CHAPTER

Mathematical models and human disease

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Abstract

Mathematical models of brain function are built from data covering anatomy, physiology, biophysics and behavior. In almost all cases, many possible models could fit the available data. Theoreticians make assumptions that allow them to constrain the number of possible model structures. However, a model that was more useful clinically would result if the constraints came from lesion studies in animals or clinical disorders. Here, we show a few examples of how clinical disorders have led to improvements in models. We also show a few examples of how models could lead to neural prostheses for patients. The best outcomes result when clinicians, basic scientists and theoreticians work together to understand brain function.

Keywords

Saccades, Oscillations, Eye movement, Motor control, Eye muscle, Models, Constraints

1 Introduction

The purpose of making a model is twofold: first, to summarize data that we already know, and second, to make predictions that can be tested with new experiments. As such, modeling is part of the classic scientific method of observation, hypothesis, and experimental testing. Modeling is simply clear thinking, expressed in a way that can make predictions. That usually means mathematically. Over time, these models improve. Why don't we start out with better models? There are two parts to that answer. First, of course, we don't know everything when we start that we will after a few cycles of the scientific method: the model itself leads to experiments that improve our knowledge. The second part is that we often have too much information that seems disconnected. The art of modeling is knowing what to include in the model, and what to exclude. Not that exclusion is permanent. Later research may reveal new information that helps us incorporate not only the new data, but some of the older

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data we had been excluding. One of the brain functions that has been most widely modeled mathematically is control of eye movements.

Eye movements have been studied quantitatively for over 100 years (Dodge, 1903), but mathematical analysis of their characteristics only started in the 1950s (Westheimer, 1954). Since then, many mathematical models have been made to describe the behavior of ocular motor control. However, the majority of this work was limited to an input/output description of eye movement dynamics. Since the 1970s, neurophysiologists have recorded neurons inside the brain during eye movements elicited in behavioral tasks. This has increased the number of constraints on models of ocular motor control. However, in most cases the neurophysiological recordings do not constrain the models very tightly. There are always a number of models that can explain the data. If we want a model to reproduce a physiological neural network as closely as possible, we need constraints on the model's structure. One way to obtain constraints is to observe, *in vivo*, the outputs of a function when the corresponding cerebral structure of a specific model's part is disrupted. This can be done experimentally by lesioning or impairing that part of the brain. However, while providing useful information, this kind of study has some limitations, including the difficulty in causing highly selective brain damage and the bias given by the investigator's preconception of what parts of the brain are involved. One important source of constraints on the models that overcomes these limitations has emerged from careful recordings of the eye movements of patients with various diseases. If the cause of the disorder is known, it can inform the structure of the model. If the cause of the disorder is unknown, existing models can be used to make hypotheses and suggest tests for discerning the underlying cause. In many cases, the eye movements of patients are so peculiar or unexpected, that they have completely changed our thinking about how ocular motor control systems are organized. In this review we will focus on how clinical eye movement disorders has helped to constrain models of rapid, or saccadic, eye movements.

2 Target tracking models

Saccades are rapid eye movements used to rotate the eyes to align their visual axes with the target. Saccades are used when examining a visual scene, or when reading. They occur about 2–4 times per second. They must be accurate because of the limited extent of the retina with high visual acuity (Hirsch and Curcio, 1989; Mandelbaum and Sloan, 1947) and the blurring caused by any drift of the image on the retina (Westheimer and McKee, 1975). Comparison with mechanical target tracking mechanisms has dominated the literature for many decades. An early example (Fig. 1A) modeled the saccadic system as an error controller with a periodic sampler (Young and Stark, 1963). In this model, the eye movement is a direct consequence of the step change in retinal error caused when a target appears in the periphery (Westheimer, 1954). This is only possible if the dynamics of the plant are linear, 2nd order and critically damped.

