A, (1993)]

Probabilidade de um estado: **C**

$$\sigma_j = 0, 1, 2$$

$$P_{N,M}(C) = \frac{1}{Z_{N,M}} \text{Tr} \prod_{i=1}^N (\delta_{\sigma_i,1} D + \delta_{\sigma_i,2} A + \delta_{\sigma_i,0} E)$$

normalização

$$Z_{N,M} = \sum_{\{\sigma_i\}} \text{Tr} \prod_{i=1}^N (\delta_{\sigma_i,1} D + \delta_{\sigma_i,2} A + \delta_{\sigma_i,0} E) \quad \sum_i^N \delta_{\sigma_i,1} = M$$
$$\sum_i^N \delta_{\sigma_i,2} = K = 1$$

estado estacionário

$$\sum_{C'} P_{N,M}(C')W(C' \rightarrow C) - P_{N,M}(C)W(C \rightarrow C') = 0$$

Derrida, Janowsky, Lebowitz, Speer, J. Stat. Phys. 1993

$$W(C' \rightarrow C) = \text{taxa processo elementar}$$

ASEP para transporte de carga

dinâmica

$$\left\{ \begin{array}{ll} 10 \rightarrow 01 & \text{taxa } k \\ 12 \rightarrow 21 & \text{taxa } w \\ 21 \rightarrow 12 & \text{taxa } p \end{array} \right.$$

álgebra

$$\left\{ \begin{array}{l} DA - xAD = E - D \\ DE = E \\ EA = E \\ EE = E \end{array} \right. \quad \begin{array}{l} \boxed{x = (k+p) / w} \\ \text{conjectura...} \end{array}$$

velocidade média da carga

$$\langle v \rangle = \frac{1}{Z_{N,M}} \left(p \sum_{\{\sigma_i\}} \text{Tr} \prod_{i=1}^{N-2} (\delta_{\sigma_i,1} D + \delta_{\sigma_i,0} E) AD - w \sum_{\{\sigma_i\}} \text{Tr} \prod_{i=1}^{N-2} (\delta_{\sigma_i,1} D + \delta_{\sigma_i,0} E) DA \right)$$

notação \rightarrow

$$\langle v \rangle = \frac{1}{Z_{N,M}} (pW_{21} - wW_{12})$$


$$Z_{N,M} = \sum_{\{\sigma_i\}} \text{Tr} \left[\prod_{i=1}^{N-1} (\delta_{\sigma_i,1} D + \delta_{\sigma_i,0} E) A \right]$$

invariância do traço \rightarrow

$$Z_{N,M} = W_{21} + W_{20}$$

traços e configurações

$$W_{12} = \sum_{\{m_i\}; \{q_i\}} \text{tr}(E^{q_1} D^{m_1} \dots E^{q_{k-1}} D^{m_{k-1}} E^{q_k} D^{m_k} A) \quad m_k \geq 1$$


$$x^{m_k} \text{tr}(E)$$

$$= \sum_{m_k=1}^M \binom{N-m_k-2}{M-m_k} x^{m_k} \text{tr}(E)$$

limite termodinâmico

$$N \rightarrow \infty \text{ e } M \rightarrow \infty$$

$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} \frac{M}{N} = \rho \quad 0 < \rho < 1$$

$$N! \sim \sqrt{2\pi N} N^N \exp(-N)$$

densidade de
motores

$$z = \frac{m_k}{N}$$

$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} W_{12} \simeq \lim_{N \rightarrow \infty} \frac{\sqrt{N}(1-\rho)^2}{\sqrt{2\pi(1-\rho)}} \int_0^\rho \left(\frac{1-z}{\rho-z} \right)^{1/2} \frac{e^{Nf(z)}}{(1-z)^2} dz$$

$$f(z) = (1-z) \ln(1-z) - (\rho-z) \ln(\rho-z) - (1-\rho) \ln(1-\rho) + z \ln x$$

limite assintótico: método de Laplace

$$\int_0^{\rho} \left(\frac{1-z}{\rho-z} \right)^{1/2} \frac{e^{Nf(z)}}{(1-z)^2} dz$$

$$z_{\max} = \frac{1-x\rho}{1-x} = \max f(z)$$

- se $x\rho > 1$ ($x > 1$) \rightarrow $0 \leq z_{\max} \leq \rho$

$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} W_{12} \sim \left(\frac{x-1}{x} \right) \exp[-N(-\ln x + (1-\rho)\ln(x-1))]$$

- se $x\rho < 1$, para $x > 1$ or $x < 1$, então $z_{\max} < 0$.

