分野1　予測する生命科学・医療および創薬基盤
課題3　予測医療に向けた階層統合シミュレーション
「神経疾患による運動機能障害解明のための全身筋骨格−神経系統合シミュレーション」

骨格筋のマルチスケールシミュレーション

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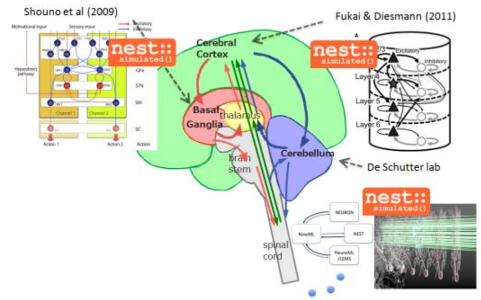
第5回HPCI戦略プログラム合同研究交流会
2013年1月16日

筋骨格-神経系統合シミュレーション:神経疾患による運動機能破綻解明に向けて

NEST

脳＝運動指令の作成

- パーキンソン病状態の大脳基底核モデルの確立
- 大規模計算により健常者・病者の運動指令を再現

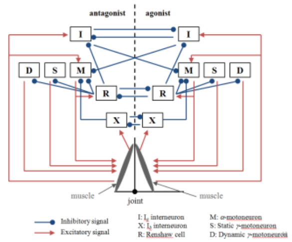


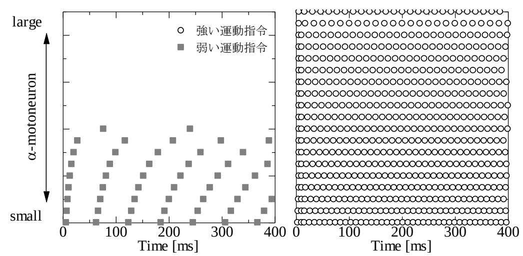
（銅谷＠沖縄科技大）

HI-MUSCL

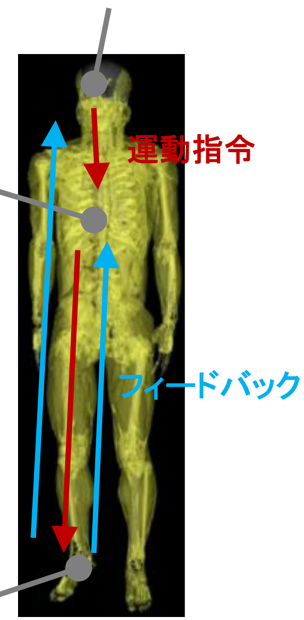
脊髄＝運動指令の伝達

- 脳から発せられた運動指令の伝達過程，ならびに筋肉からのフィードバック，主動筋・拮抗筋の協調機構を再現



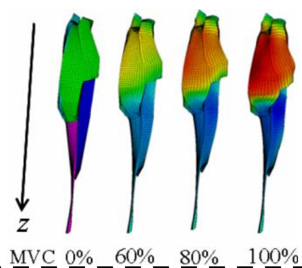


（高木＠東大）



筋・骨格＝関節運動

- 筋線維レベルからの三次元モデルに基づいた解析により特定筋の微細挙動を理解
- 関節運動持の筋肉・腱・骨の三次元挙動を再現



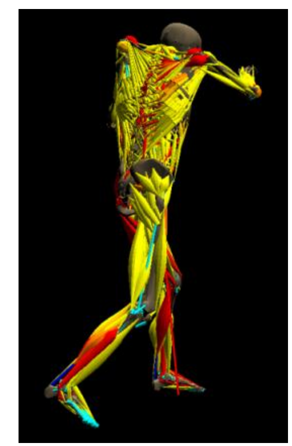
（高木＠東大）

スケールを超えた解析

K-Body

全身モデル

- 全身の分布質量筋モデルの有限要素解析
- 神経モデルを兼ね備えた神経-筋骨格モデルによる運動機能再現



（中村＠東大）

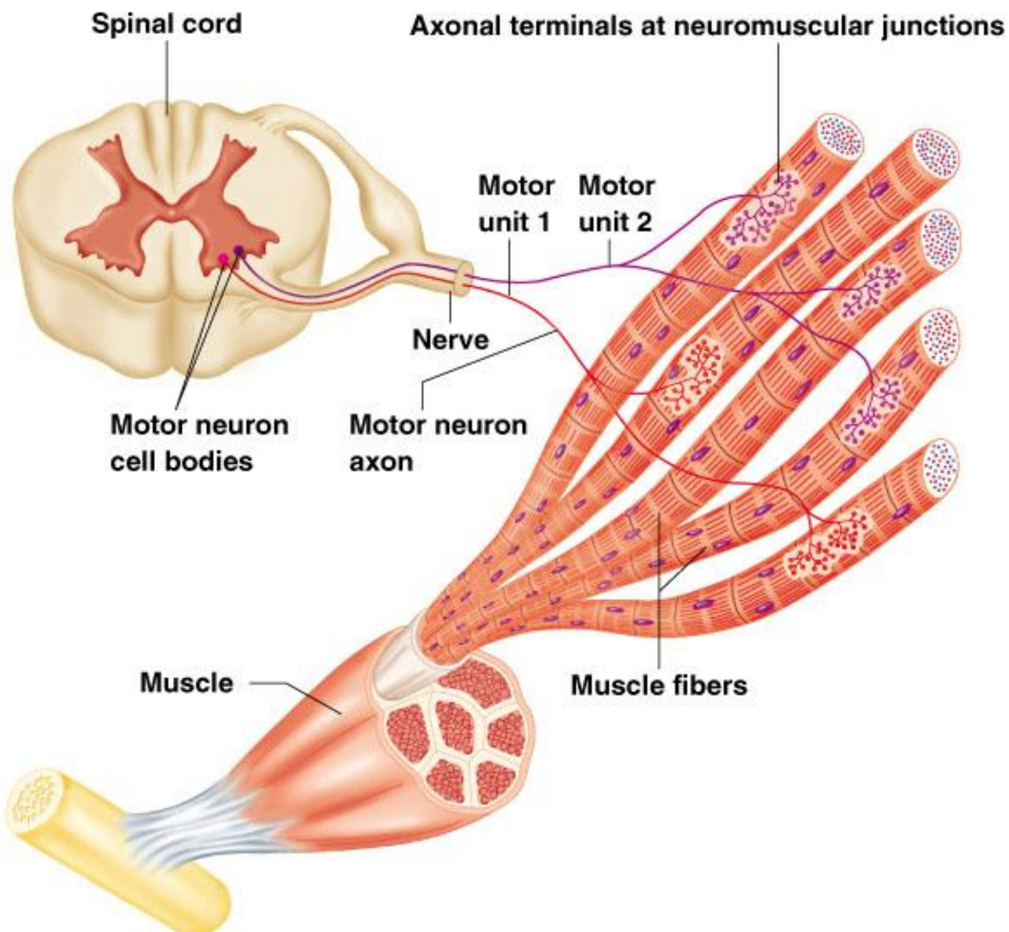
振戦・固縮などの症状の再現

患者データに基づくパーキンソン病モデル
（野村＠阪大）

姿勢保持障害などの症状の再現

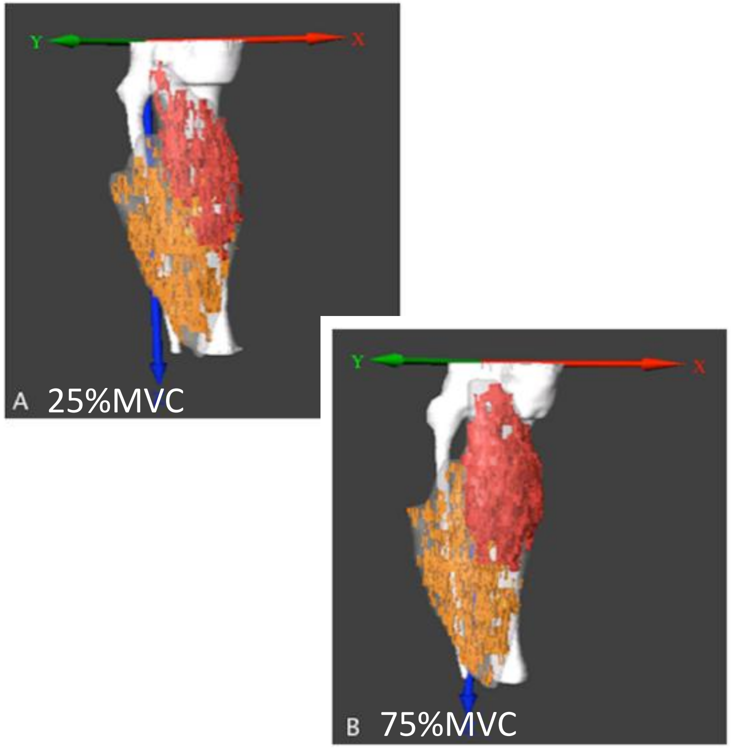
Muscle fibers and motor unit

Motor unit

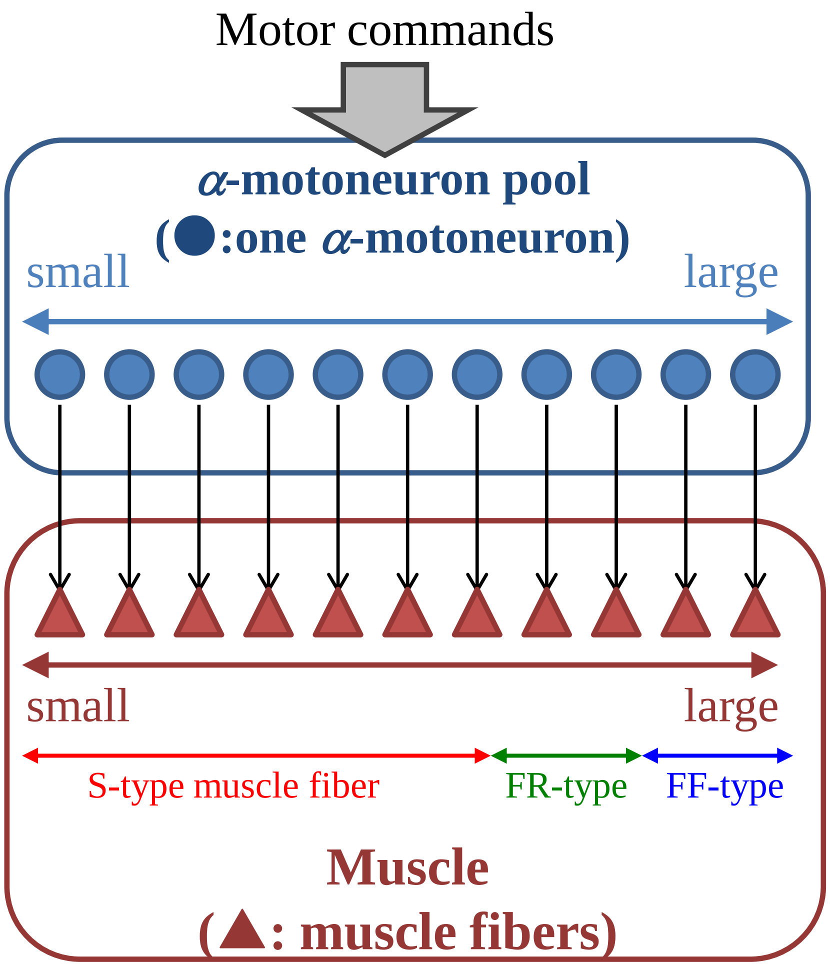


Active area in the triceps surae muscle

(Kinugasa et al. 2006)



How to control muscle force?



S: Slow fatigue-resistant — red muscle
FR: Fast fatigue-Resistant } white muscle
FF: Fast Fatiguable

Rate coding

motor commands for weak muscular force
