EOM Pulleys & Compartments – Sense & Nonsense

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Thank you for inviting me

Over the next 2 days I'll talk about:

- EOM Pulleys & Compartments
  - Why you should not be surprised that orbital connective tissues perform complex mathematical operations.

- Biomechanical Analysis of Strabismus.
- Injection Treatment of Strabismus.

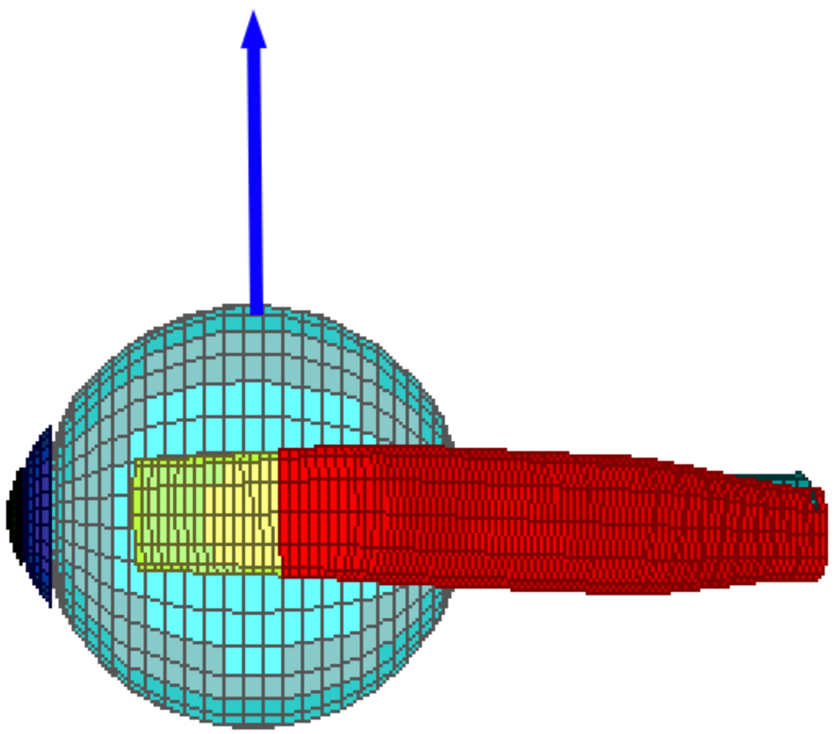
I have more material than time, so I've posted the complete lectures online at www.eidactics.com.

Abstract

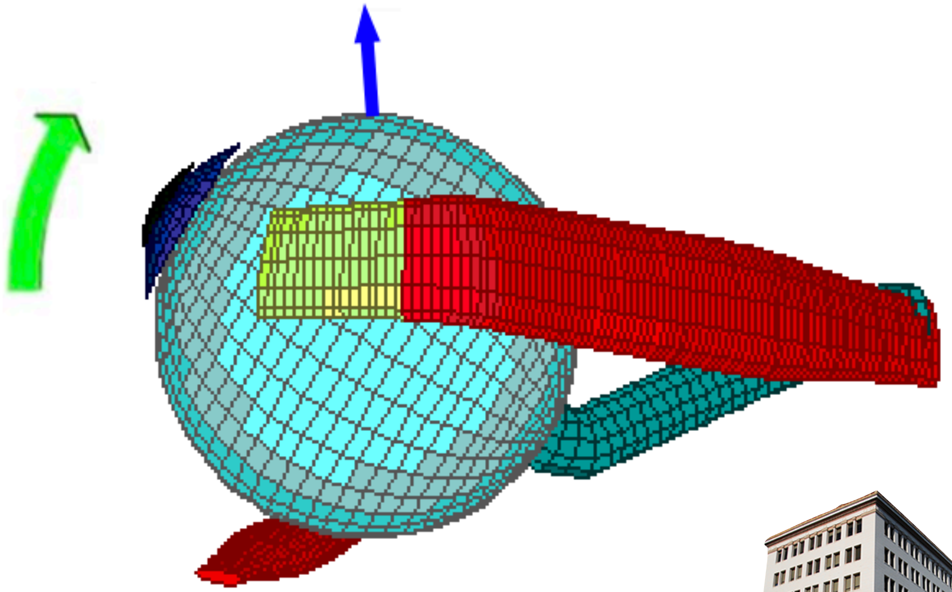
- EOM Pulleys are examples of Morphological or Embodied Computation - complex mathematical calculations, assumed to require the brain, are actually done by dumb connective tissues.
- Their unexpected discovery by Miller (1989, 1993) and elaboration by Demer (2000) resolved 2 fundamental mysteries in oculomotor physiology:
  - Brainstem control of 3D eye rotation requires coordination of horizontal and vertical eye movement centers, but no such connections can be found.
  - Listing's Law requires a particular eye torsion (ψ) for each gaze angle (H, V), but no brain center can be found that reflects these calculations.
- Unfortunately, these surprising refutations of classical ideas created an atmosphere of scientific nihilism in which dubious notions were presented as facts:
  - The Active Pulley and EOM Compartments hypotheses, which seek to replace 6 EOMs with 17 "mini-muscles", are implausible and unsupported by evidence.
  - Obsolete & invalid methodologies have been promoted, yielding a torrent of misleading research, so complex that it is difficult to evaluate.
- The purpose of this talk is to distinguish the valid insights of EOM Pulleys from the nonsense that followed.

Traditional Models of Muscle Action are Wrong

- According to classical notions (egs, Boeder, 1962; Krewson, 1951), rectus EOMs are constrained only at their ends, each following a great-circle path from its insertion to tangency with the globe, and then a straight path to its origin in the orbital apex.

