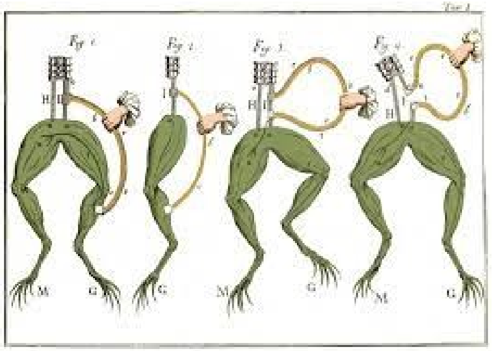
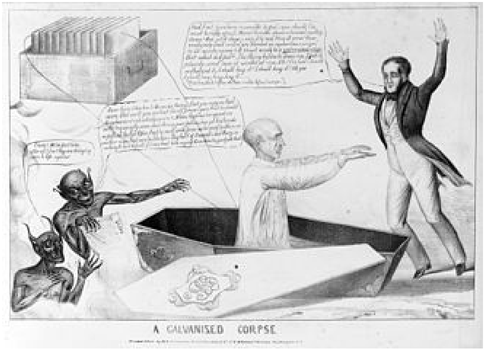
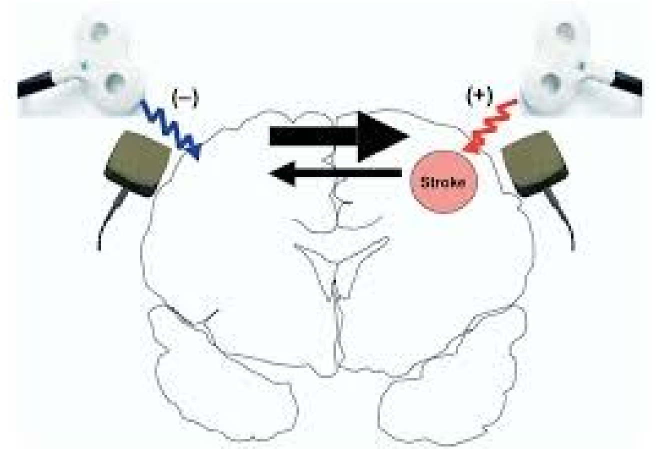
Michele Allegra

Approaches to brain controllability

Outline







Where and how should we stimulate?

Outline

What is a good theoretical framework to design neuromodulation?

- The network control theory approach

- Some issues with the network control approach

- Directions for alternatives: reduce dimensionality?

Requirements for *targeted* neuromodulation

- *In vivo* system

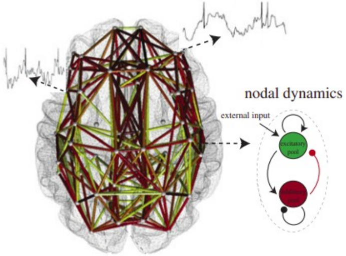
design perturbation

implement it in the system

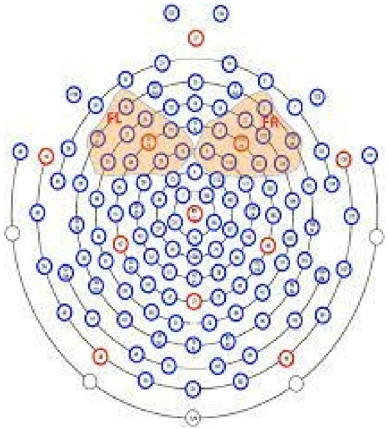
measure system

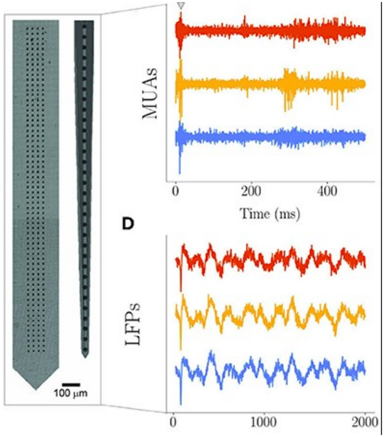
model dynamics

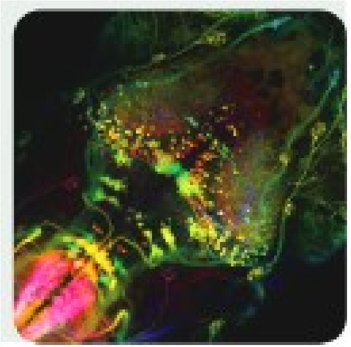
- *In silico* model



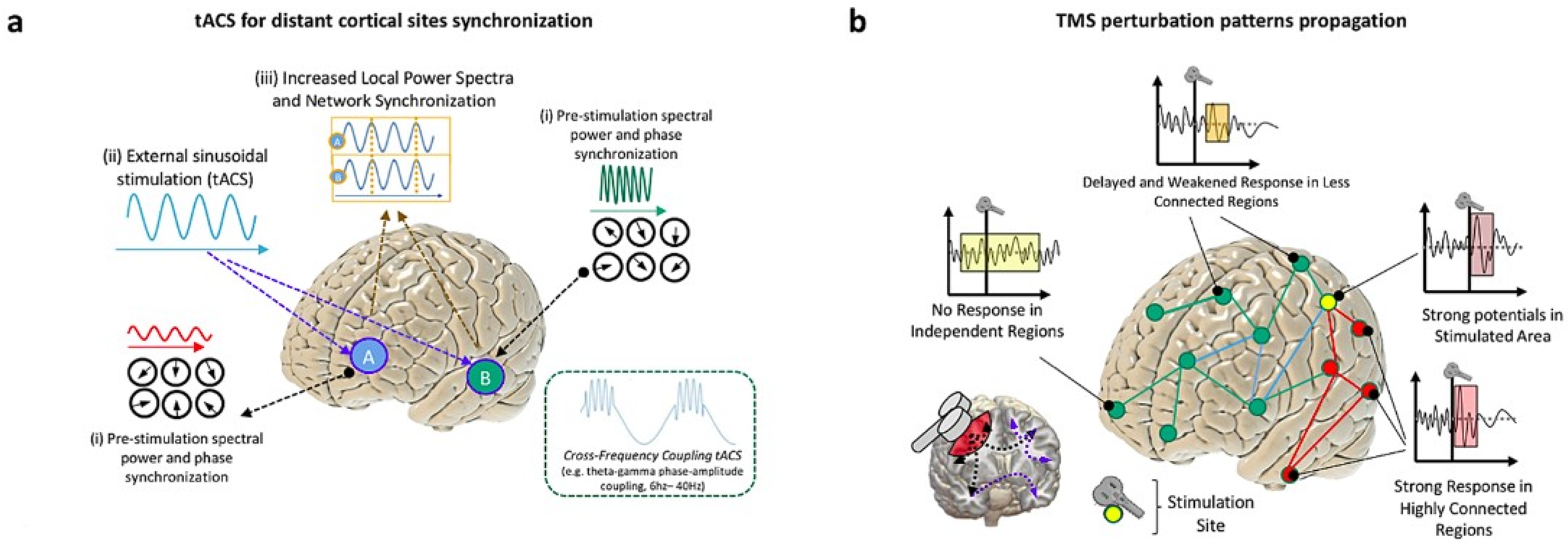
Measure: improved recording techniques are becoming available