→ spike interval is long.
motor commands for stronger muscular force
→ firing frequency becomes high.

Recruitment

motor commands for weak muscular force
→ only small motor units are activated.
motor commands for stronger muscular force
→ larger motor units are activated in sequence.

筋骨格系モデル

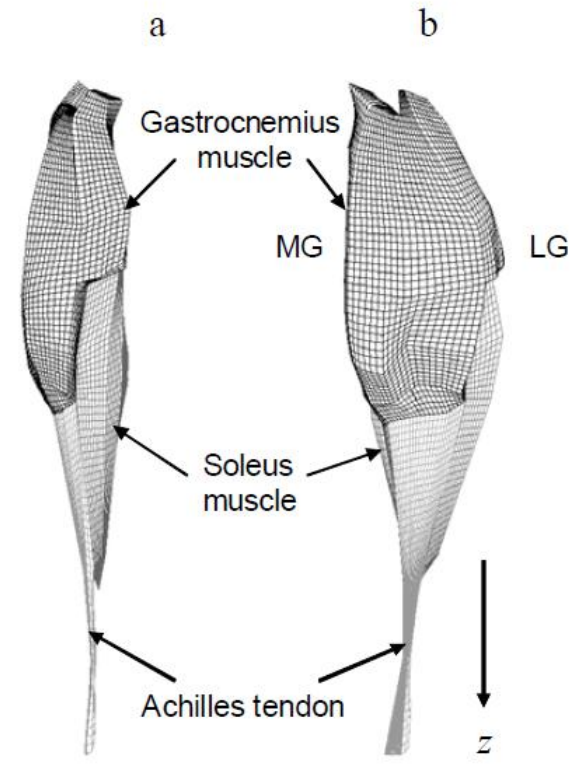
Numerical model for musculoskeletal system

- Nonlinear finite element setting for almost incompressible hyperelastic material
  - a total Lagrangian formulation
  - a mixed type displacement-pressure finite element
  - a fully implicit time integration scheme

- Material properties for passive behavior
  - Mooney-Rivlin material (isotropic part) (Chi et al., 2010)and Holzapfel model (anisotropic part) (Holzapfel et al., 2000)

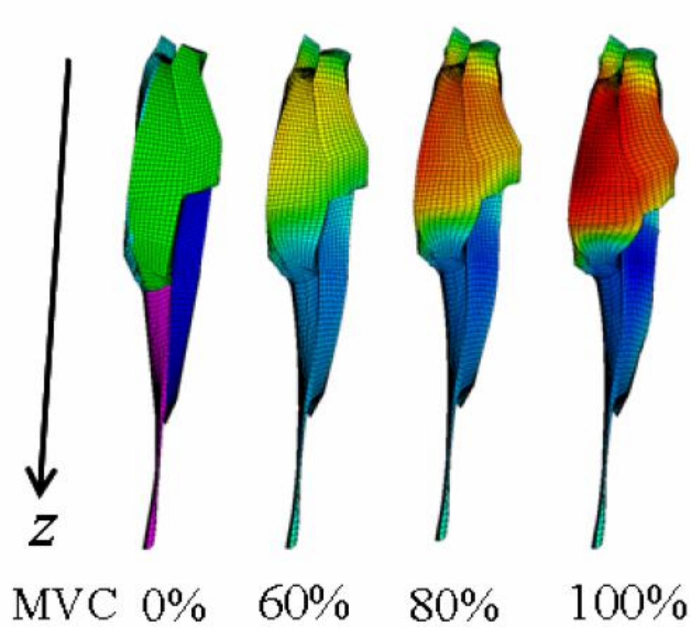
- Active behavior
  - 3D Hill-type model (Johansson et al., 2000)

- Muscle fiber distributions are constructed from fascicle arrangement measured by 2D ultrasound images (Kawakami et al., 1998) and extended to 3D fiber map.

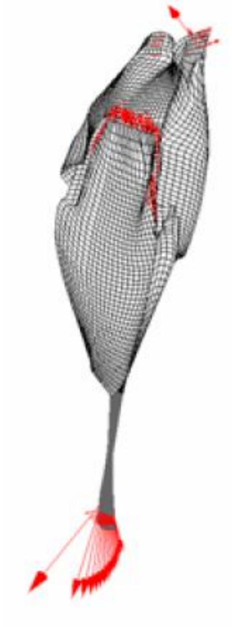


FE model of the triceps surae muscle. From the view of (a) the lateral side and (b) the back side of the human body. <u>The geometry was measured by MRI</u> and segmented into gastrocnemius, soleus muscles and Achilles tendon with the aponeurosis.