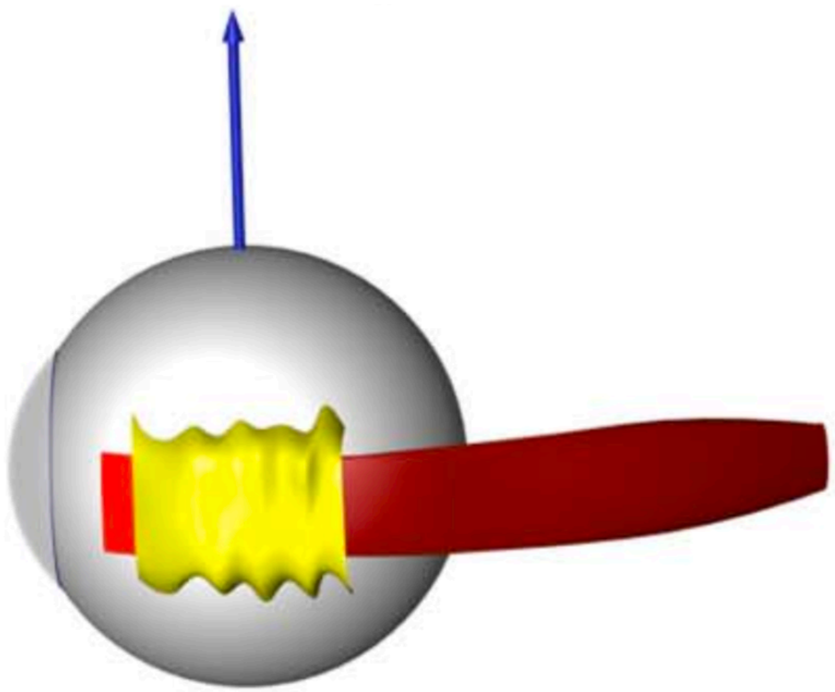


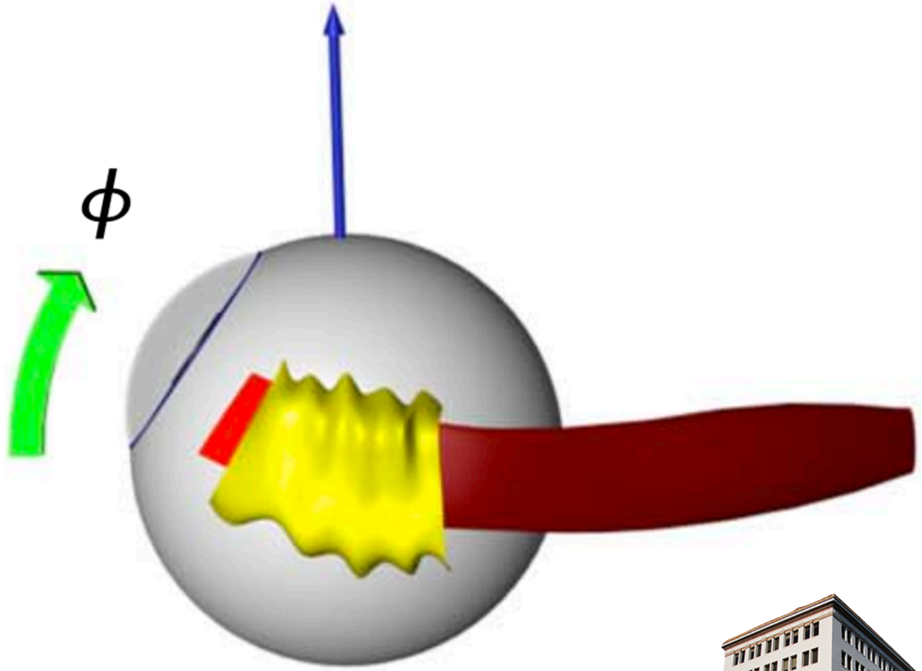
- Robinson (1975) showed by modeling that this could not be correct: during normal eye rotation such muscles would sideslip wildly about the globe, which would make eye rotation uncontrollable, and in any case did not occur.



Robinson's Permitted Sideslip Model

- Robinson proposed a sort of patch, that sideslip was prevented by connective tissues fixing the anterior muscle to the globe (yellow blob).
- The essential feature of this models is that a muscle's axis of rotation (**blue arrow**) remains roughly fixed for all gazes.
- Along with everyone else, Robinson supposed that Listing's Law was computed in the brain, though no one had a clue where or how.



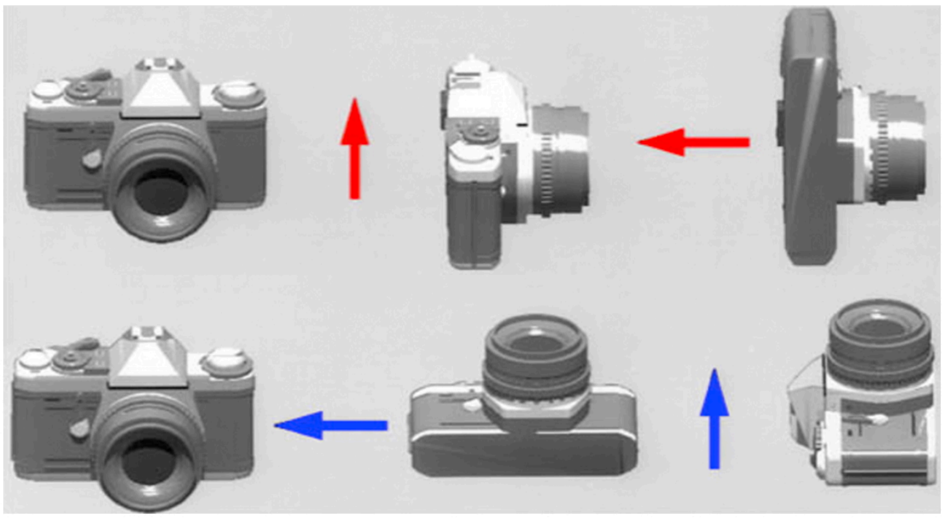


Rotations Are Noncommutative

- "Commutative" or "additive" operations are independent. Their order doesn't matter, eg: x+y = y+x.
- Translations are commutative (A): Walking 2 blocks north, then 1 block east (**red** arrows) brings you to the same place as walking 1 block east, then 2 blocks north (**blue**). Order of translations does not affect final position.
- Rotations are Noncommutative (B): Rotating 90° about an up axis, then about a left axis (**red** rotation vectors) does not get to the same orientation as rotating about a left axis, then about an up axis (**blue**). Changing the order of rotations changes the final position. Horizontal & vertical rotations must be coordinated.