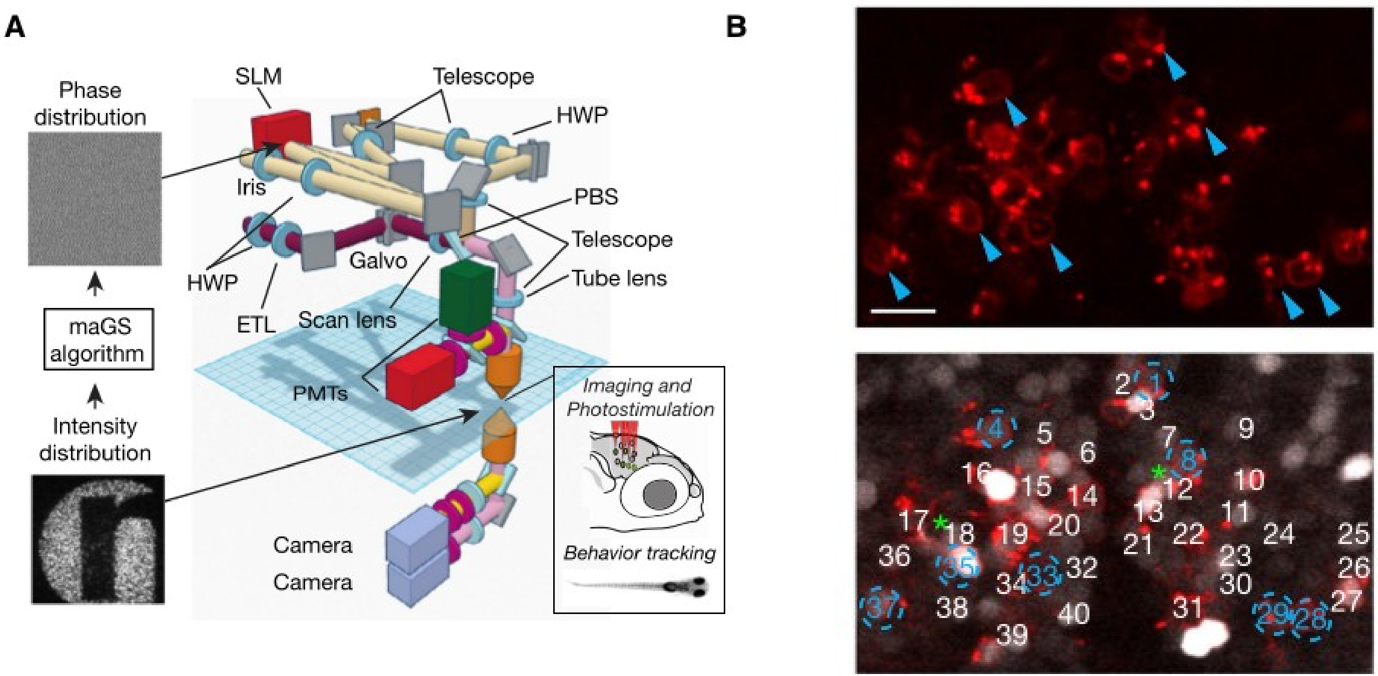




Implement: improved stimulation techniques are becoming available



Implement: improved stimulation techniques are becoming available



Dal Maschio, M., Donovan, J. C., Helmbrecht, T. O., & Baier, H. (2017). Linking neurons to network function and behavior by two-photon holographic optoge and volumetric imaging. Neuron, 94(4), 774-789.

Towards targeted modulations

- (i) measurement
- (ii) **modeling**
- (iii) **design**
- (iv) application

What is a good theoretical framework to design neuromodulation?

Control of large-scale brain activity

Open Access | Published: 01 October 2015

Controllability of structural brain networks

Shi Gu, Fabio Pasqualetti, Matthew Cieslak, Qawi K. Telesford, Alfred B. Yu, Ari E. Kahn, John D. Medaglia, Jean M. Vettel, Michael B. Miller, Scott T. Grafton & Danielle S. Bassett

Published: 18 October 2017

Network control principles predict neuron function in the *Caenorhabditis elegans* connectome

Gang Yan, Petra E. Vértes, Emma K. Towlson, Yee Lian Chew, Denise S. Walker, William R. Schafer & Albert-László Barabási

- model: *linear model* based on structural connectome
- design: use classical (linear) control theory
- implement: use neuromodulation (not even at proof-of-principle stage)