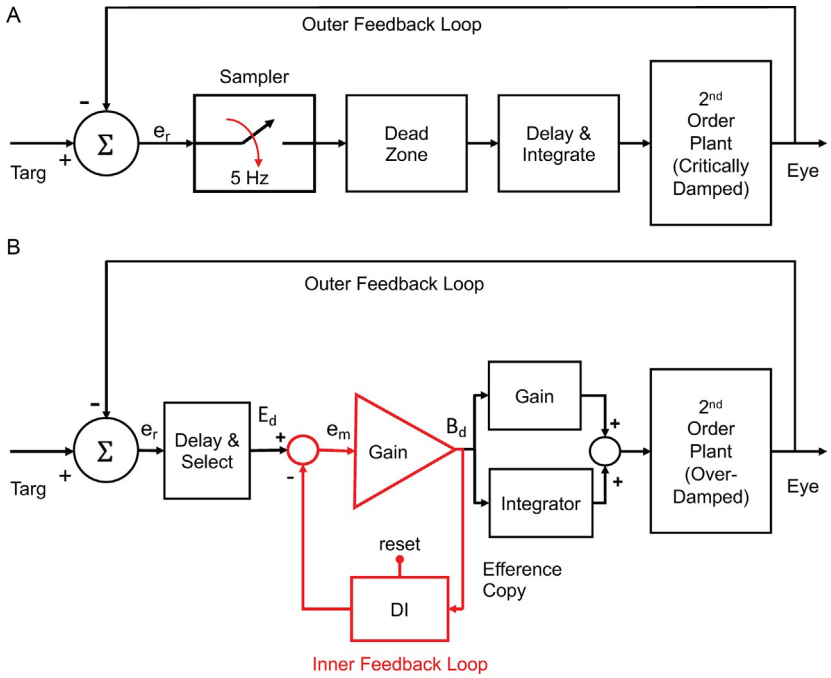

FIG. 1

Early saccadic system models. (A) Sampled data, error control model. An eccentric target position on the retina results in an error (e_r). This error is sampled about every 0.2 s. If larger than a dead zone (~0.5°) it is delayed and integrated, resulting in a step change in innervation that is sent to the plant (orbital muscles and tissues). The plant is critically damped, so the step change is converted into an eye movement without further compensation. The key element here is the summing junction (Σ). The error is the difference between the target position and the eye position. The circuit reduces this error to zero. (B) Local feedback error controller. The difference between the desired displacement (E_d) and the current displacement is the motor error (e_m). The burst drive (B_d) is just e_m times a high gain. The new element (red) computes the distance the eye has already moved toward the target with a displacement integrator (*DI*) that integrates the burst drive. The *DI* is reset before each saccade. The output plant is still 2nd order, but is now overdamped. Thus, compensation must be added to the step change in innervation. This is provided by feeding a small part of B_d around the integrator. The key element here is now the summing junction (red circle) inside the local feedback loop. The controller reduces the error, e_m, to zero.

Later, it was shown that the ocular motor plant is overdamped, nonlinear, and higher order (Collins, 1975; Robinson, 1964; Thomas, 1967). This gave rise to more complicated saccadic system models, because the brain had to compute not only the desired eye displacement, but also the innervation needed to compensate for the plant dynamics.

Early versions of these models proposed that the brain pre-computed the desired innervation for a saccade, and just sent that out to the muscles (Robinson, 1973). Those models were ballistic, i.e., the saccade trajectory could not be changed in mid-flight. Subsequent experiments showed that this was not the case (Becker and Jurgens, 1979). Researchers began to introduce more constraints by identifying different anatomical parts of the brain with the model, but no further progress was made on the model's structure.

3 Slow saccades in spinocerebellar disease

The next breakthrough in understanding the saccadic system came because of patients with slow saccades. Spinocerebellar degeneration, for example, can cause slow eye movements (Wadia and Swami, 1971). In one form, spinocerebellar ataxia type 2 (SCA2), this was eventually shown to be caused by the loss of excitatory burst neurons (EBNs) in the paramedian pontine reticular formation (PPRF) (Federighi et al., 2011; Geiner et al., 2008). When slow saccades were first observed, they were thought to be made by a defective saccadic system or by a voluntary drive of the (normally involuntary) smooth pursuit system (Newman et al., 1970; Wadia, 1973). However, in a quantitative study of saccades in patients with spinocerebellar degeneration, it was found that the movements, although slow, were saccade-like (Zee et al., 1976). In addition, if the target was jumped back during the slow saccade, the eye could turn around and saccade back to follow the target. This led to new models of the saccadic system that did not pre-compute the motor command, but instead used an internal feedback loop to generate the saccadic innervation (Jurgens et al., 1981; Robinson, 1975b; Zee et al., 1976). The inner part, or pulse-generator, of this model is shown in Fig. 1B. The new model accounted for much saccadic behavior. This model has proven useful since then, but it probably would not have been discovered as early without the careful observation and analysis of slow saccades in patients. That forced the constraint that the command could not be pre-programmed.