A

B

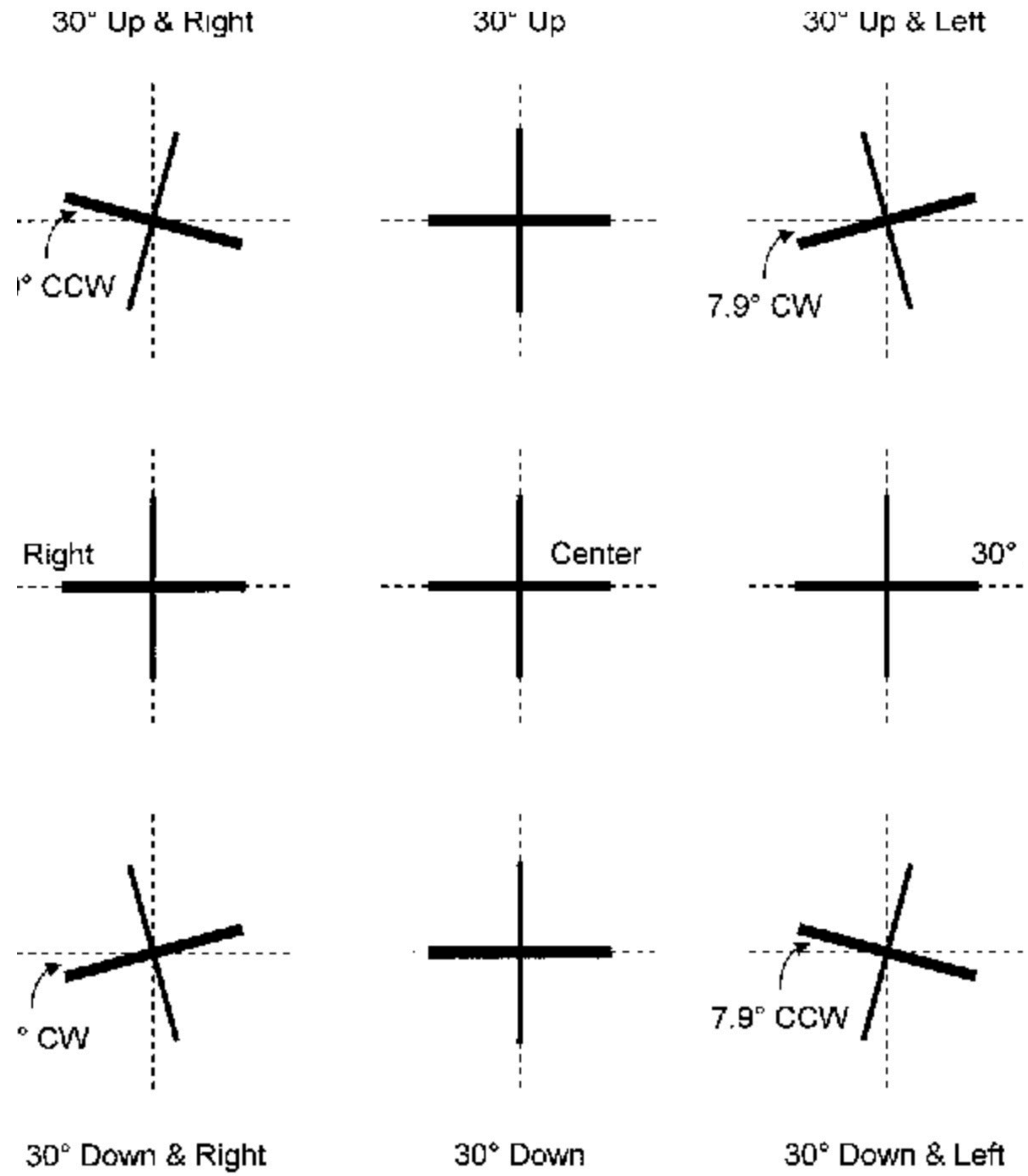


Two Big Problems

Listing's Law gives the torsional angle (ψ) normally assumed by the eye for each gaze angle (ϑ, φ):

$$\psi = \sin^{-1} \frac{\sin\vartheta \cdot \sin\varphi}{1 + \cos\vartheta \cdot \cos\varphi}$$

1. It was natural to assume that ψ was computed by a "Listing's Law box" in the brain, but physiologists could find no such center.
2. Worse, independent horizontal[1] and vertical[2] gaze centers could not possibly control non-additive eye rotation.



1. abducens nucleus & PPRF
2. riMLF & the interstitial nucleus of Cajal

Is The Brain is Necessary?

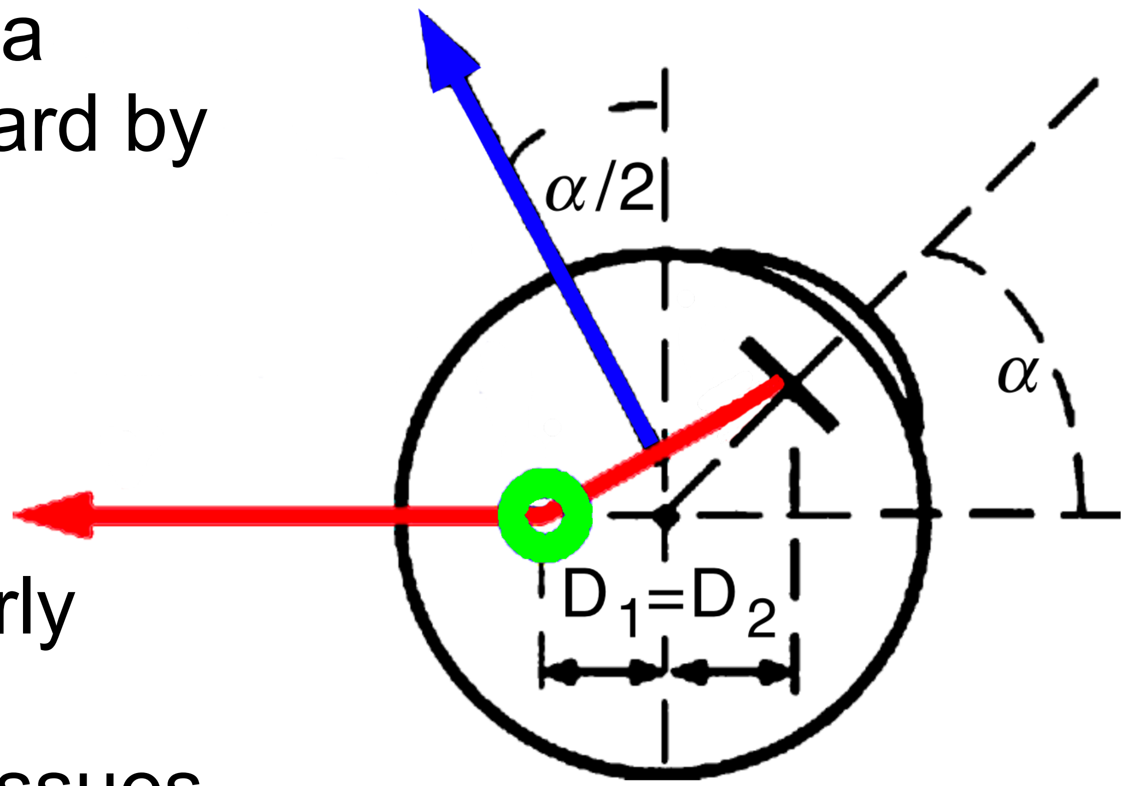
- If the brain implemented Listing’s law, cyclovertical motoneurons would have to modulate their firing during eccentric pursuit. Ghasia and Angelaki (2005) showed that they do not.
- Klier, Meng, and Angelaki (2005, 2006) stimulated the abducens nerve and nucleus, down-stream of all neural circuits that might contribute to the implementation of Listing’s law, and found that eye movements nevertheless had Listing kinematics, proving that ocular plant mechanics copes with non-additivity and implements Listing’s Law without neural assistance.
- Conclusion: The mathematical calculations of Listing’s Law are performed in the orbit. Elastic orbital connective tissues perform mathematically complex functions previously supposed to require the brain!

How Could Connective Tissue Calculate Anything?