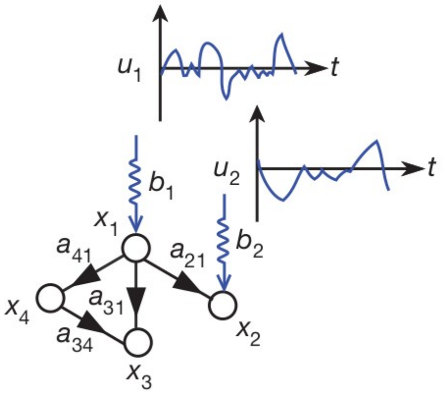
Network control theory

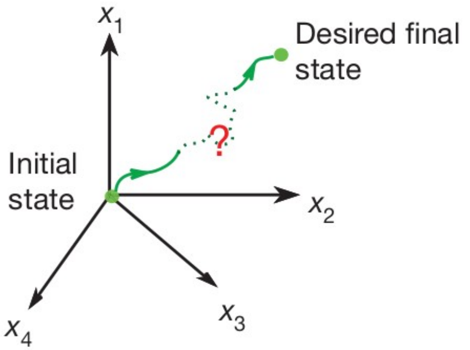
- **x**(t) - state vector for N “network nodes” at time t
- Dynamics is given by Linear Time Invariant(LTI) system:

$$\frac{d\mathbf{x}(t)}{dt} = A\mathbf{x}(t) + B\mathbf{u}(t)$$

- *A* - (N,N) connectivity matrix
- *B* - (N, r) input matrix with “r” being number of control nodes required to control the system.

$$A = \begin{pmatrix} 0 & 0 & 0 & 0 \\ a_{21} & 0 & 0 & 0 \\ a_{31} & 0 & 0 & a_{34} \\ a_{41} & 0 & 0 & 0 \end{pmatrix}; B = \begin{pmatrix} b_1 & 0 \\ 0 & b_2 \\ 0 & 0 \\ 0 & 0 \end{pmatrix};$$



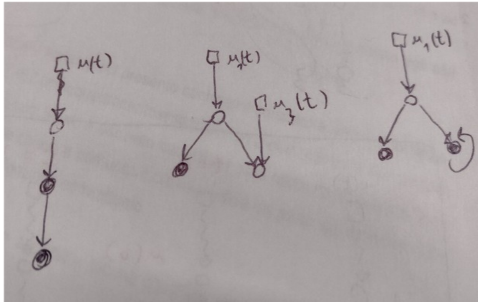


Network control theory

- The *design* problem has a complete solution (in principle)

- **Graph-theoretical criterion**
  to select minimal B (control nodes):

  unmatched nodes controlled
  with independent inputs



- **Algebraic criterion** to select u (control signal)

$$u = B^T e^{At_f} W^{-1}(e^{-At_f} x_f - x_0)$$

with Gramian

$$W = \int_0^\infty d\tau e^{A\tau} B B^T e^{A^T \tau}$$

Network control theory

- **Control energy**

$$E = \int_0^\infty d\tau ||u(t)||^2$$

$$\frac{\mathbf{dx}(t)}{\mathrm{d}t} = A\mathbf{x}(t) + B\mathbf{u}(t)$$

$$|B| \sim 1$$

- Physical meaning: depends on experimental setting

- Theoretical meaning: strength of stimulus-evoked vs intrinsic dynamics

- E.g. for fMRI, |A|$\sim$1, E $\sim$1 means stimulus-evoked and intrinsic dynamics are comparable

- Control energy is related to Gramian eigenvalues

$$E = x_f W^{-1} x_0$$

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- *N*=243 'nodes' (regions of atlas)
- *Model: linear model with dynamics = structural connectome*

$$\frac{d\mathbf{x}(t)}{dt} = A\mathbf{x}(t) + \mathbf{B}\mathbf{u}(t)$$

- *A* structural connectivity matrix (from diffusion MRI)
- *B* single-node input matrix
- Repeat the procedure over each and every node
- the brain is *theoretically* controllable from a single region

Theoretical vs pactical controllability

Tu, C., Rocha, R. P., Corbetta, M., Zampieri, S., Zorzi, M., & Suweis, S. (2018). Warnings and caveats in brain controllability. NeuroImage, 176, 83-91.

- 1) W>0 (controllability *in principle*), but **control energy is unfeasibly large**
- 2) To have $E_{min} < 10^{10}$ need to control >45% of nodes …

[scale of control input signal >> scale of normal activity fluctuations]

Table 1. The minimum number of nodes (and fraction with respect the size of the network) that are needed to control the system spending a minimum energy not greater than $\varepsilon_{min} = 10^{10}$.

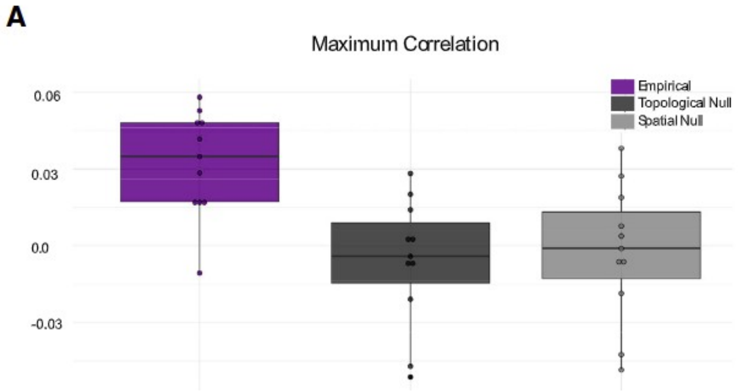
	Data		BA		SW		ER	
Centrality measure	Low	High	Low	High	Low	High	Low	High
Degree centrality	51/0.46	49/0.45	44.64/0.41	42/0.38	45/0.41	43.5/0.40	44.64/0.41	42/0.3

Control of large-scale brain activity

Stiso, J., Khambhati, A. N., Menara, T., Kahn, A. E., Stein, J. M., Das, S. R., ... & Bassett, D. S. (2019).
White matter network architecture guides direct electrical stimulation through optimal state transitions. Cell reports, 28(10), 2554-2566.