4 Ocular flutter

The new, local feedback model was applied to another strange eye movement type that could be seen in patients and even some normal subjects. This is flutter, or back-to-back saccades without intersaccadic intervals. Normally, the intersaccadic interval is 150–250 ms. Zee and Robinson (1979) showed that by introducing a time delay into the local feedback loop (of an extra 10 ms) their system could be made to oscillate. The frequency of the oscillations would be a function of the time delay. This model was successful at reproducing the flutter seen in the patients, but did not give much insight into the mechanism that controlled the frequency, because the mechanism that led to the delay was unspecified. Furthermore, the model showed the

necessity of turning off the omnipause neurons that inhibited the burst neurons to allow oscillations, but no mechanism for doing this was given.

At about that time, it was shown that the brain has at least two pathways for controlling saccades, one involving the superior colliculus in the midbrain, and one involving the frontal eye fields (FEF) in the cerebral cortex (Schiller et al., 1979). A model with two parallel pathways was later proposed to account for differences in effects of ablations of superior colliculus and cerebellum (Lefevre et al., 1998; Optican and Quaia, 2002; Quaia et al., 1999). The new feature of this model was that the feedback loop was closed through the midline cerebellum, and not in the brain stem as previously thought (Fig. 2). A key element of the old error feedback models, the summing junction used to compute instantaneous motor error (e_m in Fig. 1B), was not needed in the new dual-pathway model. In fact, the cerebellar model only achieved partial corrections for saccade errors, as has been seen in monkeys (Quaia et al., 2000).

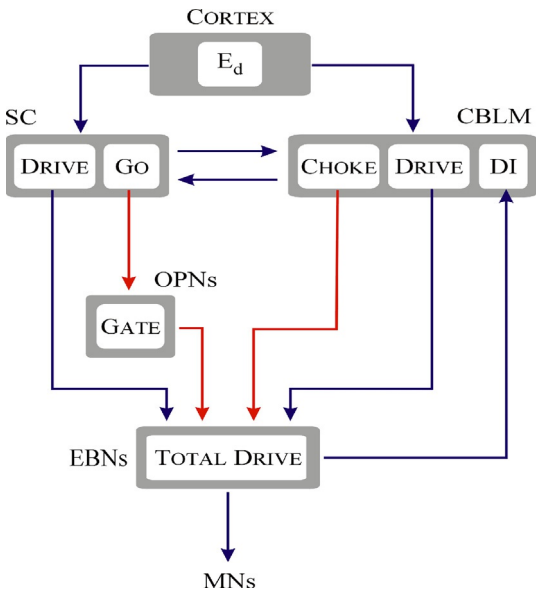

FIG. 2

Dual-pathway model of the saccadic system. The desired eye displacement (E_d) in this model comes from the cortex (e.g., the frontal eye fields). That signal goes to both the Superior Colliculus in the midbrain (SC) and the cerebellum (CBLM). When the gate closes, the signal from the SC drives the EBNs. The signal to begin also goes to the CBLM, which also provides a drive signal. The output of the EBNs feeds back to the CBLM, which acts as a displacement integrator (DI). When the signal from the DI is big enough, the choke turns on, shutting off the drive to the motor neurons (MNs).

After Lefevre, P., Quaia, C., Optican, L.M., 1998. Distributed model of control of saccades by superior colliculus and cerebellum. Neural Netw. 11, 1175–1190.

The new model was a drastic departure from the older error-control model, and did not catch on. However, Ramat et al. (2005) found a patient who had had a surgical ablation in the cerebellum that included the caudal fastigial nuclei. That patient had small ocular oscillations at ~30 Hz. This presented a problem for the cerebellar feedback model. A paradox would ensue if oscillations were due to delays in the local feedback loop, and that feedback loop went through the caudal fastigial nucleus. Both things can't be true. Of course, neither could be true, but which one is more likely to be true? Surprisingly, there is no evidence, whatsoever, behind the Zee and Robinson model. That model and its earlier versions were based on top-down assumptions about what engineering tracking systems looked like. Take the key element in that model, the summing junction that computes the dynamic motor error: in almost five decades, no experiment has identified that error signal, despite its obvious centrality to the whole theory. Furthermore, the range of frequencies found in ocular oscillations in different studies is huge (6–33 Hz). If these oscillations were due to a delay in the feedback loop, that delay would have to vary from about 36 down to 6 ms. It was not clear what could cause such a sixfold range of delays.