- Morphological or Embodied Computation - “the body does the math”:
    - Structure & elasticity alone allow bat & bird wings to adapt instantly to turbulence.
    - The passive mechanics of human hands adapts to grasp irregular objects, supplementing neural control.
    - Humans can walk down a slight incline without computing each step, because of the legs’ mechanical structure and gravity.
    - Venus flytrap plants snap shut when its hairs are disturbed in a particular sequence. Stimuli are integrated by the structure itself, releasing stored mechanical energy.

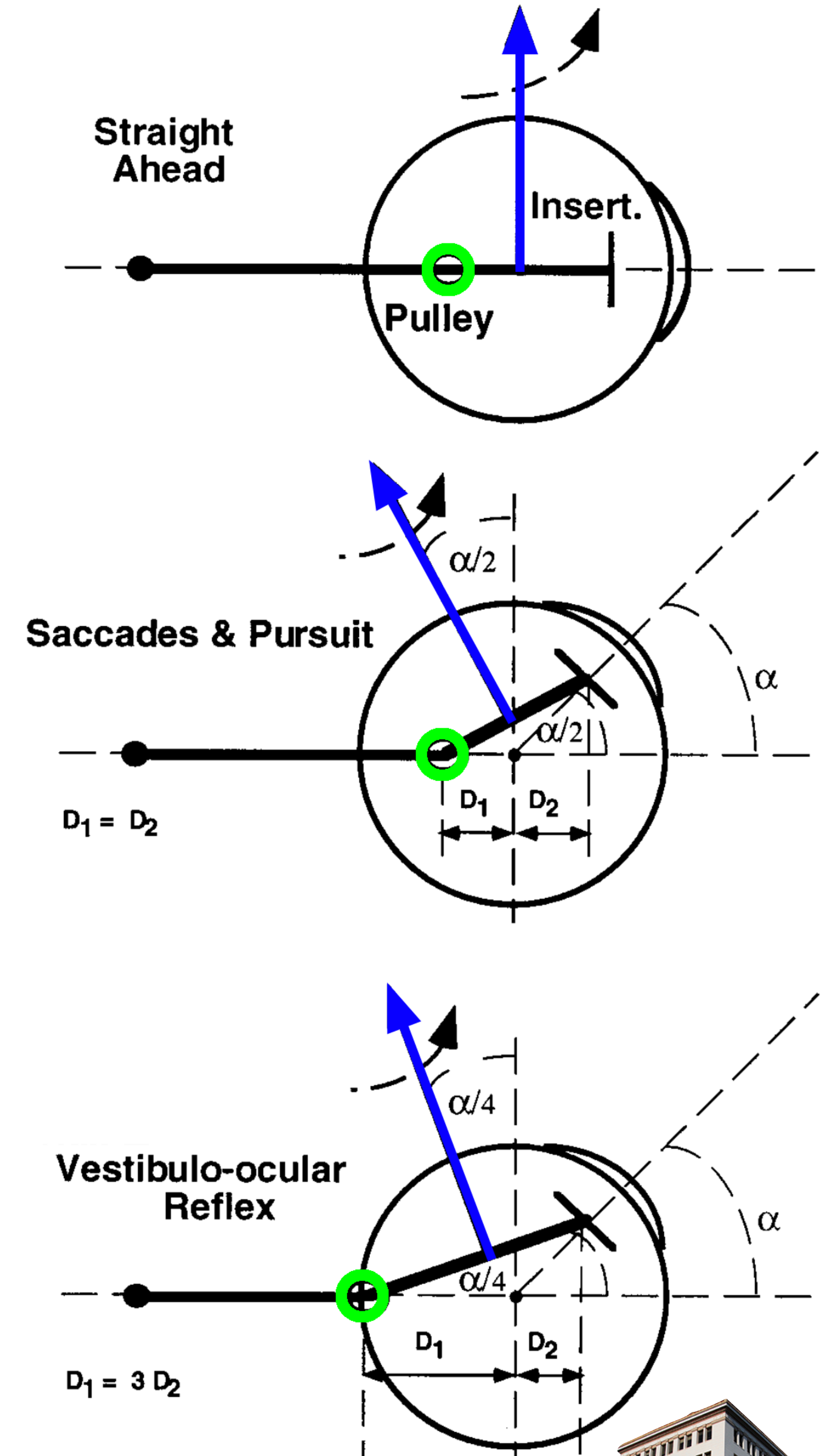
M-D Pulleys

- M-D Pulleys "calculate" Listing's Law.
- M-D Pulleys are condensations of orbital connective tissue:
  - Elastically stabilized to the orbital wall (**M**iller's original concept).
  - Dragged longitudinally by EOM contraction (**D**emer's contribution).
- A properly placed **pulley** would cause a muscle's **axis of rotation** to tilt backward by <u>half</u> the angle of rotation.
- "Half-angle" behavior is equivalent to Listing's Law.
- MRI studies of muscle paths, particularly before and after muscle transposition surgery, show that orbital connective tissues indeed behave like pulleys at the location required to implement Listing's Law.