Simulation results for an isometric contraction



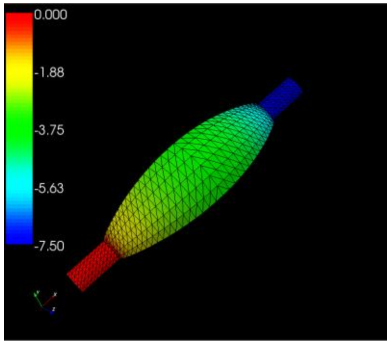
Deformation and displacement distribution of the longitudinal *z*-direction

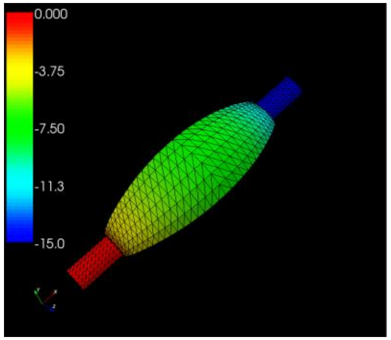


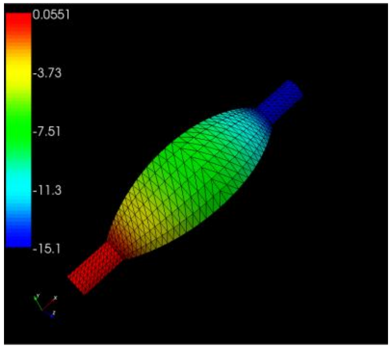
The nodal force vectors at the end of the contraction

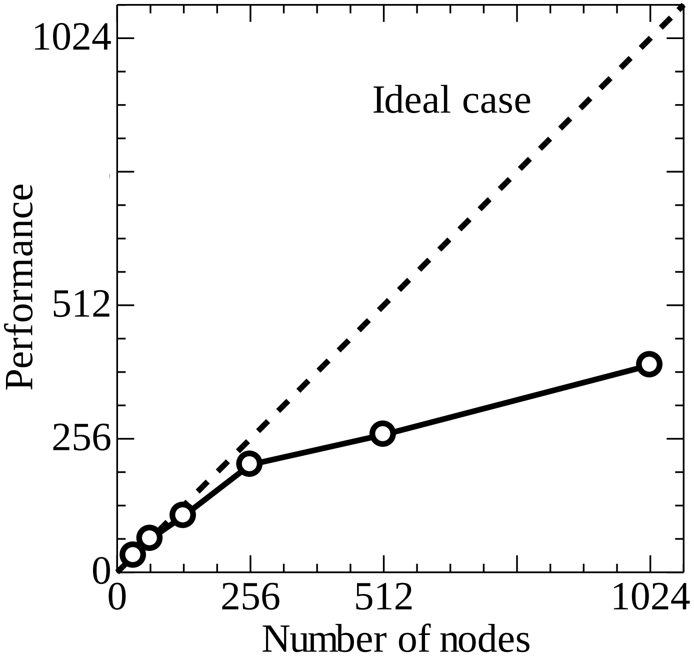
- The numerical results show
  - the muscle behaviors and force generation at Achilles tendon during isometric contraction.
  - each muscle causes a contraction in the fiber directions.
  - the Achilles tendon is stretched by the aponeurosis existing between gastrocnemius and soleus, resulting in the force generation.