In contrast, there is a lot of evidence behind the dual-pathway model. Lesions in monkeys (e.g., in caudal fastigial nucleus) cause saccadic dysmetrias (hypometric contralaterally and hypermetric ipsilaterally) that are predicted by the model. The model also predicts that activity in the cerebellum should advance or retreat as saccades need to become smaller or larger, thus saccadic waveforms should be different for targets with different velocities (i.e., toward or away from fixation) or with adaptation (Eggert et al., 2005; Guan et al., 2003, 2005; Scudder, 2002).

From these considerations we were led to propose a new mechanism for ocular flutter (Ramat et al., 2005). It would not be sufficient to alter the cerebellar part of the model, because the patient with the cerebellar ablation had oscillations. Instead, the new model added to our cerebellar model a more detailed picture of the brain stem circuit (Fig. 3). Here, the brain stem circuit is divided into left and right halves, and the anatomically known cross-couplings are included (Büttner-Ennever and Büttner, 1992; Strassman et al., 1986). The motor neurons are controlled by burst neurons in the paramedian pontine reticular formation (PPRF, wherein lie the excitatory burst neurons, or EBNs), and in the nucleus paragiganto-cellularis dorsalis (PGD, the caudal part of the PPRF, wherein lie the inhibitory burst neurons, or IBNs). The burst neurons are held off by the omnipause neurons (OPNs) in the raphe interpositus nucleus (RIP). To make a rightward saccade, the OPNs first shut off, then the right EBNs and IBNs turn on. The EBNs drive the right abducens motor neurons (MN) and interneurons (IN), while the IBNs inhibit the left abducens nucleus, and the left EBNs and IBNs. Neurons exhibit post-inhibitory rebound (Aizenman and Linden, 1999) (Fig. 4), thus if the OPNs are held off, the mutually inhibitory connections between the IBNs (red, dashed lines) can lead to oscillations (Ramat et al., 2005).

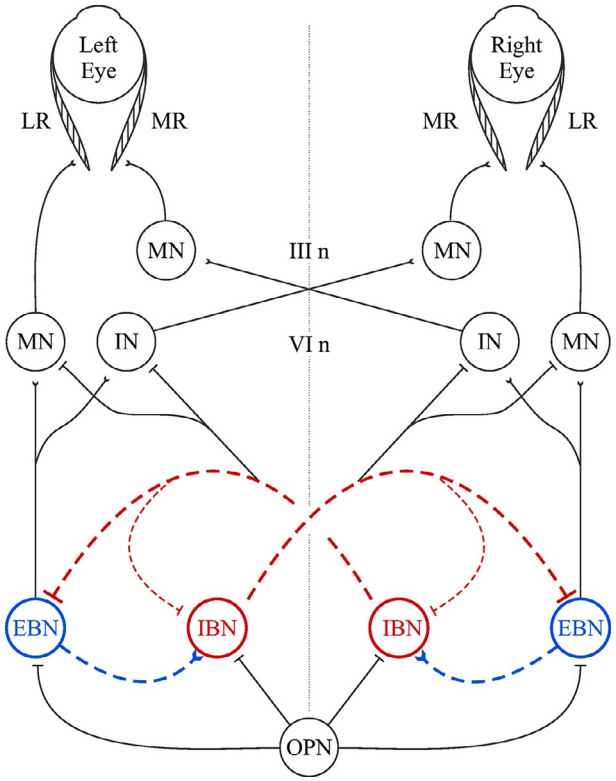

FIG. 3

Brain stem circuit for horizontal saccades. Eye movements are made by the horizontal recti muscles (medial and lateral recti, MR and LR), which are innervated by the motor neurons of the abducens (VIn) and oculomotor (IIIn) nuclei. The motor neurons are controlled by excitatory burst neurons (EBNs) in the PPRF, and IBNs in the PGD. The burst neurons are held off by the OPNs in the raphe interpositus nucleus. To make a rightward saccade, the OPNs first shut off, then the right EBNs and IBNs turn on. The EBNs drive the abducens motor neurons (MN) and interneurons (IN), while the IBNs inhibit the left abducens nucleus, and the left EBNs and IBNs. Neurons exhibit post-inhibitory rebound, thus if the OPNs are held off the mutual inhibition between the left and right IBNs (red, dashed) can lead to oscillations. The EBNs (blue, dashed) may also be involved in the oscillations. Lines ending with a "-" are inhibitory, lines ending with a "v" are excitatory.