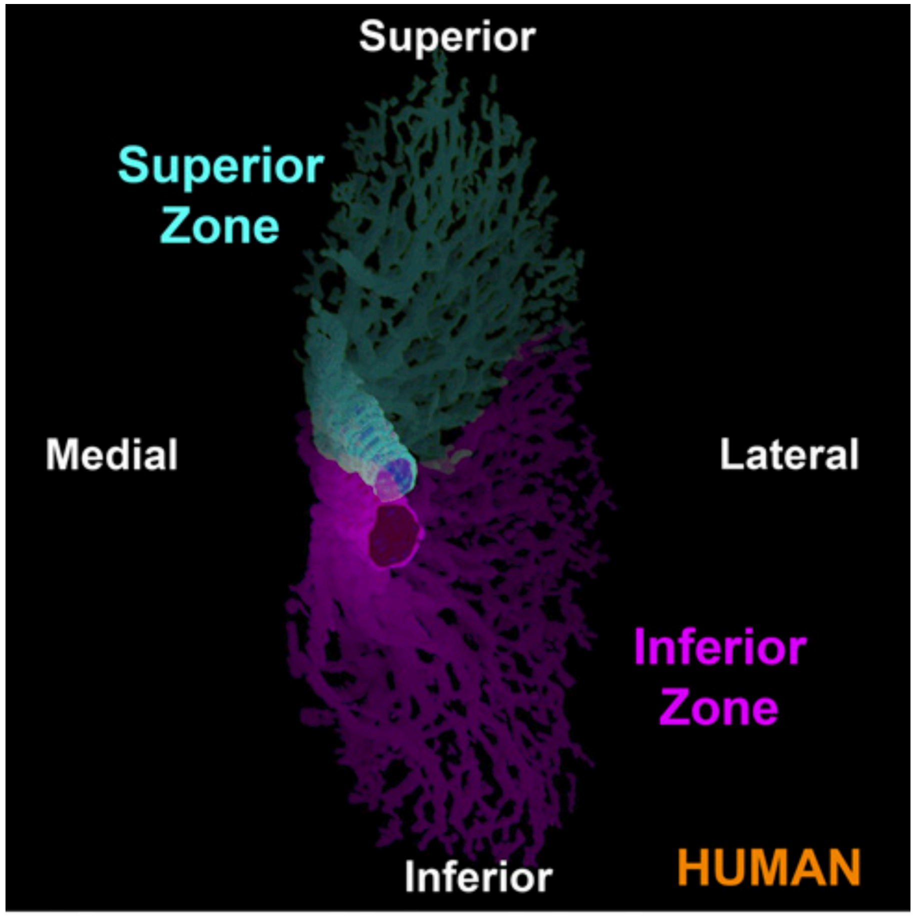
The Active Pulley Hypothesis is Wrong

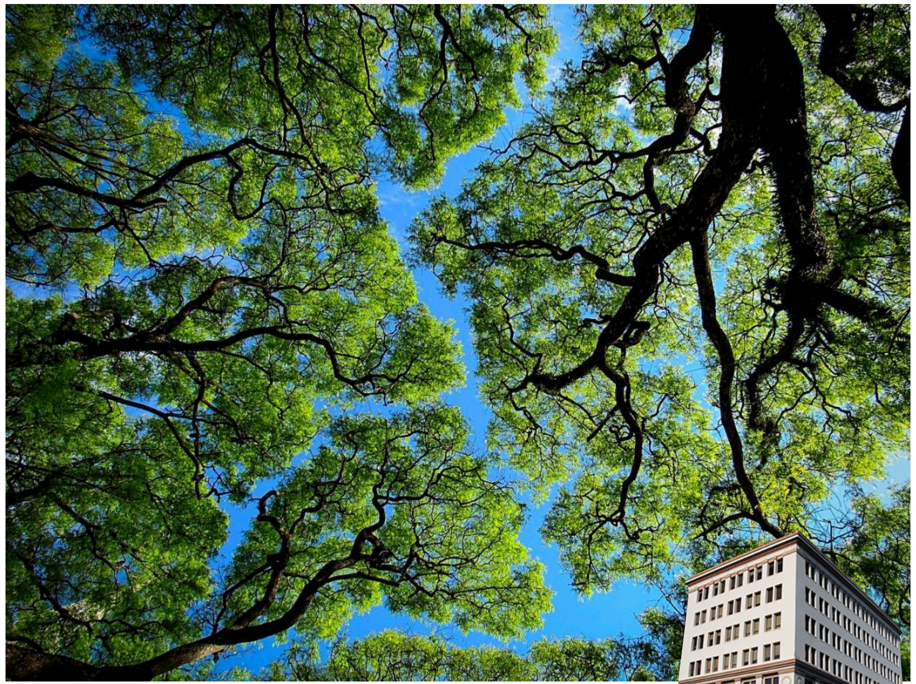
- Saccades & pursuit obey the <u>half-angle rule of Listing's Law</u>, but the vestibulo-ocular reflex (VOR) follows a different, "quarter-angle rule".
- The APH was born of the well-known micro-anatomic fact that mammalian EOMs generally have a thin layer of small myofibers facing the orbital wall (OL), with different fiber types than the bulk of the muscle (the GL).
- Demer, Oh & Poukens (2000), hoping to also explain "quarter-angle" behavior, proposed that, whereas GLs rotate the eye, OLs move pulleys independently. This is the APH.
- ❌ But there is no evidence that global and orbital layers move independently, and certainly not by the several millimeters required by the APH.
- ❌ Surgical attempts to separate the layers fail (Scott).
- ❌ Shall (et al 1995) & Goldberg (et al 1997) found that many abducens motor neurons innervate both OL and GL. Peng (et al 2010a) and da Silva Costa (et al 2011) found no separation of nerve branches to OL and GL in any muscle. An intermixed nerve supply means that independent control is impossible, clearly disconfirming the APH.
- ❌ Misslisch & Tweed (2001) showed mathematically that APH was neither necessary nor sufficient to account for VOR kinematics.



EOM Compartments are Fantasy

- The EOM Compartments notion assumes <u>mechanical</u> and <u>innervational</u> independence of OL half-widths. Both are <u>necessary</u> to support this notion, but neither is <u>sufficient.</u>
- ❌ Significant <u>mechanical independence</u> of such “mini-muscles” seems unlikely from micro-anatomy and direct observation.
- Nerve tracing studies, taken to indicate innervational independence, are the main evidence for EOM Compartments: Peng (et al 2010a), Da Silva Costa (et al 2011) and Le (et al 2015) showed that innervation to the LR, MR, IR & SO bifurcates as it enters the muscle, and then branches to fill roughly separate regions.
- ❌ But such arborization is common in nature and implies nothing about central control. Trees arborize to expose leaves to sunlight (“crown shyness”), and bronchi to increase contact of air from the trachea with circulating blood. Motor nerves traverse long distances and then branch repeatedly to synapse throughout target muscles.
- ❌ Active processes, such as molecular self-avoidance, support “innervational tiling” (Jan et al 2010), minimizing the inefficient overlap of neighboring domains, which would occur with purely random growth.
- ❌ Branching into non-overlapping neighborhoods is an efficient way to fill space, implying nothing about differential function.
- Nevertheless, these authors subsequently cite the “newly recognized segregation of intramuscular innervation into distinct compartments”, as though differential control was fact.



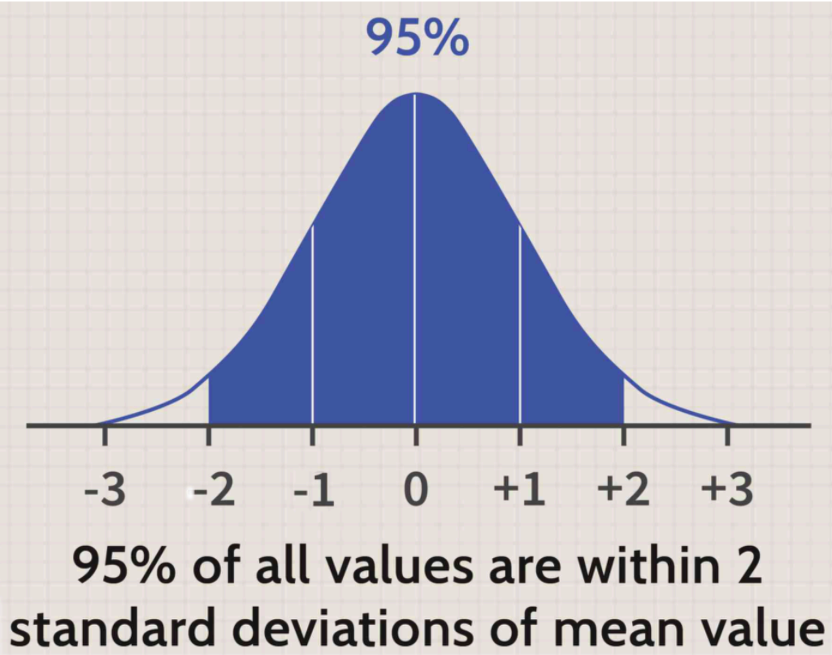


Data Dredging (p-Hacking)