Parallelization test



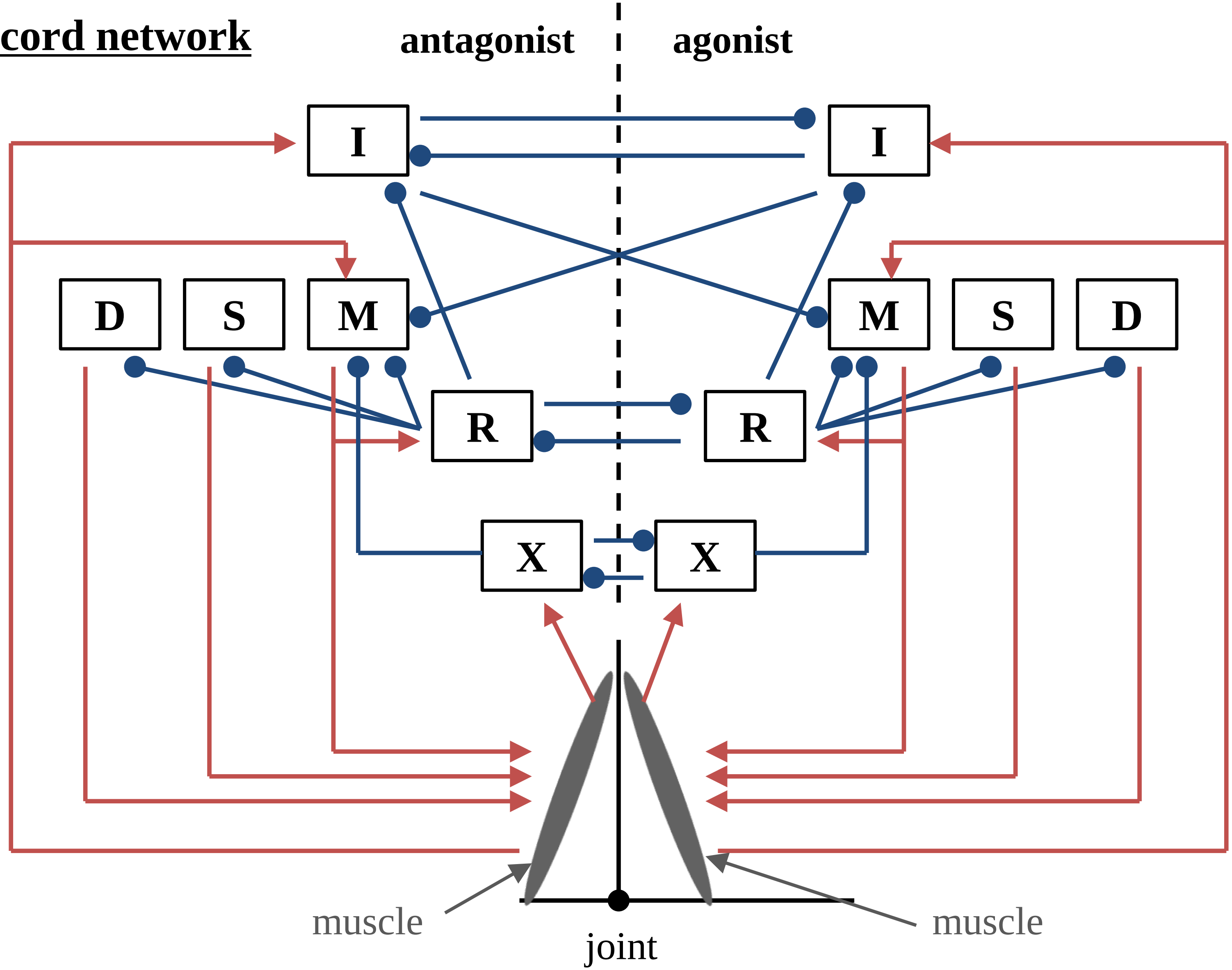






脊髄中枢神経系モデル

Spinal cord network



Inhibitory signal

Excitatory signal

I: I_a interneuron
X: I_b interneuron
R: Renshaw cell

M: α-motoneuron
S: Static γ-motoneuron
D: Dynamic γ-motoneuron

Numerical model for α-motoneuron

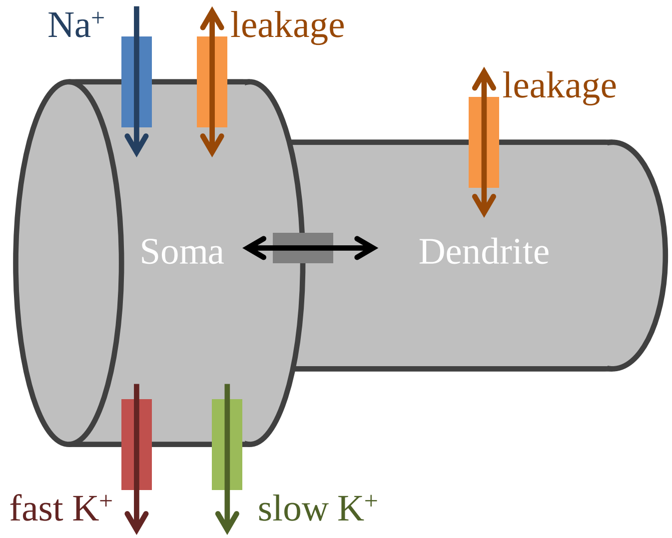
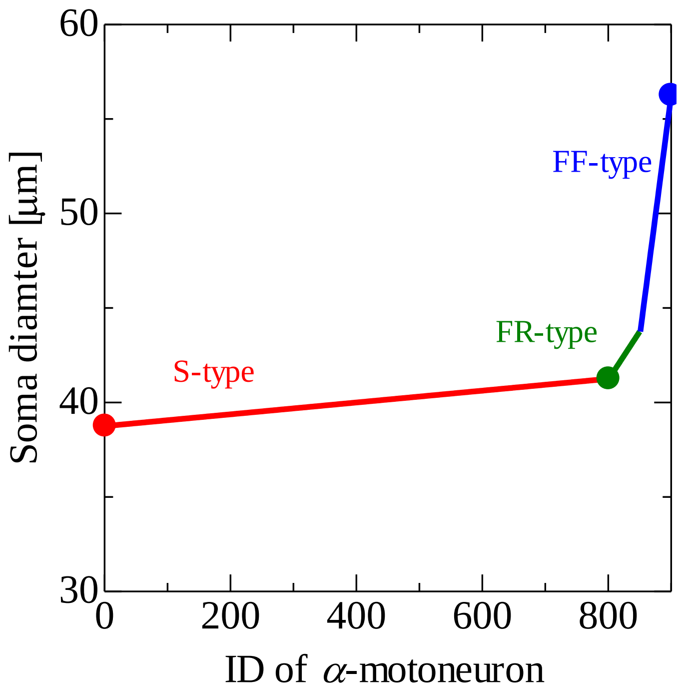


Illustration of α-motoneuron (Rogerio R. L. Cisi and Andre F. Kohn, 2008)



Example of size distribution of soma

Mathematical expressions

$$C_s \frac{dV_s}{dt} = -I_{syn,s} - g_{ls}(V_s - E_l) - g_c(V_s - V_d) - I_{ion} \quad (+I_{inj})$$

$$\frac{ds}{dt} = \alpha_s(V_s)(1-s) - \beta_s(V_s)s \quad (s = m, h, n, q)$$

$$I_{ion} = g_{Na} m^3 h (V_s - E_{Na}) + g_{Kf} n^4 (V_s - E_{Kf}) + g_{Ks} q^2 (V_s - E_{Ks})$$

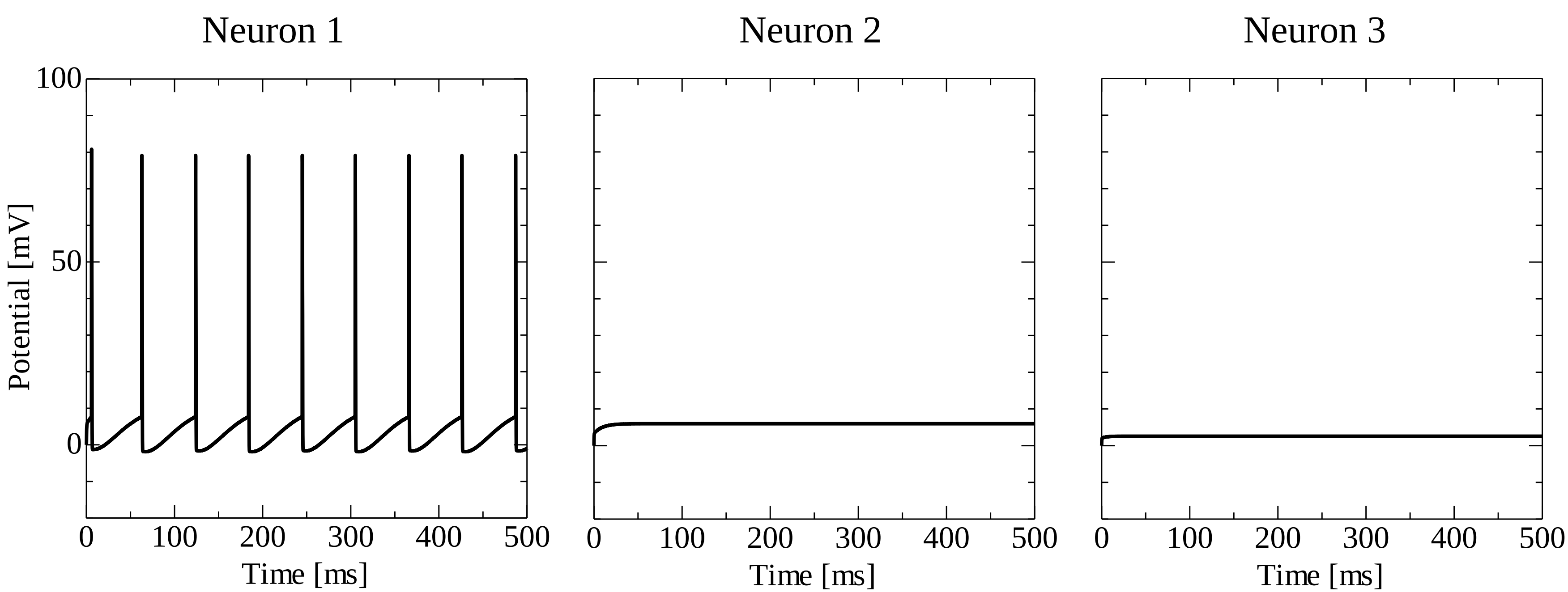
- Changing physical size of α-motoneurons

↓

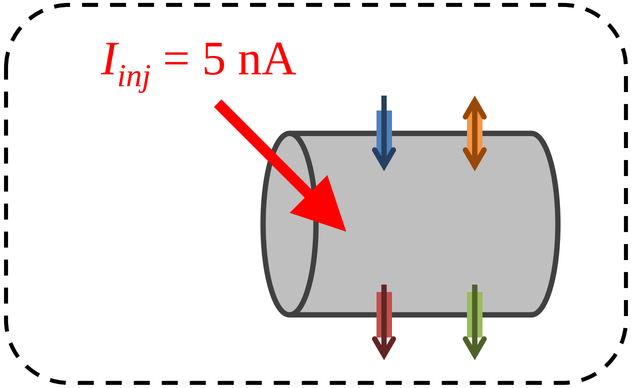
- Changing behaviors for electrical stimulation

Results

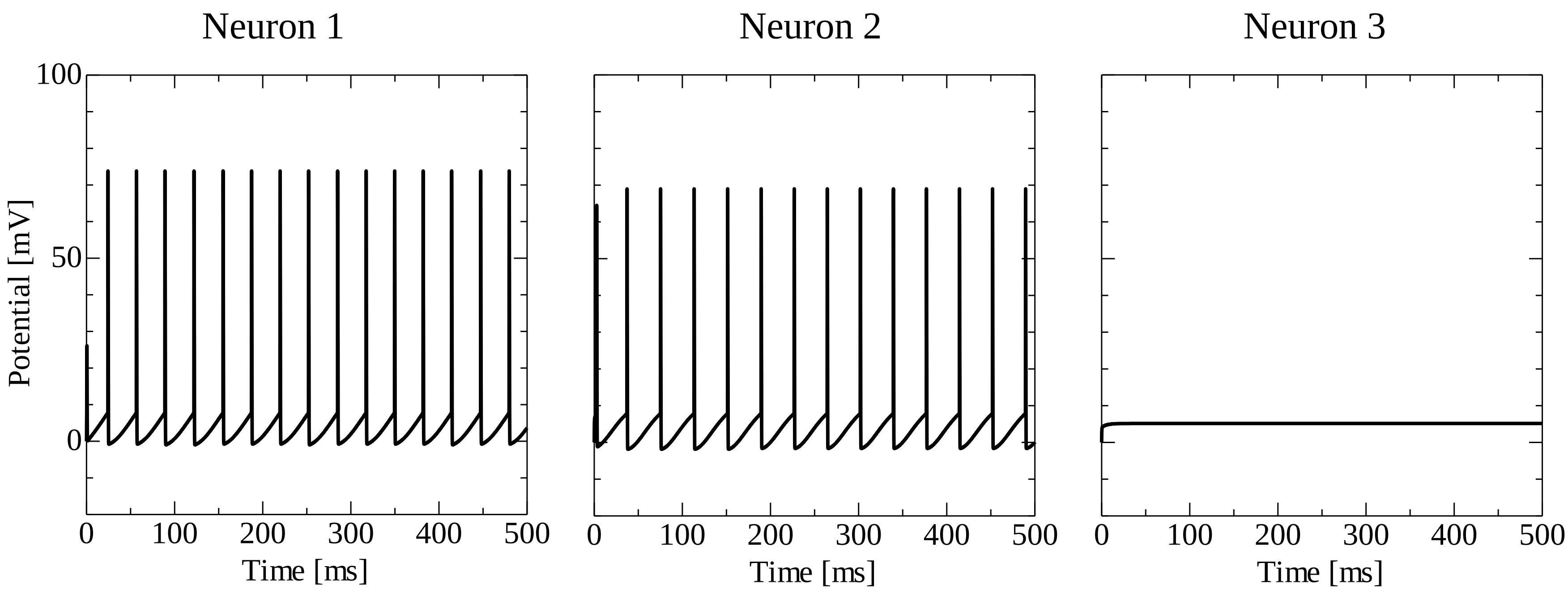
Time course of membrane potential for I_{inj} = 5 nA