After Ramat, S., Leigh, R.J., Zee, D.S., Optican, L.M., 2005. Ocular oscillations generated by coupling of brainstem excitatory and inhibitory saccadic burst neurons. Exp. Brain Res. 160, 89–106.

The findings from this one patient thus led to a revolution in our thinking about saccadic system models. It conferred some legitimacy on the cerebellar feedback model and led to a completely new understanding of brain stem function. Importantly, the details of the oscillations in the new model (amplitude and frequency)

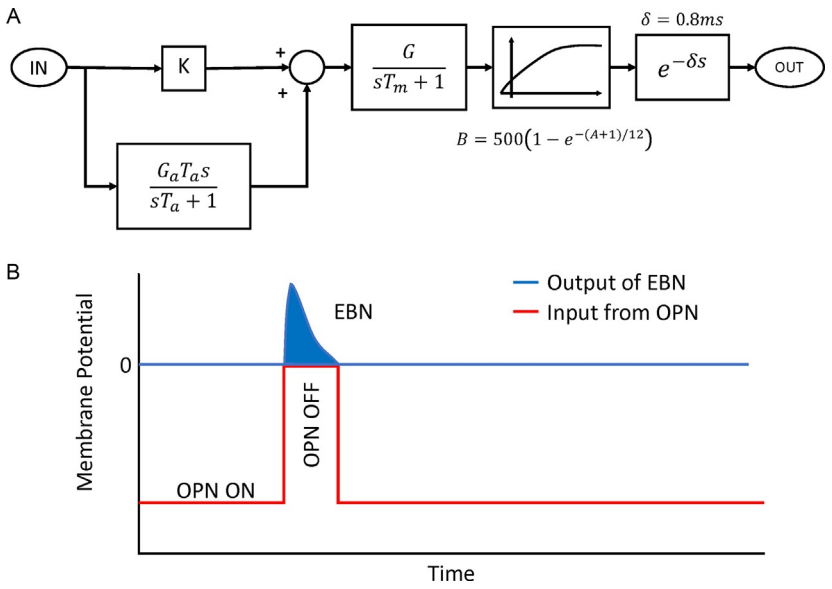

FIG. 4

Model of the dynamics of neurons (excitatory burst, inhibitory burst, and omnipause neurons—EBN, IBN, and OPN) in the saccadic system. (A) Block diagram showing the membrane properties of the neuron. The neuron has gain G and membrane time constant T_m. The burst comes from a saturating nonlinearity (B). The output of the cell is also delayed. The post-inhibitory rebound (PIR) comes from the adaptation block in the lower left, with gain G_a and time constant T_a. The letter s in the transfer functions stands for the Laplace variable. (B) When the OPN (red trace) is on, massive inhibition prevents the EBNs (blue trace) from firing. When the OPNs turn off, the adaptation block outputs a rebound (blue filled trace). If the system were linear, there would be a rebound both when the OPNs turn on and off. However, a nonlinearity prevents the EBN from firing negatively when the OPNs turn on.

After Ramat, S., Leigh, R.J., Zee, D.S., Optican, L.M., 2005. Ocular oscillations generated by coupling of brainstem excitatory and inhibitory saccadic burst neurons. Exp. Brain Res. 160, 89–106.

were a function of membrane properties, which could be controlled by the time constants of the receptors on the membrane that receive neurotransmitters. These receptors are made up of transmembrane subunits or α-helical segments. Many different alleles govern each of the subunits or segments. Thus, genetic factors can change the makeup of the receptors and thereby change the time constants. This can easily give rise to the sixfold range of oscillation frequencies seen in patients. This model has been used successfully to analyze oscillations in many subsequent studies (e.g., Fong et al., 2017; Ghasia and Shaikh, 2014; Karam et al., 2017; Kobayashi, 2015; Optican and Pretegiani, 2017; Ramat et al., 2007; Shaikh, 2012; Shaikh et al., 2008a,b; Zaltzman et al., 2017).

Further developments of this model can account for another form of ocular oscillations, opsoclonus. The details of this disorder are given in two other papers in this issue, by Dr. Janet Rucker and colleagues, and by Dr. Lance Optican and colleagues. See those papers for a full discussion of opsoclonus.