- APH → independent orbital & global layers.
- Compartments → half-widths of most global layers are independent.
- Thus, in place of the familiar 6 EOMs, Demer & colleagues allow themselves 17 mechanically and innervationally independent "mini-muscles" (11 GL Compartments and 6 OLs).
- They pool eye position data in multiple ways, and use invented (and invalid) measures of contraction on these 17 mini-muscles, generating dozens or hundreds of potential comparisons. These are evaluated with t-tests and correlations to find those yielding the largest (of usually tiny) differences, which are then reported as either confirming and extending previous claims or suggesting new, "revolutionary" EOM capabilities.
- The strategy of performing multiple *ad-hoc* tests – referred to as "p-hacking" – is problematic because as the number of comparisons increases, so does the probability of finding a "significant difference" by chance, where none exists.

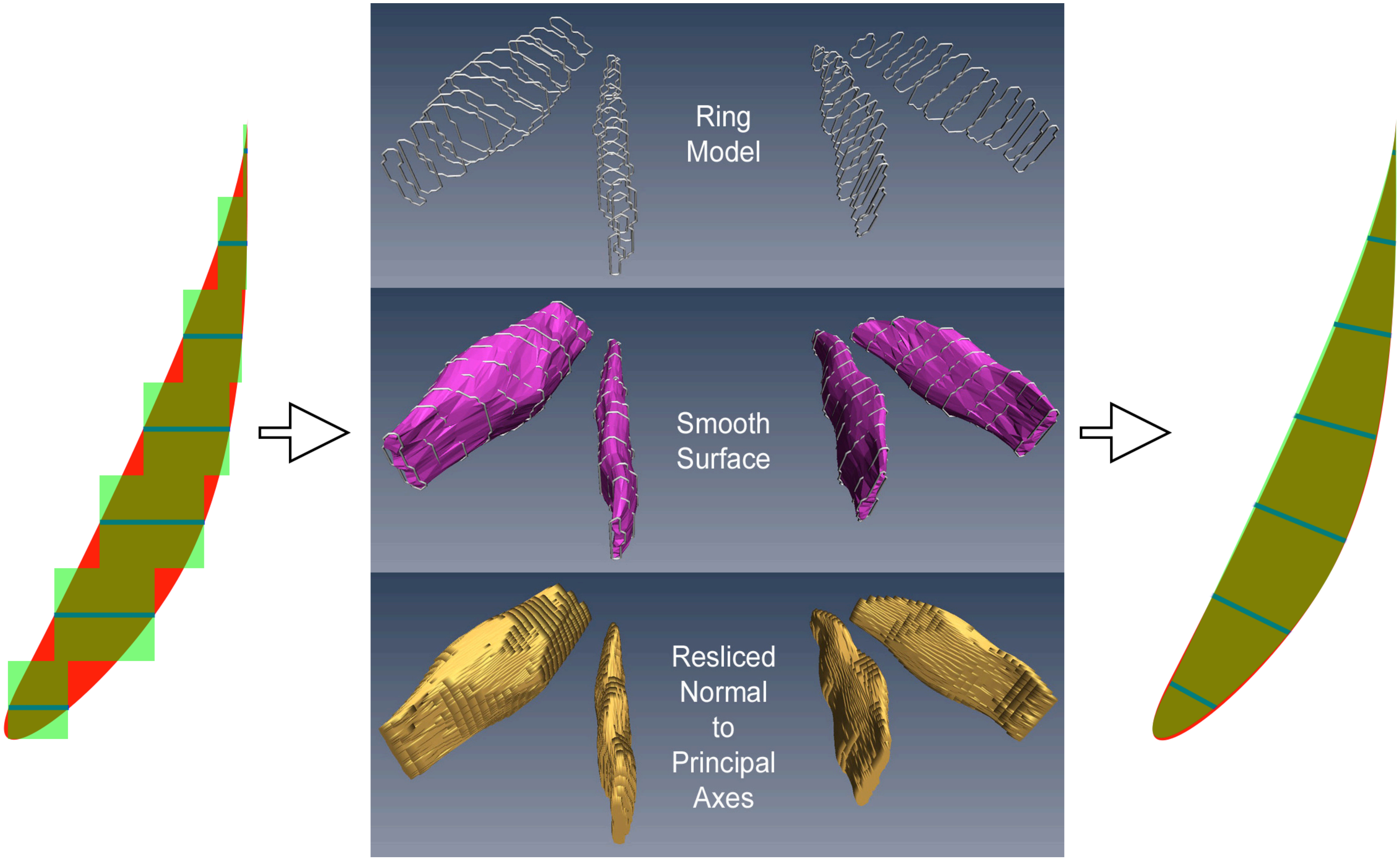
  - Probability of a False Positive = 5% or .05
  - Probability of a Correct Rejection = .95
  - Probability of Correct Rejections in all N tests = $(.95)^N$

N	Probability of at least 1 False Positive in N tests = $1 - (.95)^N$
1	0.05
2	0.10
5	0.23
10	0.40
20	0.64
50	0.92