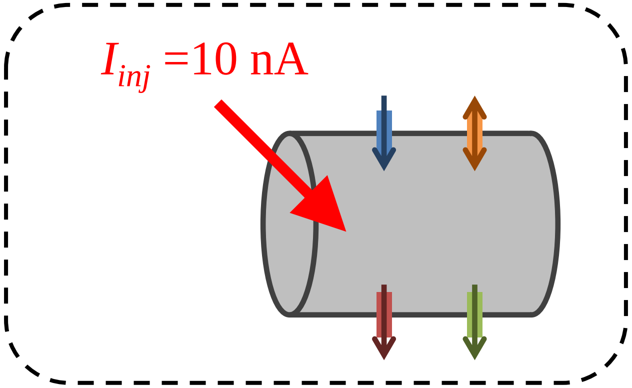
- Only the smallest motoneuron is firing.
- Larger motoneurons are not activated.



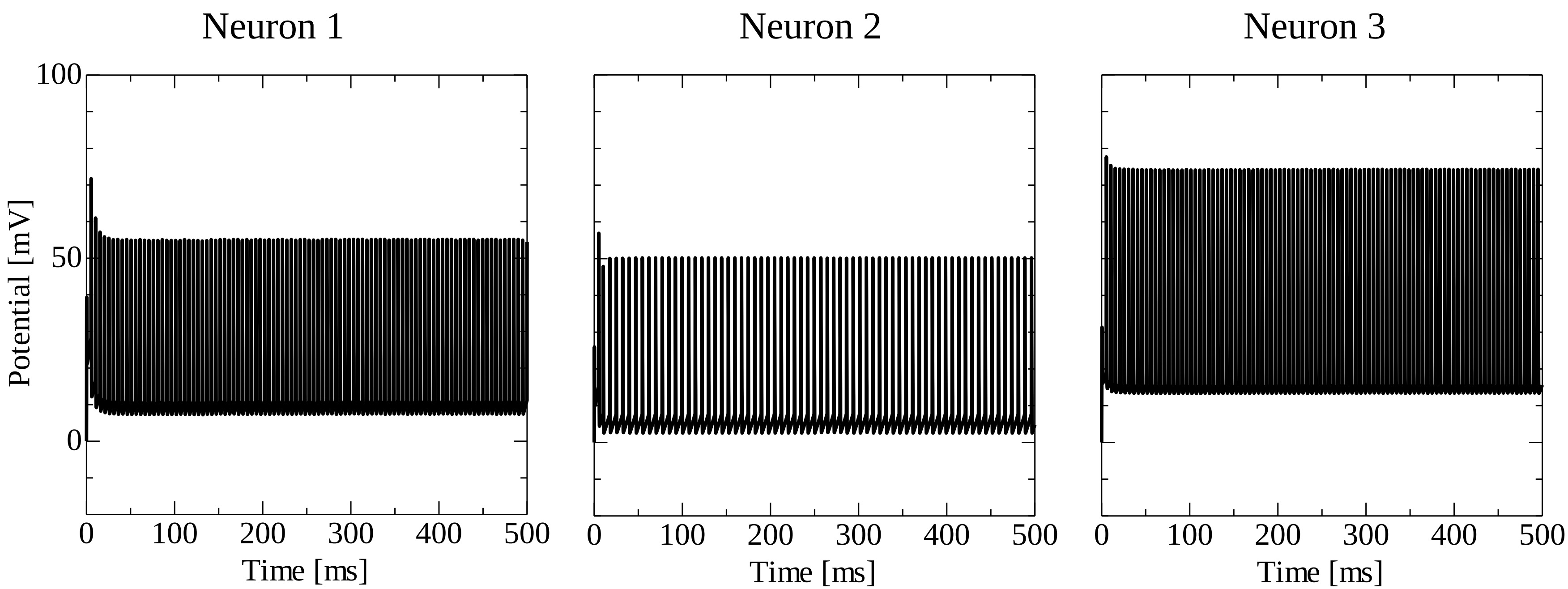
Time course of membrane potential for I_{inj} = 10 nA



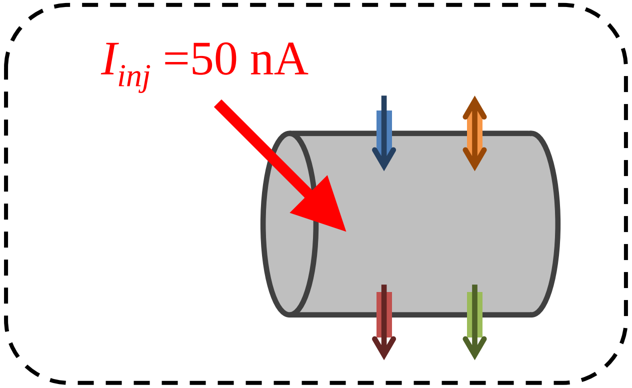
- Middle size α-motoneuron becomes activated.
  → recruitment
- The firing frequency of the smallest neuron becomes higher.
  → rate coding
- The largest motoneuron is not firing yet.



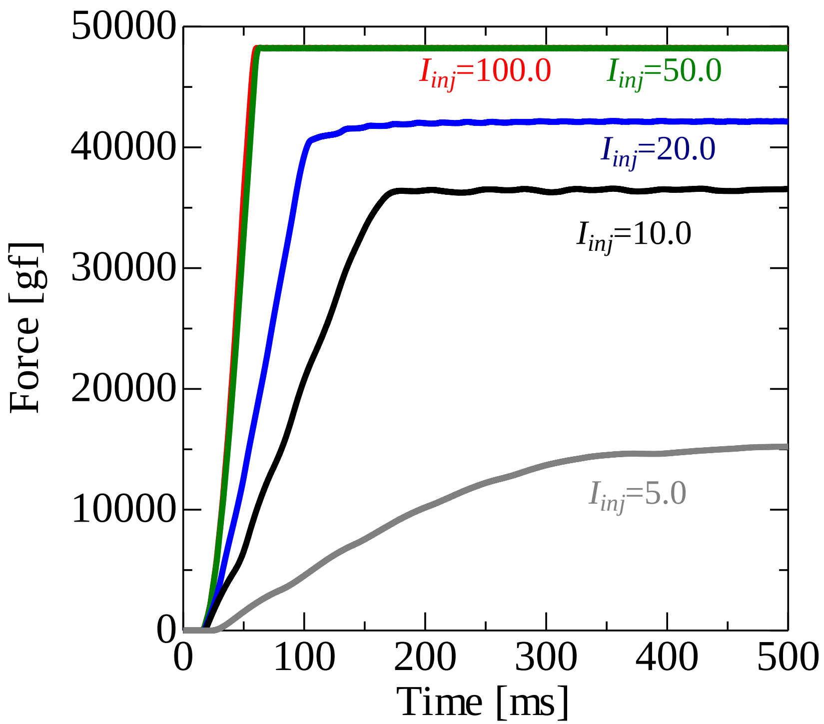
Time course of membrane potential for I_{inj} = 50 nA



- The largest neuron is firing.
- Smaller motoneurons are firing with much higher frequency.