5 Strabismus

As a final example of constraints on models from patients, let's look at a different kind of problem. In the models we have discussed above, the purpose of the brain circuitry is to generate an innervation for the six extraocular muscles (EOMs) that move the eye. The globe, the EOMs, and the orbital tissues form an incredibly complex mechanical and dynamical system, called the *plant* in engineering jargon. Amazingly, for most purposes this can successfully be approximated by a simple, overdamped 2nd-order lumped, linear model. However, when something goes seriously wrong in the orbital tissues, or in the cranial nerves that innervate the muscles, the lumped model of the plant breaks down. A good example of this breakdown occurs in strabismus, the inability to maintain alignment of the two eyes. Strabismus causes diplopia (double vision). When strabismus occurs in children the brain often suppresses the images coming from one eye, leading to amblyopia. A better understanding of the plant would help in the diagnosis and treatment of strabismus.

One common form of strabismus is caused by a superior oblique palsy (SOP), often resulting from head trauma that damages the trochlear nerve (IVn). The eye movements in SOP are complex, and questions arise as to how many of the problems are caused by loss of innervation, as opposed to adaptive changes in the orbit. To answer these questions, an experiment was performed in monkeys that surgically sectioned the IVn intracranially, thus preserving the orbital contents. Surprisingly, the monkey showed not only the expected pattern of misalignment, but changes over time, indicating adaptation (Shan et al., 2007a,b). An attempt was made to fit an earlier model (Quaia and Optican, 2003) to these eye movements (Quaia et al., 2008).

Robinson (1975a) pioneered the use of plant models to determine the relationship between innervation and ocular orientation. To see what results from SOP, one first performs an inverse calculation with a normal plant to obtain the innervations for a given orientation. Then, the IVn innervation is turned off and a forward calculation gives the SOP eye orientation. With Robinson's original model, this fails to match the data. The reason is that Robinson assumed a symmetric relationship between agonist and antagonist muscle pairs. After reanalyzing Robinson's original data, it was found that the relationship was in fact, not symmetric. Changing the model to use an asymmetric agonist/antagonist relationship, the model was able to fit the data more closely. However, there still remained a small discrepancy, of about 5% of muscle force. We ascribed this discrepancy to a failure to accurately model viscoelastic properties of muscles.

The length vs. tension (elasticity) and force vs. velocity (viscosity) has been studied in humans and cats (Collins, 1971; Robinson, 1964; Robinson et al., 1969). These values have gone into existing plant models. One possibility was that these measurements were not accurate enough to represent the failures in SOP. Thus, we set out to measure the viscoelastic properties in primate and rabbit eye muscles *in vivo* (Quaia et al., 2009a,b, 2010). It turned out that the measurements were fairly accurate, but the basic assumption of the model, that it was linear for small changes in length, was wrong.

As a muscle elongates, its stiffness increases. This has been assumed to be the only consequential nonlinearity in the muscle. Early models assumed that muscles could be modeled by locally linear models (Buchthal and Kaiser, 1951). Fung (1972) described the mechanics of biological tissues with a quasi-linear viscoelastic (QLV) model, which separated out a static nonlinearity from the linear dynamics. In both these types of model, the assumption is that superposition holds. In particular, that means that large movements can be simulated by integrating a large number of small movements. A later improvement to this model that does not separate out the nonlinearity was provided by Nekouzadeh et al. (2007), called the adaptive QLV (AQLV) model.

We tested the superposition hypothesis by making double-steps of length changes on eye muscles *in vivo* (Quaia et al., 2009b). Surprisingly, the muscle forces induced by the double-steps did not match either the QLV or the AQLV model. The force after the second step was lower than that predicted by the superposition model. Indeed, the force by about 20 ms after the second step was always the same, irrespective of the first step. That means that muscles do not show memory for their previous history, which should make neural control simpler.

Instead of representing muscle as lumped linear systems of springs and dashpots (elastic and viscous elements), we used a nonlinear model based on thixotropic materials (e.g., gels, creams, suspensions, silly putty). In these materials external stresses and strains induce reversible microstructural changes, resulting in temporary reductions in viscosity and elasticity (Quaia et al., 2010). The new model added dynamic changes to the AQLV model, which we then called the attenuated nonlinear viscoelastic model (ANLV). An example of the performances of the AQLV and ANLV models is shown in Fig. 5. The results clearly indicate that during a change in muscle length with a time and speed similar to physiological saccades, the superposition assumption for muscle force does not hold, even approximately. The new ANLV model gives a much better fit, suggesting that it is better to think of muscles as complex materials with internal structure, rather than as lumped springs and dashpots. The genesis of this improved model came from studying a clinical problem, superior oblique palsy, which led to focused experiments in animals and new theoretical studies. This is exactly the interdisciplinary approach that will be necessary in the future to improve our understanding of biological systems in health and disease.