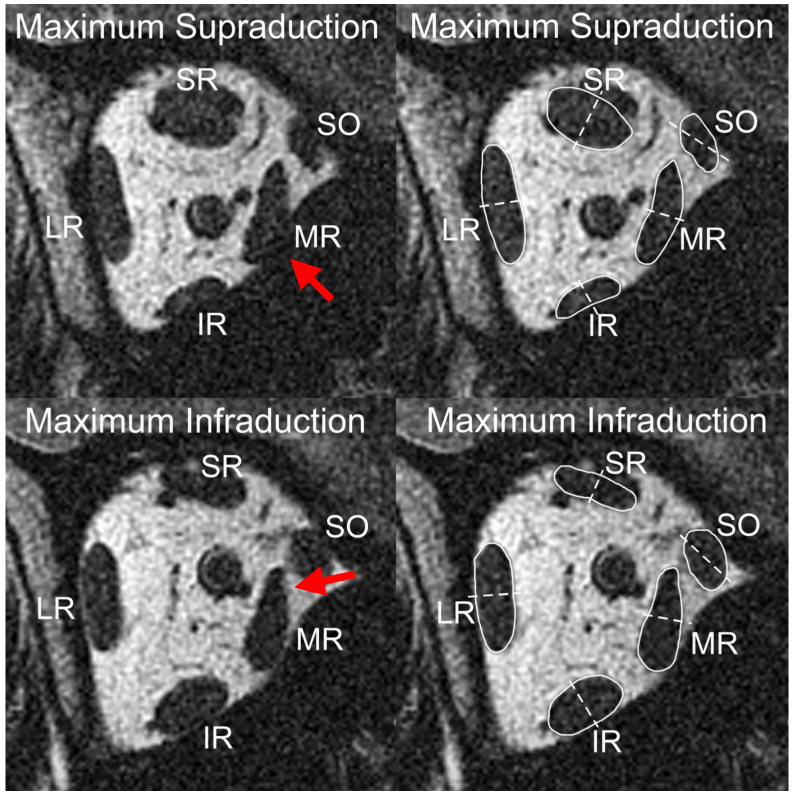
Obsolete Methodologies

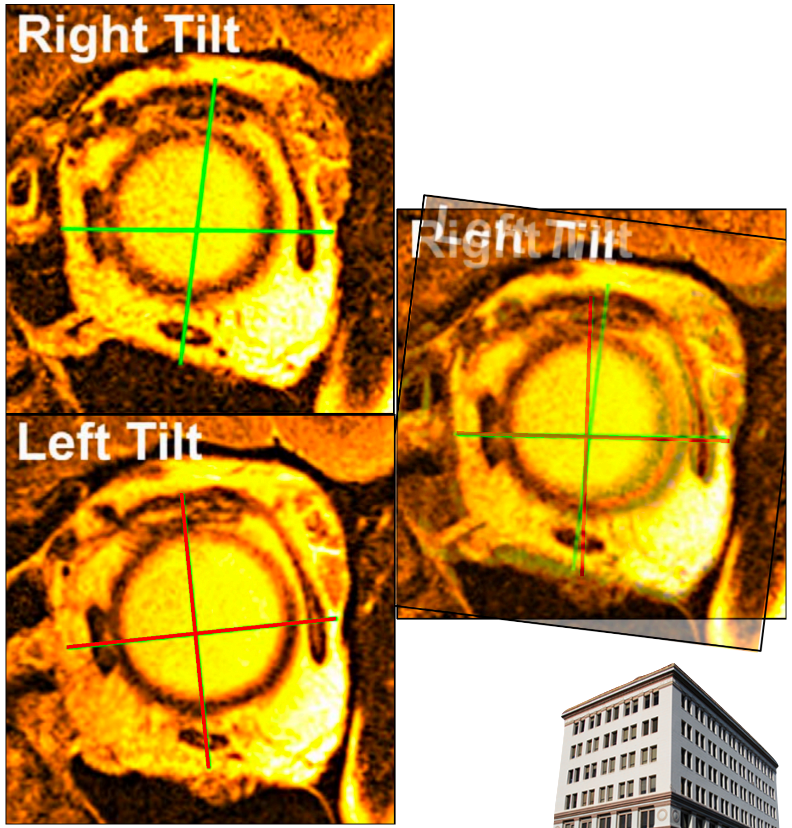
- Calculation of muscle volumes is central to their conclusions about muscle contractions, but unfortunately they use obsolete methods that introduce errors that could easily have been avoided (Miller et al 2013).



Published Images Reveal Bias

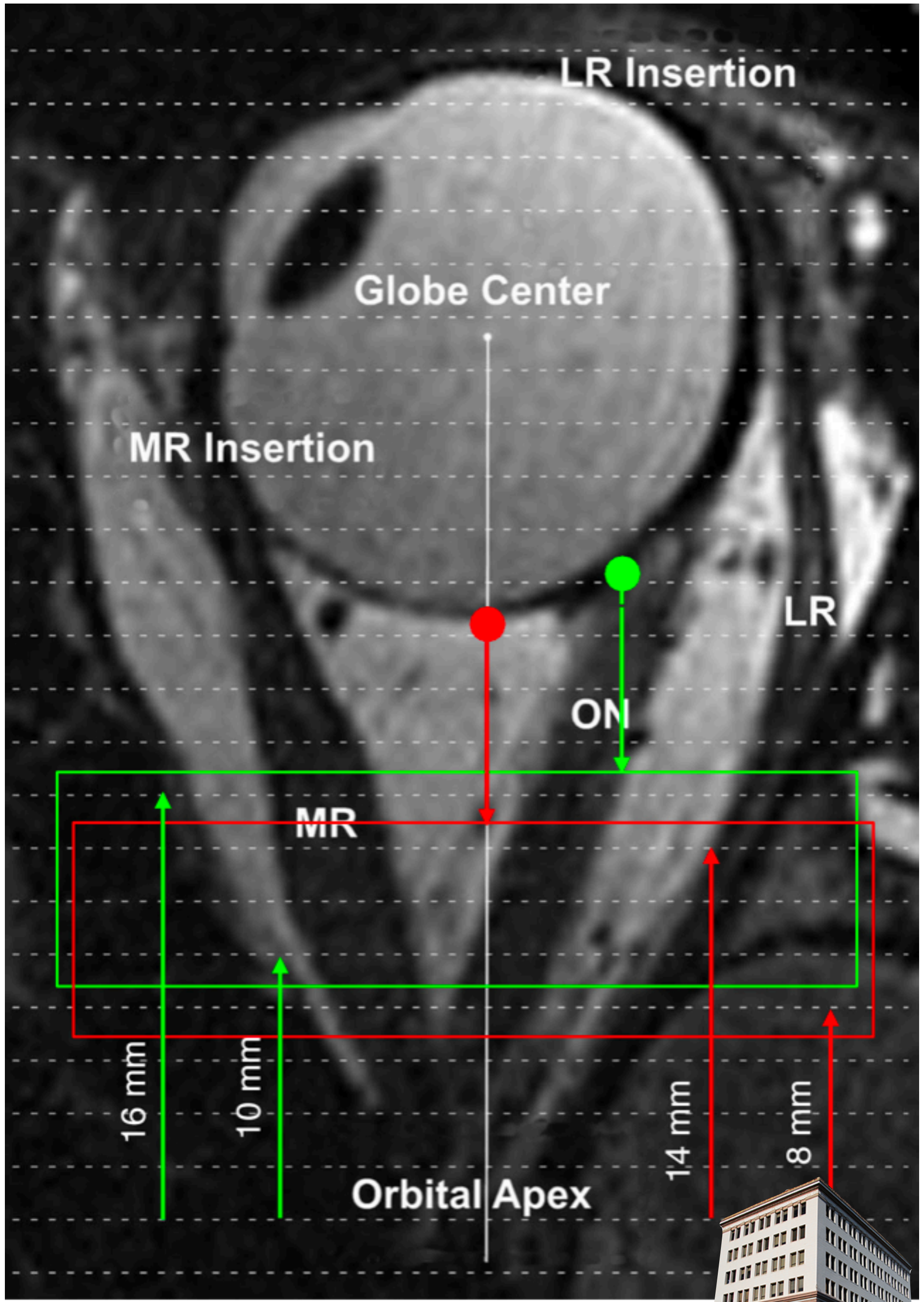
- An image from Clark & Demer's (2016b; fig 3) study of vertical duction claims to show differential contraction of the inferior MR mini-muscle, although it is clear that the apparent increase in the inferior MR crossection is the result of biased segmentation. No explanation is offered for why the inferior LR mini-muscle does not also contract.
- Clark & Demer (2012b) measured ocular counterrolling relative to the interhemispheric sulcus, a soft tissue referent likely to be unstable with head tilt, and which can be seen to have misaligned orbits in the two tilt conditions, creating the appearance of counterrolling where there was actually little or none. Because the head tilt manipulation evidently failed, this experiment provides no support for compartmental contraction during ocular counterrolling.