Stimulation with tDCS, recording with EcoG, structure measurement by diffusion MRI

Target state associated to successful memory encoding
[subject-level power-based biomarkers of good memory encoding extracted with a multivariate classifier from ECoG data collected during a verbal memory task]



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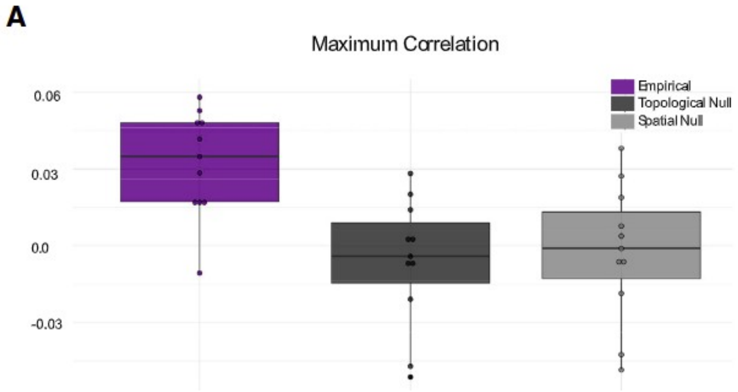


Whole-brain controllability through EC

K. Kabbur, ...,M. Corbetta, S. Suweis, A. Bertoldo, M. Allegra, in preparation.

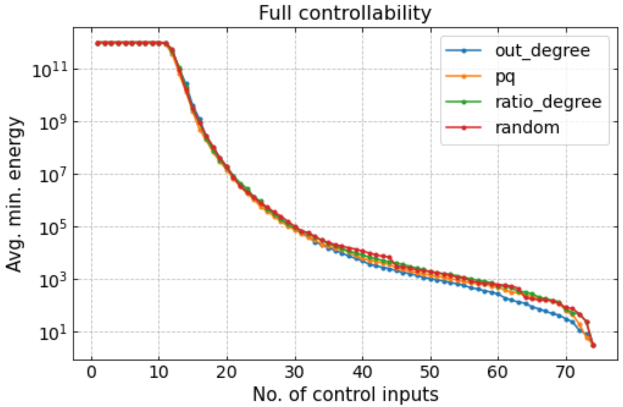
Improve modeling:

- Use effective connectivity (EC) instead of structural connectivity
- EC is directed and gives more accurate representation of dynamics (e.g. much better fit of functional connectivity)
- Sparse Dynamic Causal Modelling (spDCM)   [Prando et al., NIMG 2021]
- SpDCM *infers* dynamics *(A)* from observed fMRI activity

Controllability through EC

K. Kabbur, ..., S. Suweis, A. Bertoldo, M. Allegra, in prep.

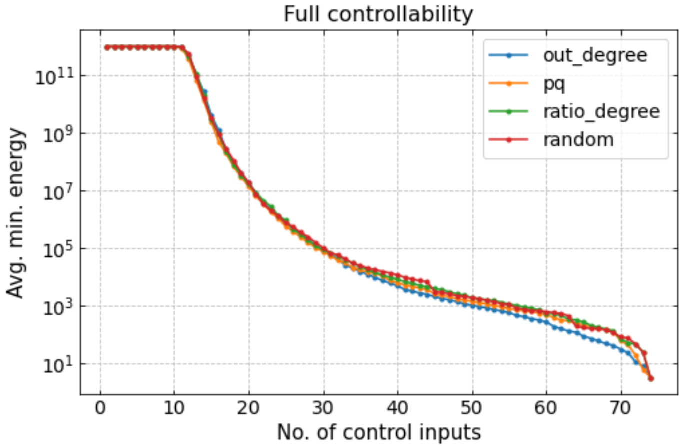
- The overall picture is qualitatively consistent with the one obtained by SC
- There are no unmatched nodes and *in principle* the system can be controlled by a single node (W>0)
- *In practice,* control energy is very large, ($>10^{10}$) unless at least **15% of nodes** are controlled

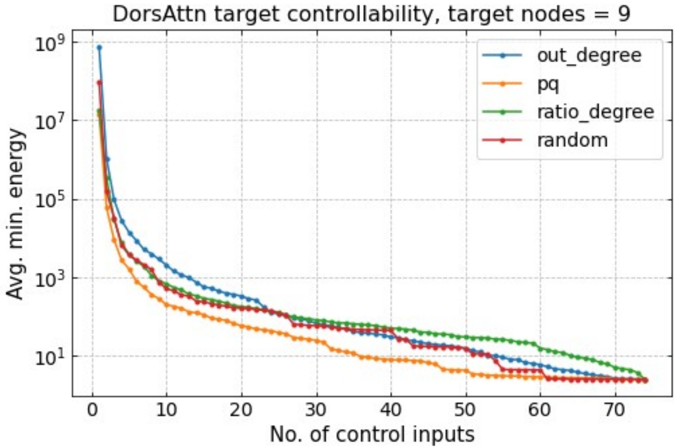


Controllability through EC

K. Kabbur, ..., S. Suweis, A. Bertoldo, M. Allegra, in prep.

- *target controllability:* we only wish to control only a subset of nodes [Gao, Jianxi, et al. "Target control of complex networks." Nat. Comm. 5.1 (2014): 1-8.]
- the control energy required is significantly lower but still large





A theoretical issue

- Gao, Sun, J., & Motter, A. E. (2013). Controllability transition and nonlocality in network control. Physical review letters, 110(20), 208701]

- Trajectories are long and energy is large unless a significant fraction of nodes is controlled

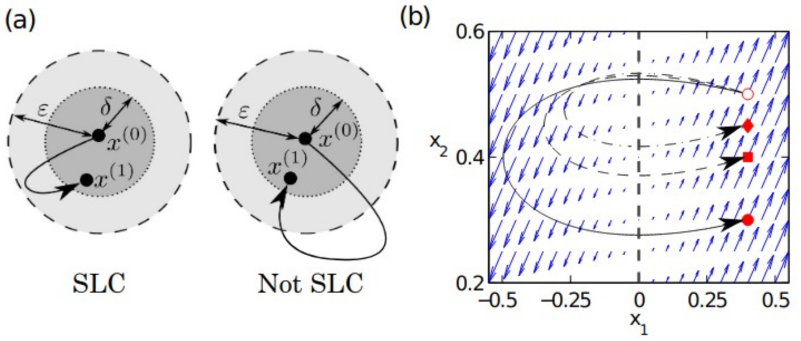


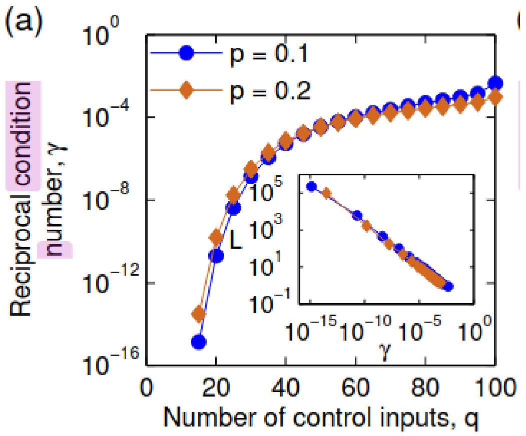
FIG. 1. (a) Illustration of a state that is SLC (left) and of a state that is not (right). (b) Example system $\dot{x}_1 = x_1 + u_1(t)$, $\dot{x}_2 = x_1$, where any state not on the line $x_1 = 0$ is not SLC; the curves in-