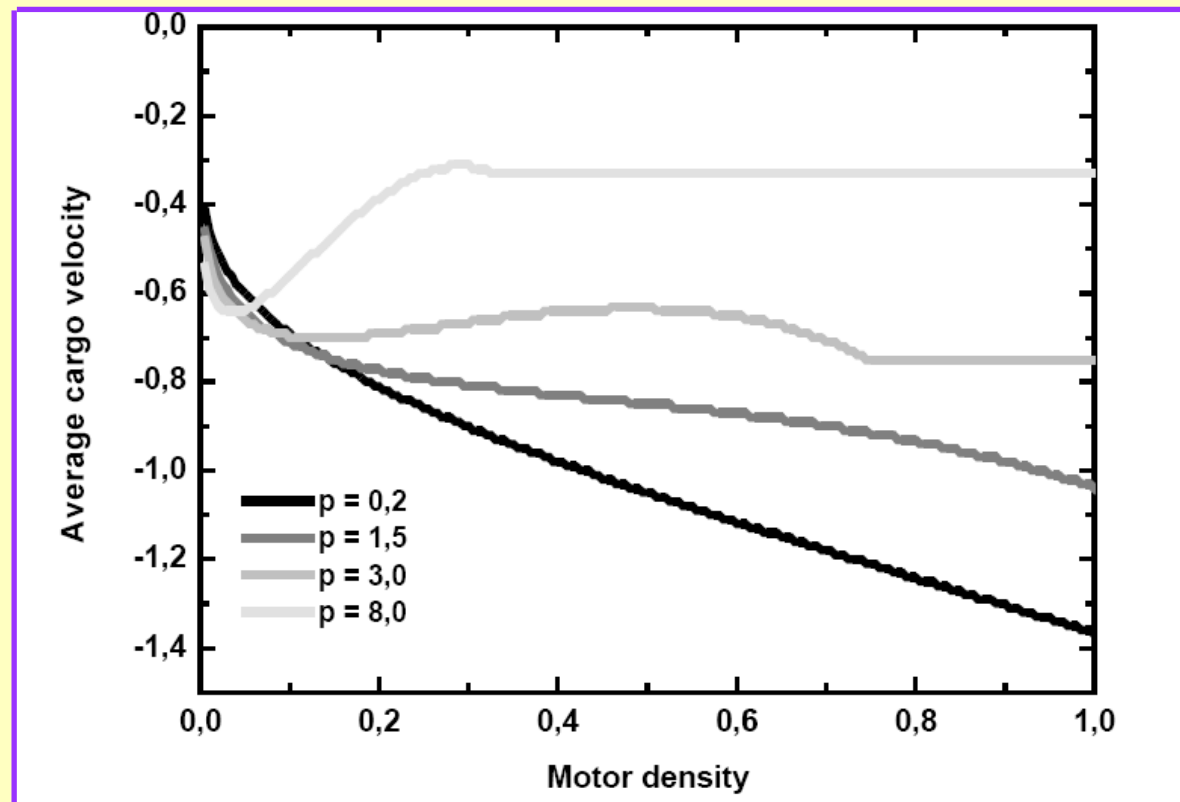
$f(z)$ é positiva e monótona decrescente e assume valores positivos no intervalo, a integral é dominada pelo valor em $z = 0$

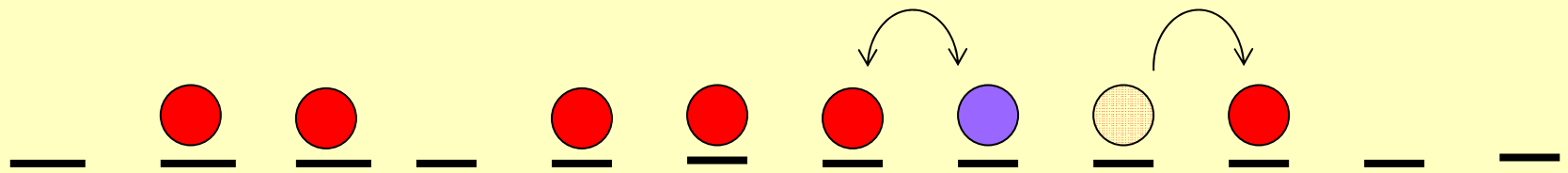
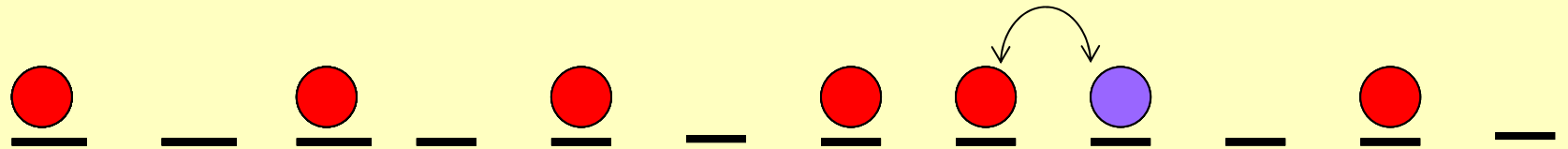
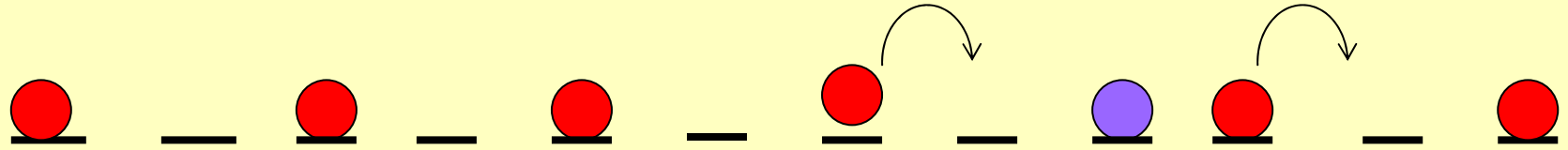
$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} W_{12} \sim -\frac{(1-\rho)^2}{\sqrt{2\pi N\rho(1-\rho)}} \frac{1}{\ln(\rho x)} \exp[-N(\rho \ln \rho + (1-\rho)\ln(1-\rho))]$$



$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} \langle v \rangle \sim -\frac{k\omega}{k+p}, \quad x\rho \geq 1$$

$$\lim_{\substack{N \rightarrow \infty \\ M \rightarrow \infty}} \langle v \rangle \sim p\rho + \frac{\omega}{\ln(\rho x) - 1}, \quad x\rho \leq 1$$





conclusões

- não explica bidirecionalidade ainda....
- *hand-over-hand* à nível de muitas partículas
- presença da “carga”
- distribuição de motores X movimento da carga