Generated force



Force model

$$F_M(t) = \sum_{i=1}^{N} F_i(t)$$

$$F_i(t) = \sum_{j=1}^{N_j} f_{i,j}(t - t_{i,j}) \qquad t - t_{i,j} \geq 0$$

$$f_{i,j}(t) = g_{i,j} \frac{P_i \cdot t}{T_i} e^{1-t/T_i}$$

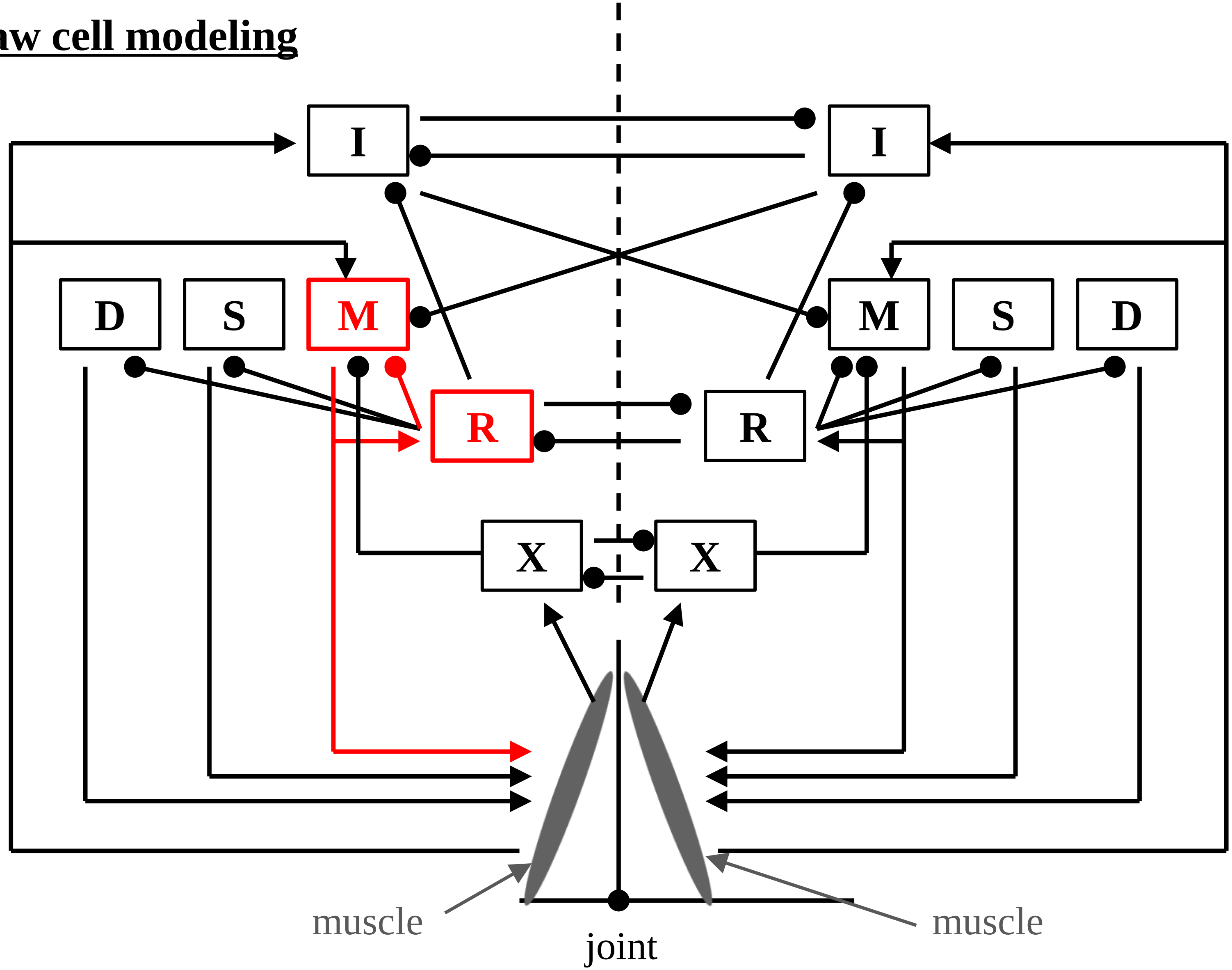
$$g_{i,j} = \begin{cases} 1 & (T_i/ISI_j \leq 0.4) \\ \dfrac{1}{T_i/ISI_j} \cdot \left[1 - e^{-2(T_i/ISI_j)^3}\right] & (0.4 \leq T_i/ISI_j) \end{cases}$$

➢ The injected current is increased

⇨
- Generated muscle force becomes strong,
- Time to the maximum force generation is reduced.

Rate coding and recruitment are reproduced!

Renshaw cell modeling



Inhibitory signal
Excitatory signal

I: I_a interneuron
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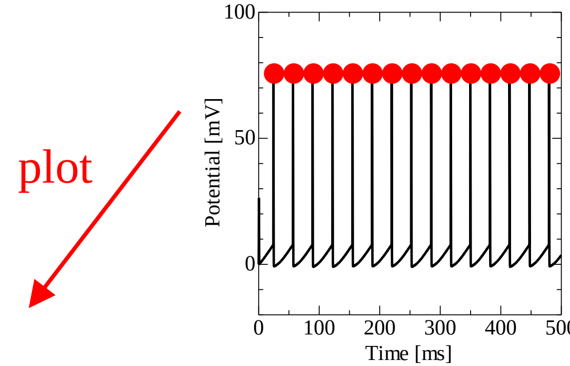
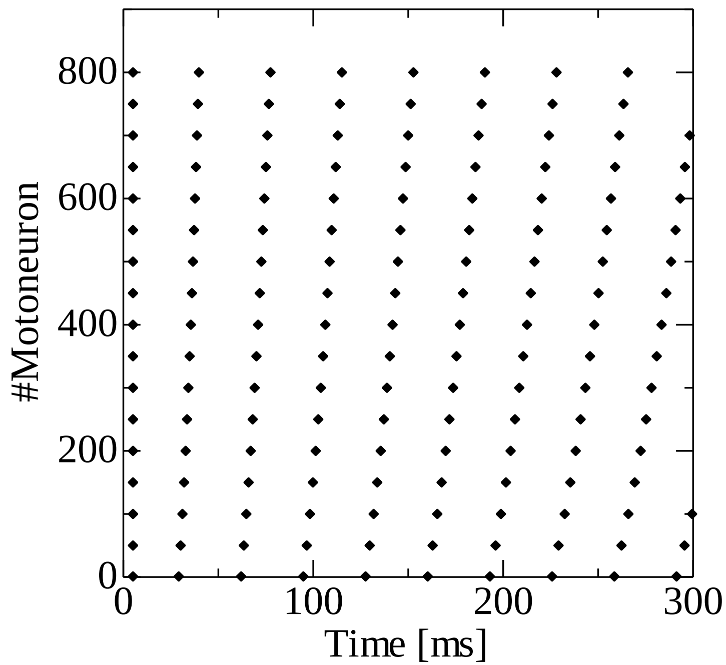
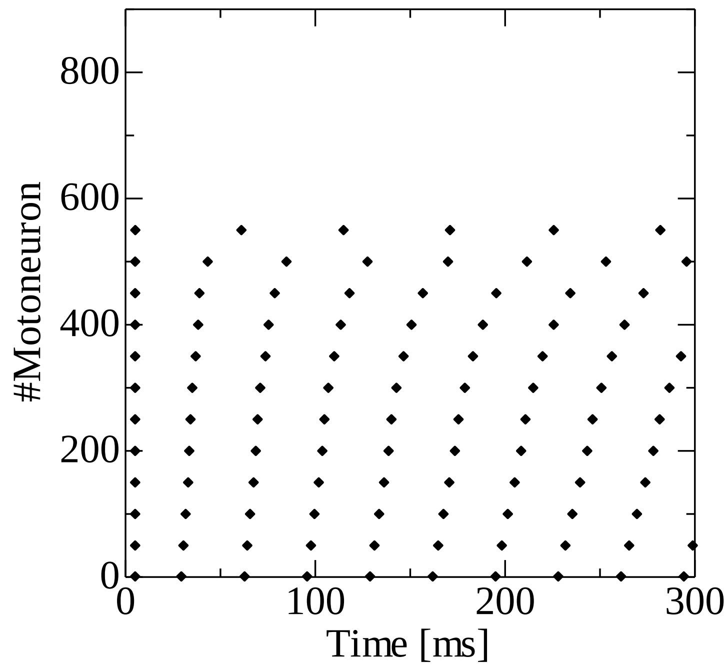
R: Renshaw cell