A theoretical issue

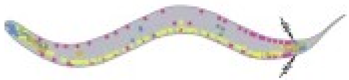
- Gao, Sun, J., & Motter, A. E. (2013). Controllability transition and nonlocality in network control. Physical review letters, 110(20), 208701]

- *numerical error* in final state is related to condition number = inverse of energy

$$x_f - \tilde{x}_f \propto \frac{1}{|\gamma|} = E$$



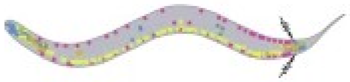
linear controllability in a simpler animal model



- *(measurement)* the connectome can be completely measured (~2000 connections)
- *(modeling)* Due to exhaustive knowledge, the model is faithful
- *(implementation)* we can perform well localized perturbations
- However, controllability was used only to identify neurons that are necessary for muscle control, not to induce state

linear controllability in a simpler animal model

Yan, G., Vértes, P. E., Towlson, E. K., Chew, Y. L., Walker, D. S., Schafer, W. R., & Barabási, A. L. (2017). Network control principles predict neuron function in the Caenorhabditis elegans connectome. Nature, 550(7677), 519-523.



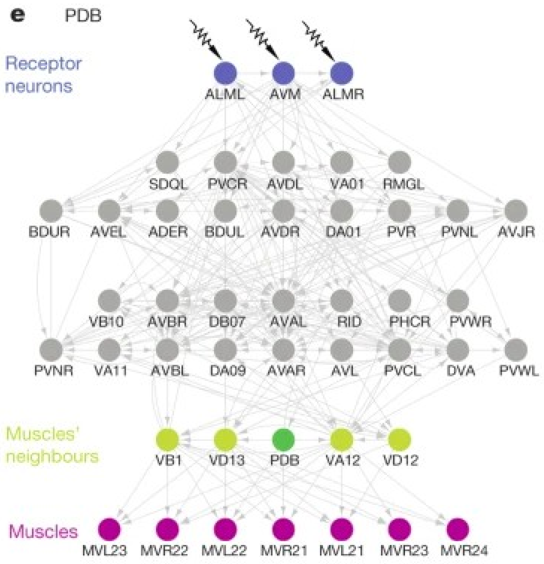
- Linear controllability of C. Elegans (279 neurons)

- Target controllability: try to identify neurons that directly control specific muscles

- Linear control theory with SC predict which neurons are necessary for moving specific muscles

- However, controllability with SC was used only to identify neurons that are necessary for muscle control

- not used to induce specific movements via neuromodulation



An alternative approach to control?

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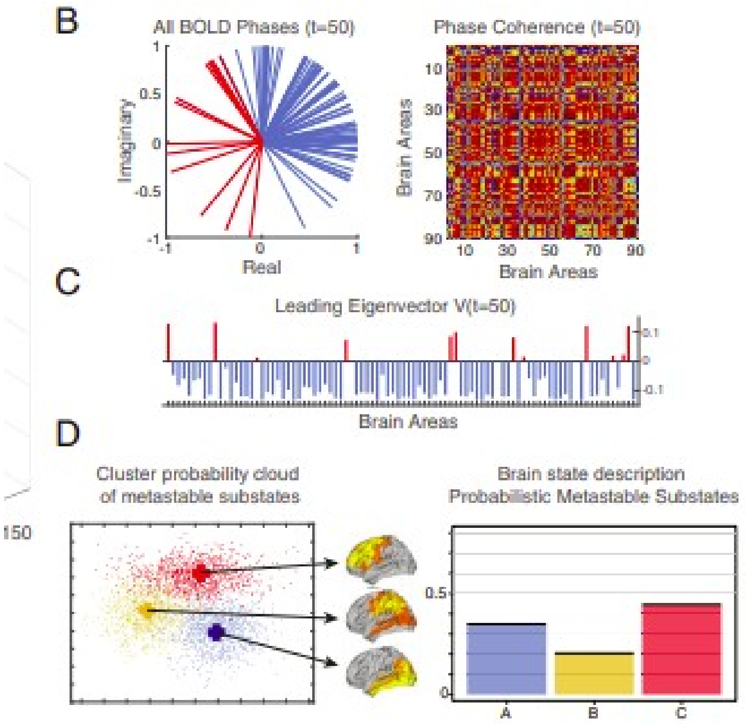
Can we exploit dimensionality reduction to address the controllability problem?

- the target is not a “*microstate*” (activity state **x***), but a “*macrostate*” (activity regime)

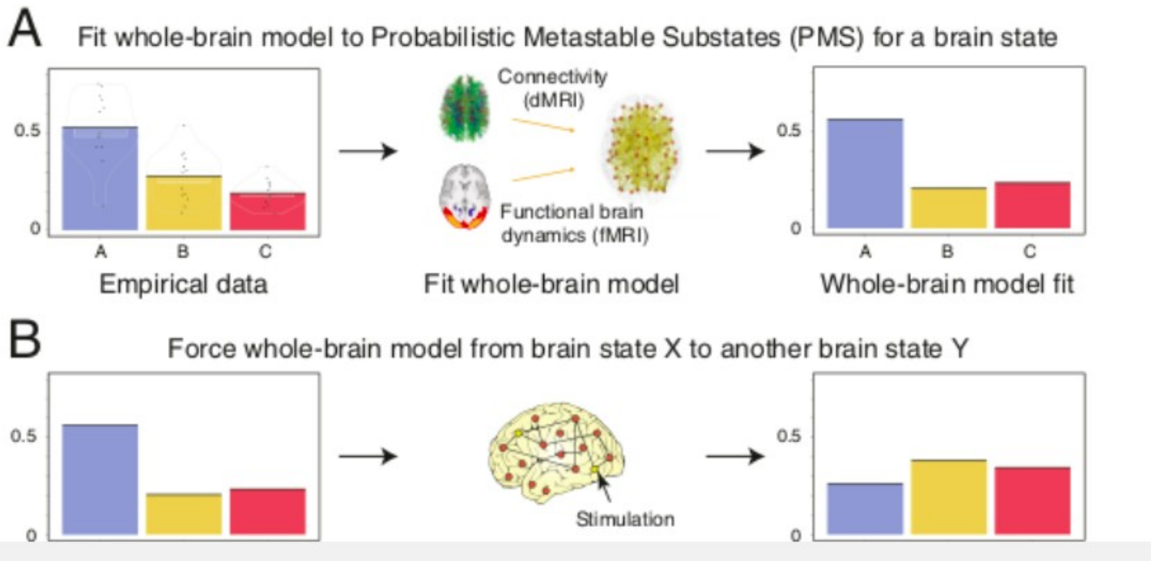
- try to control balance between dynamic connectivity patterns
  [Deco et al. PNAS 116.36 (2019): 18088-18097.]