Posterior Partial Volume (PPV) Does Not Measure Muscle Contraction

- Demer's group measures muscle contraction with an invented measure they call PPV.
- PPV is defined as the volume in an 8 mm thick ROI posterior to the muscle's maximum crossection in central gaze, and moving with the globe-optic nerve junction.
- This ROI is neither fixed in the orbit nor moving with the muscle, but something in between, so as the eye rotates, different parts of a muscle are measured.
- PPV was chosen from many candidate measures for its high correlation with duction (Clark et al 2012a, 2016b), and is therefore a (poor) measure of eye position, and not a measure of muscle contraction at all.
- Eye position, of course, results from contractile and elastic actions of multiple muscles and tissues, and is not interchangeable with the contractile state of any single muscle. Indeed, nontrivial mathematical models are needed to relate the two (Robinson 1975b; Miller et al 1984; Miller et al 1999)



Data Dredging (p-Hacking) Examples

- Clark & Demer (2016b) collected data in central and 6 eccentric gaze positions. Sometimes they pooled all infraductions, other times all supraductions, and still others, changes from maximum infraduction to maximum supraduction. A small 4% compartmental PPV difference pooled across infraductions is reported for LR, although there was no difference across supraductions or across maximal gaze changes (which included infraductions), and nevertheless was taken as support for EOM Compartments and the broad conclusion that all EOMs have complex actions.
- Clark & Demer (2012b, 2016b) wished to show differential compartmental contraction during ocular counterrolling and vertical duction. Although nerve tracing (Peng et al 2010b; Da Silva Costa et al 2011; Le et al 2015) predicts particular compartment boundaries, they created multiple segmentations (12 in the case of the SO!) with the expressed aim of finding the “most likely intercompartmental border”, but actually finding segmentations yielding the largest differences, regardless of whether they corresponded to nerve tracing predictions (Clark et al 2016b; page 372). These differences were then tested with paired comparisons.

APH & EOM Compartments - Conclusions

- The APH requires OL-GL relative movements of several mm, which are not observed.
- Nerve tracing, experimental surgical manipulations, connective tissue studies and mathematical analysis – have disproven the APH.
- Nerve tracing raises the possibility that LR, MR, SO, and possibly IR might have differentially controlled half-width compartments, and it is possible that they strain the connective tissue matrix sufficiently to exert differential oculorotary forces at their tendons, although there is no good evidence that they do so.
- MRI studies from the Demer lab use incorrect measures of muscle contraction that are dominated by artifacts, use statistics that do not reasonably account for overall error rates, show evidence of bias, are unconvincing about cause and effect, and lack confirmation from other labs.
- It is unwarranted to state as if proven that eye position is controlled by some 17 extraocular mini-muscles, and to urge tests, diagnoses, and treatments on the basis that it is (Clark et al 2014; Demer 2018; Clark 2019).
- APH and EOM Compartment papers are so abstruse and difficult to read that almost no one does. Journal reviewers and others likely skim them uncritically, supposing they must be true because of their complexity, their apparent thoroughness, and the authority of the investigators, failing to see that just below the surface they are deeply defective in concept, methodology, analysis and interpretation.

No, That's Not Why MR Surgery Is More Potent Than LR Surgery

Riddled with misrepresentations, errors & nonsense, this could be a hoax paper designed to ridicule the journal review process, but alas, Clark and Demer intend it seriously:

- The *raison d'être* of the study was a bad-faith misrepresentation of existing biomechanical strabismus models.
- Their "eccentric axis" hypothesis is based on a naive and misleading muscle model. Ignoring the fact that muscles produce force, and that a longer lever arm produces more rotational torque, they suppose that EOMs are like "bicycle-chains", so that a longer lever arm gives less eye rotation.
- Results are invalid because their methodology is not what they describe, indeed it is nonsensical, yielding results having nothing to do with center of rotation.
- Their MRI measurements are obviously inaccurate.
- The discussion of their results is innumerate.

And yet, this travesty of science passed peer review at a top ophthalmology journal!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RETRACTED

The Globe's Eccentric Rotational Axis

Why Medial Rectus Surgery Is More Potent than Lateral Rectus Surgery

Robert A. Clark, MD,[1,2,6] Joseph L. Demer, MD, PhD[1,2,3,4,5,6]

Purpose: Tables typically recommend greater lateral rectus (LR) than medial rectus (MR) surgical doses for horizontal strabismus of any given magnitude, a difference unexplained by mechanical models that assume globe rotation about its center. We tested this assumption during horizontal ductions.
Design: Prospective observational study.
Participants: Eighteen adult subjects with normal binocular vision.
Methods: Surface coil magnetic resonance imaging at 390 or 430 µm resolution was obtained using 2-mm–thick contiguous axial planes while subjects fixated targets in central, right, and left gaze. Angular displacements of lines connecting the corneal apex through the minor lens axis to the retina were measured to approximate clinical ductions. Globe centers were calculated from their area centroids. Apparent lens and globe-optic nerve (ON) junction rotations around the globe center were then compared with clinical ductions.
Main Outcome Measures: Apparent angular rotations of lenses and globe-ON junctions during horizontal ductions.
Results: Globe-ON junctions appeared to rotate significantly less around globe centers than did lenses for abduction (20.6°±[illegible] vs. 27.4°±[illegible] ± standard deviation (SD), $P < 0.001$) and adduction (25.3°±6.7° vs. 31.9°±8.3°, $P < 0.001$). Both rotations differed significantly from clinical adduction (27.9°±8.3°, $P < 0.007$), but only in abduction was globe-ON junction rotation significantly less than clinical abduction (28.6°±9.4°, $P < 0.001$). The true geometric globe rotational center was 2.2±0.5 mm medial and 0.8±1.0 mm posterior to the geometric globe center and was displaced farther medially and posteriorly during adduction. This eccentricity imbues each millimeter of MR recession with approximately 30% more trigonometric rotational effect than equivalent LR recession.
Conclusions: The medial and posterior eccentricities of the normal ocular rotational axis profoundly influence horizontal rectus action. The proximity of the globe's rotational axis to the MR shortens its lever arm relative to the LR, explaining why mechanical effects of smaller MR recessions are equivalent to larger LR recessions. *Ophthalmology 2018;■:1–5 © 2018 by the American Academy of Ophthalmology*

The authors admitted their analysis was "flawed", substituted a new analysis, claimed to give substantially the same results, and submitted to a different journal.