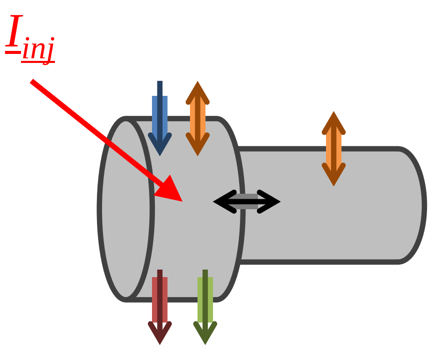
M: α-motoneuron
S: Static γ-motoneuron
D: Dynamic γ-motoneuron

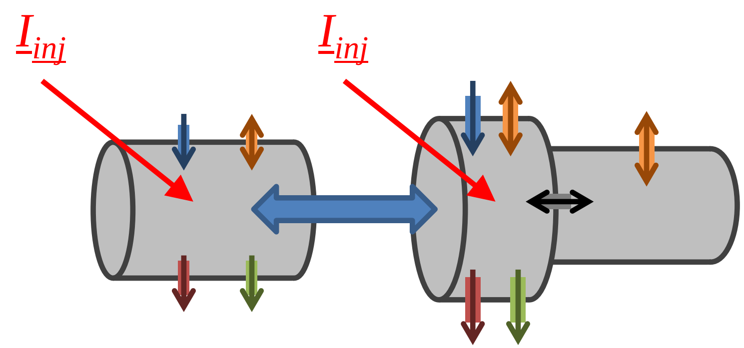
Time course of firing for I_{inj} = 10 nA