- The probabilities of different states determine “macrostate”



An alternative approach to control?

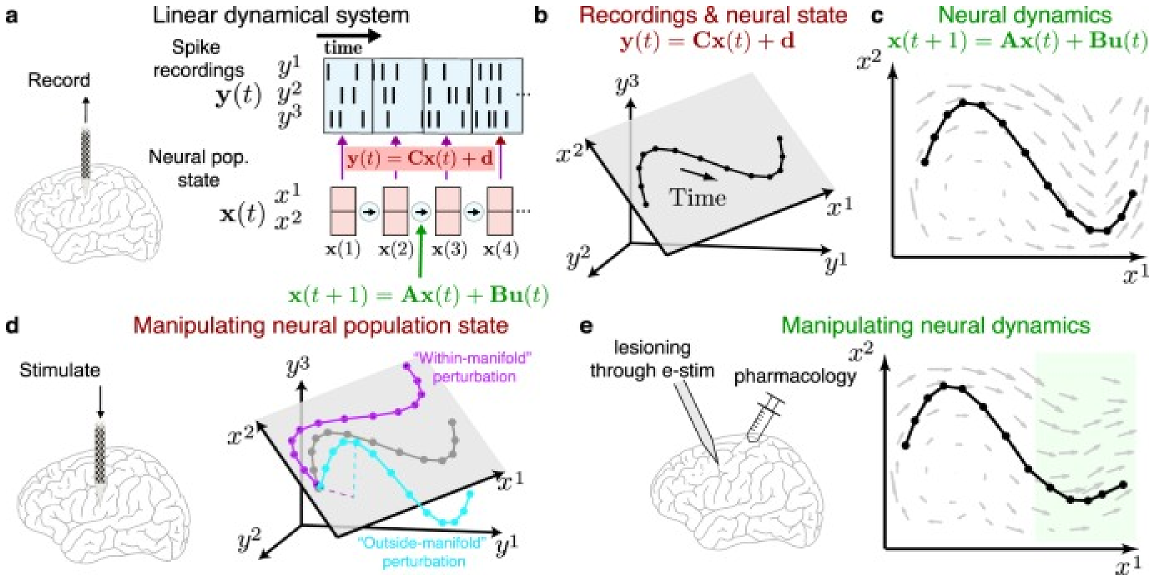
Can we exploit dimensionality reduction to define an easier control objective?



An alternative approach to control?

dynamics (approximately) unfolds on low-dimensional manifolds

can we try to control the key "directions" in neural space?

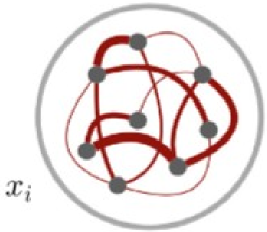


[Shenoy & Kao. Nat. Comm. 12.1 (2021): 1-5]

An alternative approach to control?

M Beiran, A Dubreuil, A Valente, F Mastrogiuseppe, S Ostojic
Neural Computation 33 (6), 1572-1615

$$\tau \frac{dx_i}{dt} = -x_i + \sum_{j=1}^{N} J_{ij}\phi\left(x_i\right) + I_i^{ext}\left(t\right),$$

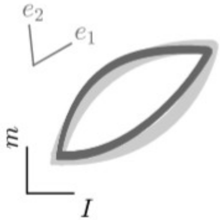


high D

$$J_{ij} = \frac{1}{N}\sum^{R} m_i^{(r)} n_j^{(r)}.$$

$$x_i\left(t\right) = \sum_{r=1}^{R} \kappa_r m_i^{(r)} + \sum_{s=1}^{N_{in}} \kappa_{I_s} I_i^{(s)}.$$

$$\tau \frac{\quad}{dt} = -\kappa_r + \tilde{a}_{n_r} + \sum_{l=1} \tilde{\sigma}_{n_r m_l}\kappa_l.$$



low D

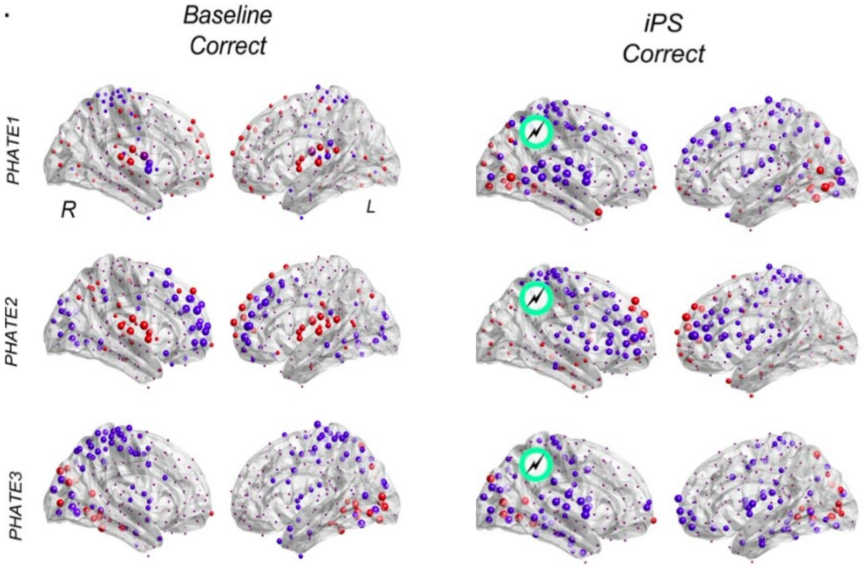
problem: control signal are applied locally (x), not on hidden degrees of freedom ()

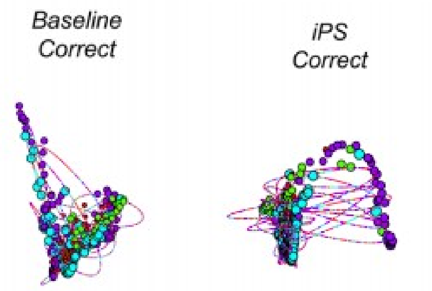
An alternative approach to control?

dynamics (approximately) unfolds on low-dimensional manifolds

can we try to control the key “directions” in neural space?