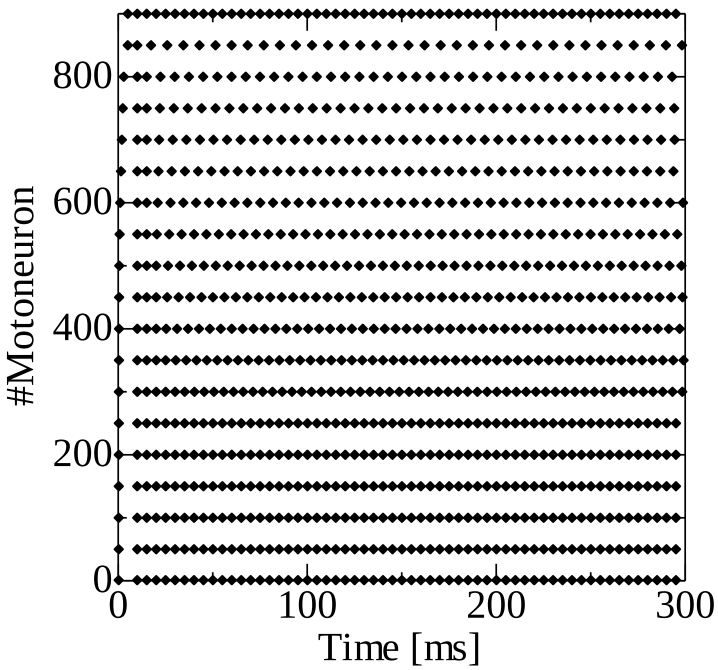


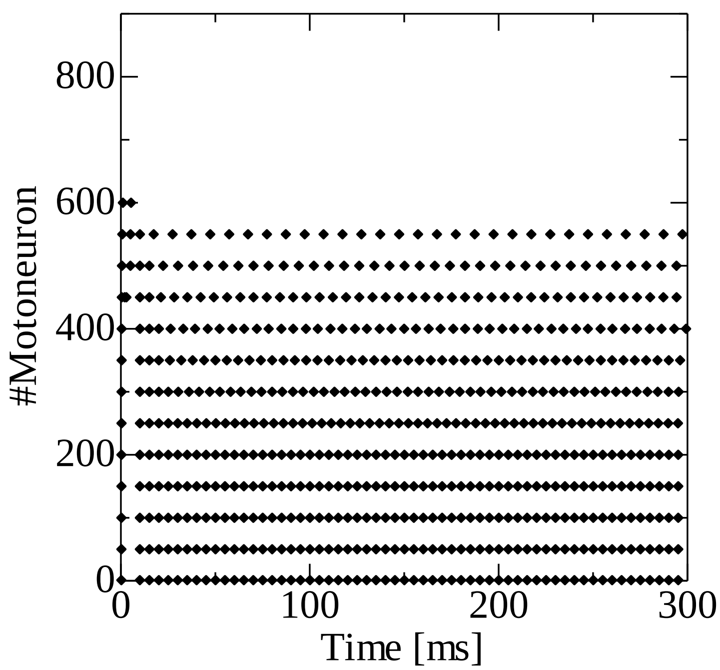


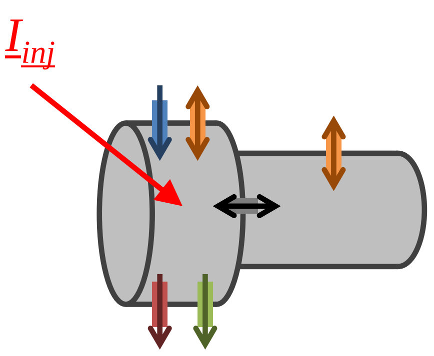


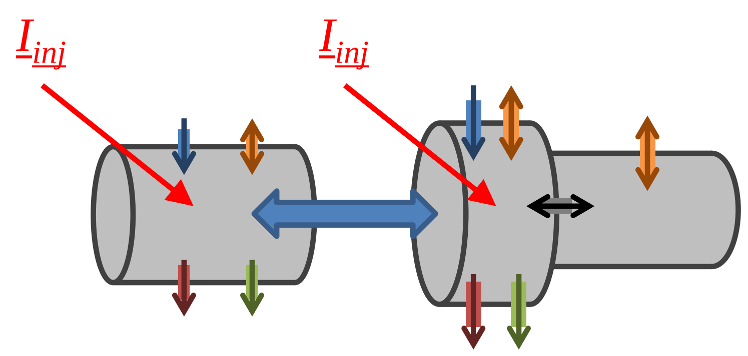


Time course of firing for I_{inj} = 50 nA

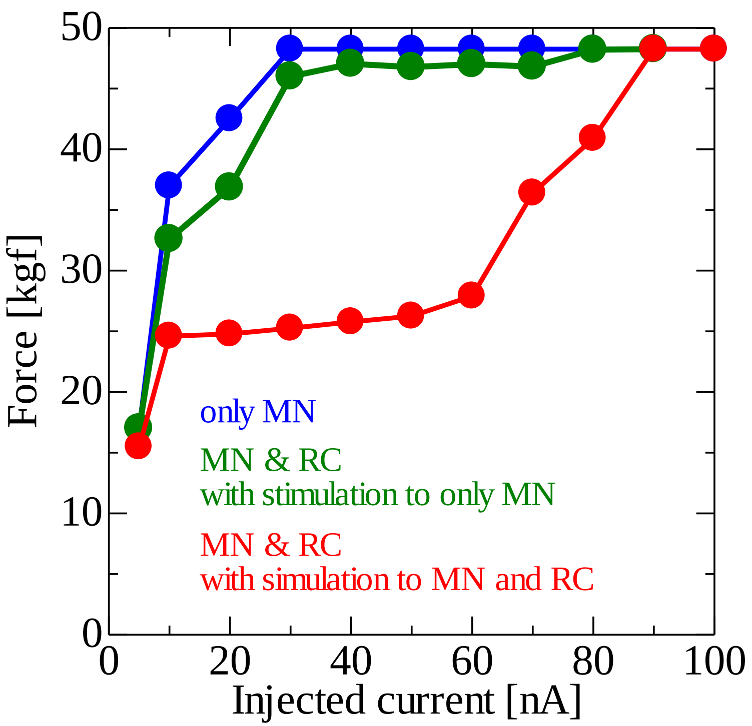






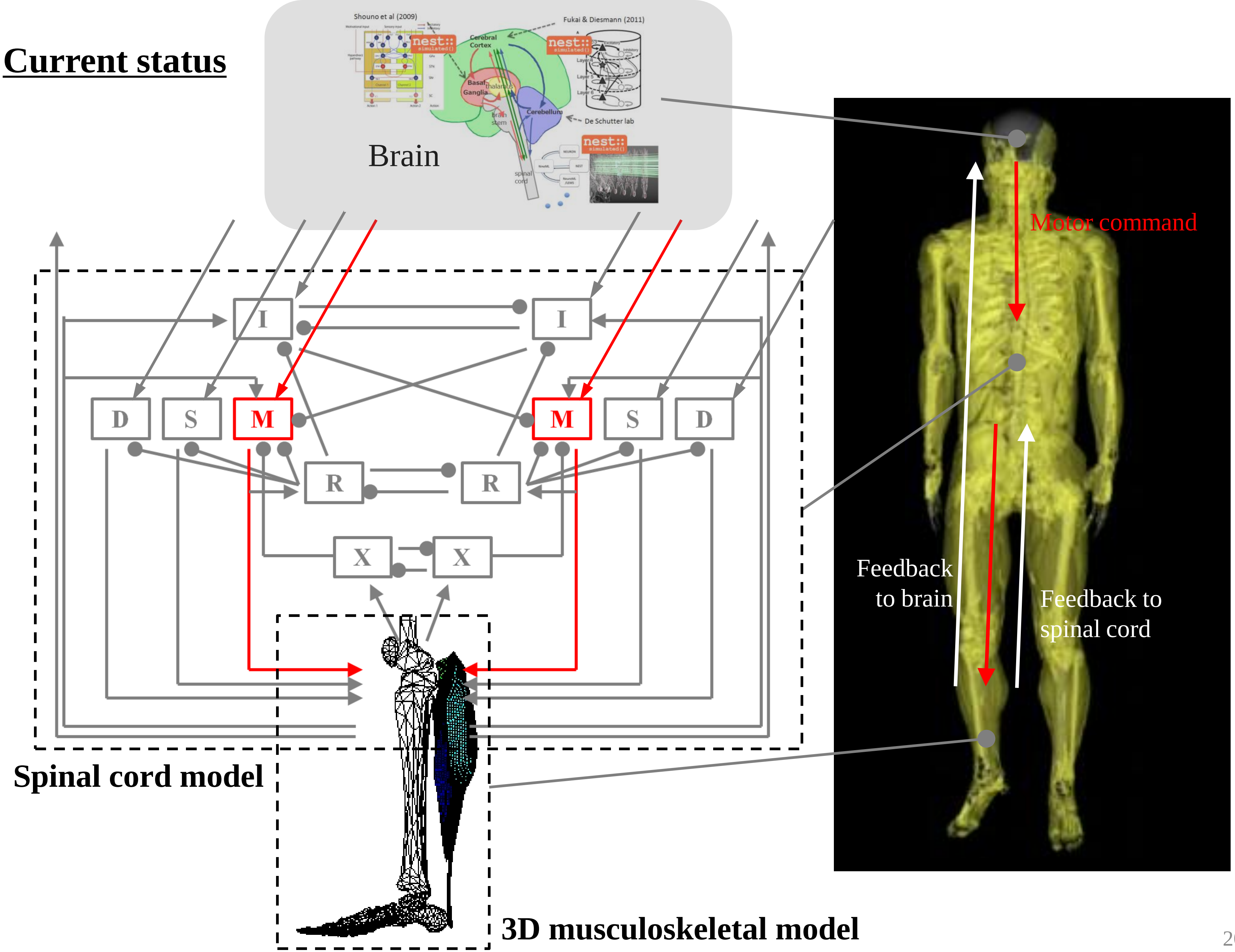


Generated force

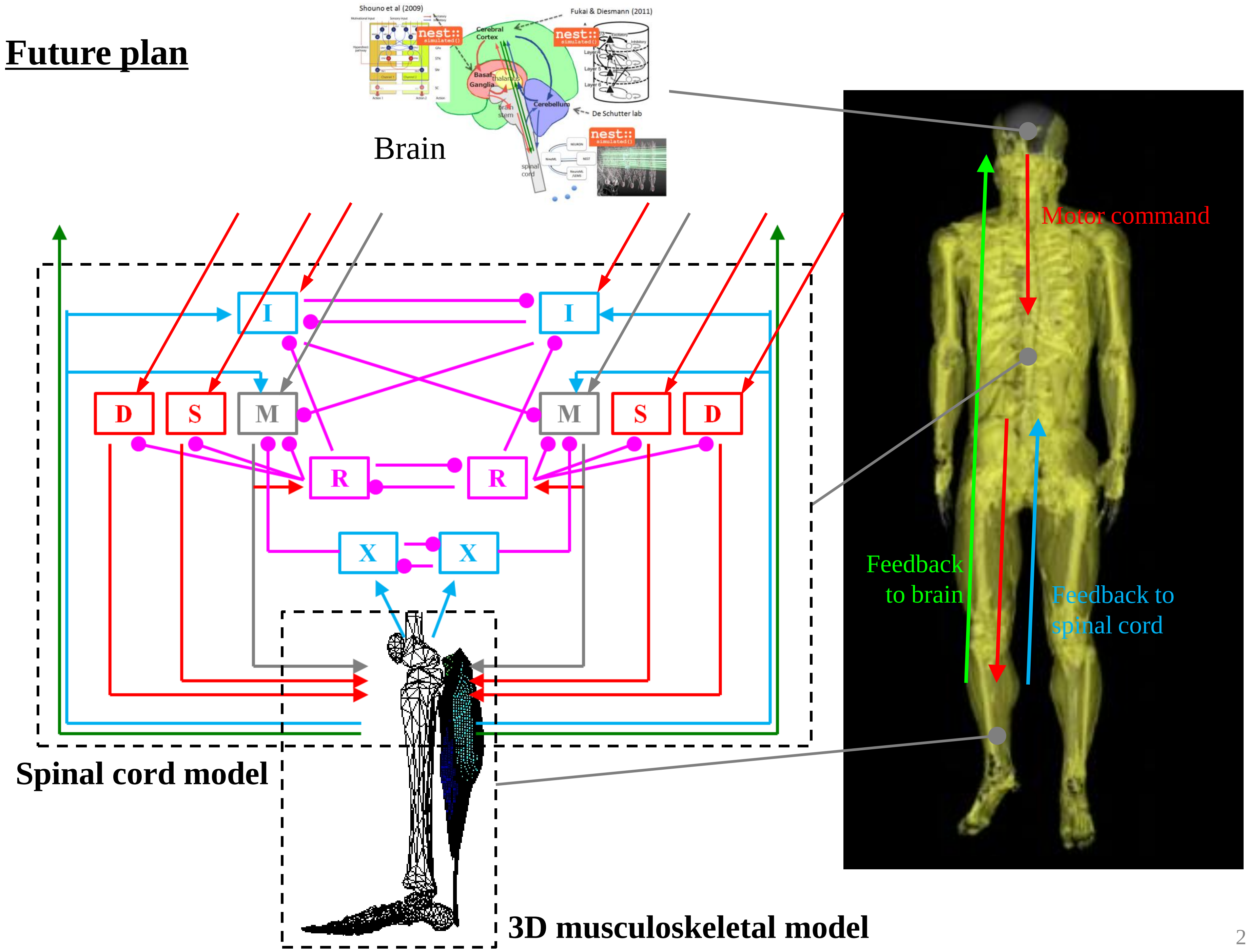


- Recurrent inhibition from Renshaw cell depresses exerted force.
- Inhibition has a large effect on recruitment of α-motoneuron.

Current status



Future plan



Shouno et al (2009)
Fukai & Diesmann (2011)
De Schutter lab
Cerebral Cortex
Basal Ganglia
thalamus
Cerebellum
brain stem
spinal cord
Brain
I
I
D
S
M
M
S
D
R
R
X
X
Motor command
Feedback to brain
Feedback to spinal cord
Spinal cord model
3D musculoskeletal model

まとめ

- 本発表では，分野1課題3「予測医療に向けた階層統合シミュレーション」の中で，「神経疾患による運動機能障害解明のための全身筋骨格-神経系統合シミュレーション」に関連する内容について解析モデルの開発状況を報告した.

- 脳から発せられた運動指令を伝達する脊髄中枢神経系ネットワークについて，ニューロン発火モデルに基づいた運動ニューロンおよび介在ニューロンの数理モデル構築について紹介し，Recruitment と Rate coding という主要な筋力調整メカニズムを再現するモデルを構築したことを報告した.

- 筋骨格系の3次元有限要素法に関しては，能動的な筋力発揮メカニズムを考慮した数値解析モデル開発の現状について紹介した. 医療画像データに基づいたふくらはぎ筋肉に対する解析結果から，力の発揮メカニズムやその際の三次元データを報告した.