Iyer, K. K., Hwang, K., Hearne, L. J., Muller, E., D’Esposito, M., Shine, J. M., & Cocchi, L. (2022). Focal neural perturbations reshape low-dimensional trajectories of brain activity supporting cognitive performance. Nature communications, 13(1), 1-8.





Recap

- "Controllability" of neural activity requires the ability to model the activity and to design external interventions
- We need an appropriate theoretical paradigm to address the design problem
- The simplest approach (linear modeling + classical linear controllability) is poorly effective for large networks
- Possibly, improvements may be obtained by leveraging dimensionality reduction
- In particular, we should try to manipulate global, hidden degrees of freedom

I neuroni non hanno più segreti grazie alle ricerche di Eugenio Piasini

Obiettivo dare nuova vita ai paralizzati e malati agli occhi

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PADOVA neuroscience CENTER

UNIVERSITÀ DEGLI STUDI DI PADOVA

Dipartimento di Fisica e Astronomia Galileo Galilei

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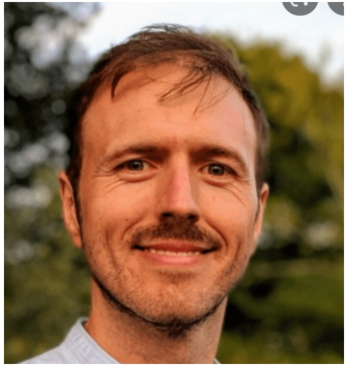


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Sparse DCM

Prando, G., Zorzi, M., Bertoldo, A., Corbetta, M., Zorzi, M., & Chiuso, A. (2020).
Sparse DCM for whole-brain effective connectivity from resting-state fMRI data. Neuroimage, 208, 116367.

- Linear model + hemodynamics

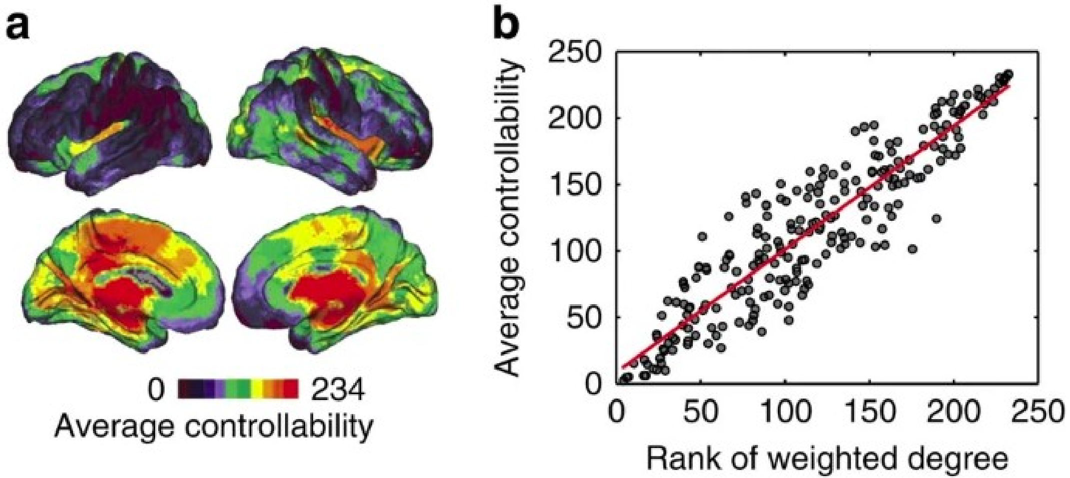
$$\dot{x}(t) = Ax(t) + v(t)$$

$$y(t) = h(x(t); \theta_h) + e(t)$$

- ODE → finite difference equation (discretization)
- Nonlinear hemodynamic response → linear response (linearization)
- Bayesian inference with EM algorithm
- Sparsity-inducing prior on connectivity

Control of large-scale brain activity

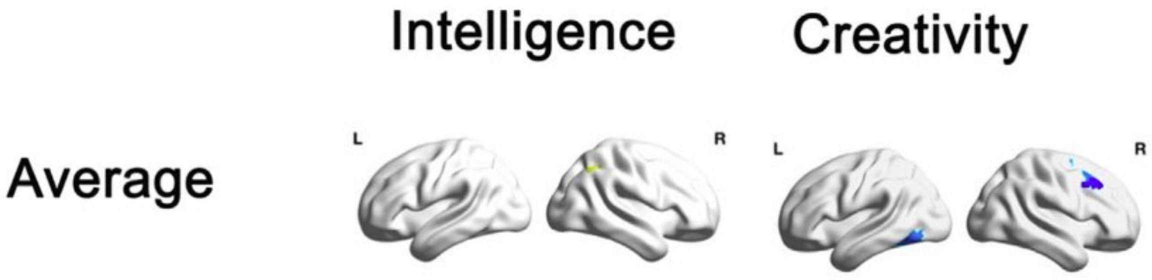
1) the brain is theoretically controllable from a single region (W>0)
2) when controlling one node “average energy” is proportional to node degree (# structural connections)



Control of large-scale brain activity

Kenett, Y. N., Medaglia, J. D., Beaty, R. E., Chen, Q., Betzel, R. F., Thompson-Schill, S. L., & Qiu, J. (2018). Driving the brain towards creativity and intelligence: A network control theory analysis. Neuropsychologia, 118

study on relation between controllability and intelligence (Raven test)



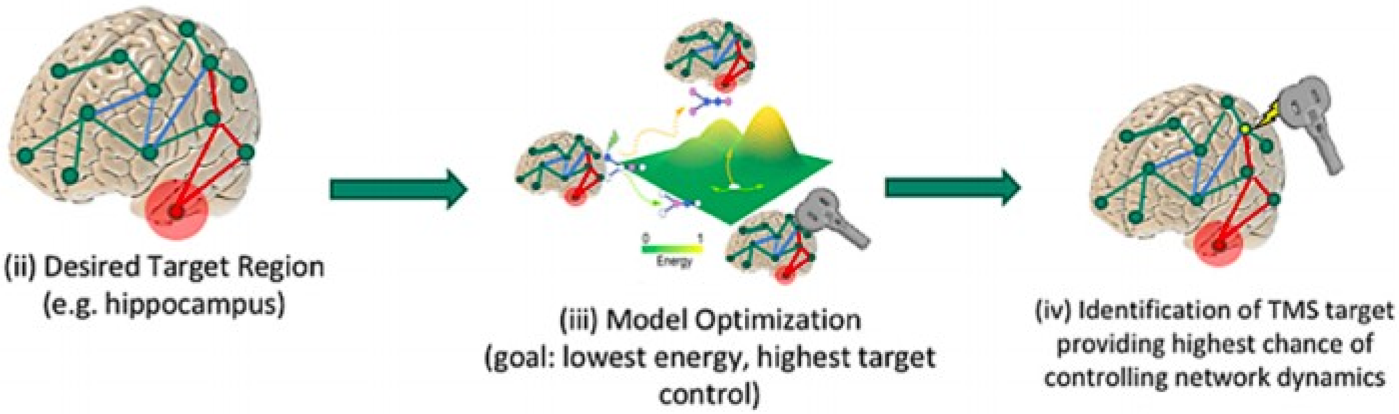
"We find that intelligence is related to the ability to "drive" the brain system into easy to reach neural states by the right inferior parietal lobe and lower integration abilities in the left retrosplenial cortex."

… a node's " average controllability" is correlated with structural topological properties (degree) of the node, which may be the actual relevant feature

Target controllability through EC

K. Kabbur, ..., S. Suweis, A. Bertoldo, M. Allegra, in prep.

- *target controllability:* we only wish to control the state of a subset of nodes
  [Gao, Jianxi, et al. "Target control of complex networks." Nat. Comm. 5.1 (2014): 1-8.]



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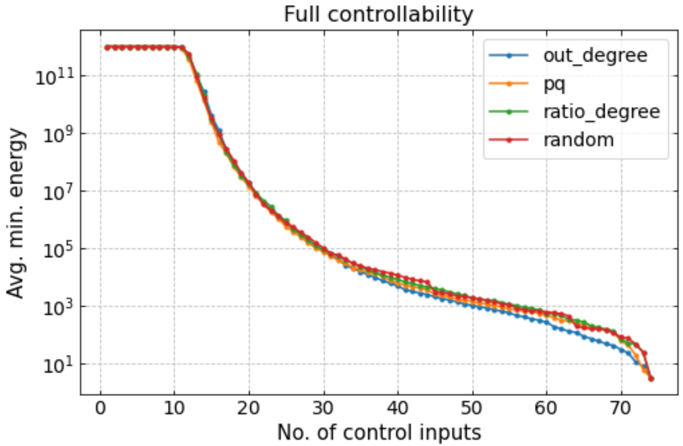

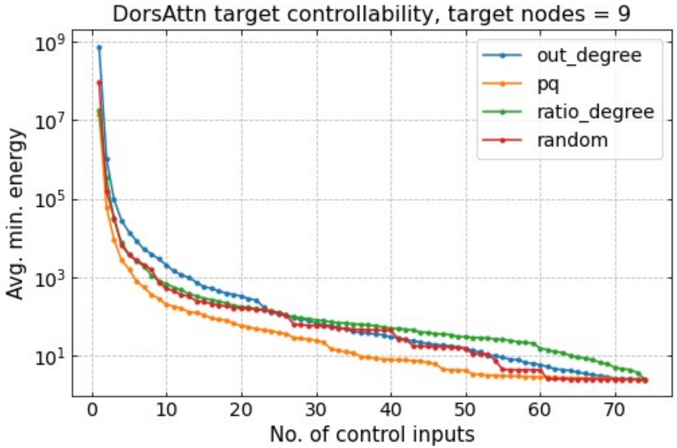

Limitations

Modeling:

[Tu, C., Rocha, R. P., Corbetta, M., Zampieri, S., Zorzi, M., & Suweis, S. (2018). Warnings and caveats in brain controllability. NeuroImage, 176, 83-91.]

- 1) No dynamical information, only structural
- 2) the proper model requires a *diagonal decay term* …

$$A = -\frac{1}{\tau}\mathbb{I} + cS$$

- 3) structural connectivity from dTI is symmetric. Cannot exploit directionality
  (in particular, cannot define unmatched inout nodes)
- 4) relation between "controllability" and structural degree is not specific to brain networks

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Issues with current controllability approach

- Provided the linear model provides accurate description of dynamics, linear controllability theory solves the problem of designing targeted interventions

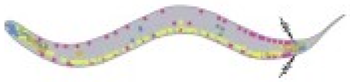
- *(measurement)* neuroimaging may not provide an accurate enough representation of brain activity

- *(modeling)* The linear model may not be accurate enough, and it is nontrivial to retrieve it from data (one should go beyond structural connectivity)

- *(design)* due to the size of the system, controlling the whole system requires very large amount of energy

- *(implementation)* in practice, we have o easy means of performing well-localized perturbations

linear controllability in a simpler animal model



Advantages of animal model:

- *(measurement)* the connectome can be completely measured (~2000 connections)
- *(modeling)* Due to exhaustive knowledge, the model is faithful
- *(implementation)* we can perform well localized perturbations

However:

- However, controllability with SC was used only to identify neurons that are necessary for muscle control
- not used to induce specific movements via neuromodulation

Issues with current controllability approach

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- Provided the linear model provides accurate description of dynamics, linear controllability theory solves the problem of designing targeted interventions

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