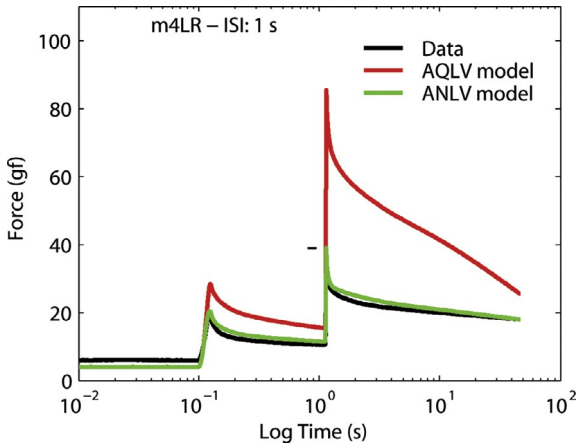

FIG. 5

Predictions of lateral rectus (LR) muscle forces elicited by two saccade-like elongations of 1.6 mm each (separated by an inter-stimulus interval of 1 s) from monkey number 4. The prediction of the adaptive quasi-linear viscoelastic (AQLV) model (red) is too large for the first saccade, and very much too large for the second saccade. The forces predicted by the attenuated nonlinear viscoelastic (ANLV) model (green) are very close to the observed forces (black). The maximum observed force is indicated by the "-" on the second peak (at about 40 gf). (Gram force (gf) is the unit of force commonly used in strabismus studies.) The actual muscle force is much less than that predicted by superposition models, indicating that the most fundamental assumption of earlier models of muscles, that superposition holds, is false.

After Quaia, C., Ying, H.S., Optican, L.M., 2010. The viscoelastic properties of passive eye muscle in primates. III. Force elicited by natural elongations. PLoS One. 5, e9595.

6 Neuroprostheses

When disease or injury causes a loss of brain function, it is the goal of some biomedical engineers to substitute external circuits for that function. Such neuroprostheses are an important application of modeling, because it requires a good mathematical model of the brain function underlying the disability to be able to replace it. Although we are far from desired goals such as creating visual prostheses for the blind, or motor prostheses for the paralyzed patient, much progress can be made by building and verifying models of brain function.

For example, several groups have been working on neuroprostheses to restore cerebellar function. Herreros et al. (2014) have shown that a circuit embodying a cerebellar model can restore classical conditioning in anesthetized rats. Luo et al. (2016) built a bio-realistic network-on-chip cerebellar system to study how a cerebellar prosthesis could contribute to passage-of-time calculations. Gilja et al. (2015) used a neural prosthesis developed in animals to control a cursor in patients with

amyotrophic lateral sclerosis. Nachev et al. (2017) implanted a magnet in extraocular muscles to damp the oscillations of a patient with upbeat nystagmus. This resulted in a significant increase in visual acuity.

7 Conclusion

For neuroscience to progress, it needs to bridge basic and clinical research. In the examples above, we have shown how models were created based on both knowledge and assumptions. The assumptions are critical, or there will be too many models that could fit the data. For saccades, the classic assumption has been that the eye moves to acquire the target, much as an engineering tracker, say for a camera, would move to follow a target. However, later experiments failed to find evidence to support this assumption. That removed some constraints from saccade models and led to new thinking about the goal of the saccadic system. In other examples, clinical cases showed behavior that was completely outside the behavior seen in experiments in monkey or human subjects. Again, this completely shifted model constraints, requiring completely new models that could incorporate a lot of data that had previously been excluded.

7.1 Whereas diseases are useful for models, are models useful for diseases?

Models can be used to design drugs and prostheses, but there are not that many successful cases of this approach. Why haven't models been more useful to clinicians? This is a simple question with a multifactorial answer. Part of the reason may be that clinicians do not receive adequate training in understanding how to build and apply models. It may also be that clinicians tend to clump together many disorders that have similar symptoms, but that may have completely different causes (such as opsoclonus). Scientists, on the other hand, tend to winnow such clumps until they have a homogeneous set of patients with a problem so specific that understanding it gives no clues that are generally useful in the more complex and variegated reality of the clinic. Finally, it may be that our models are still too simplistic.

If models are to become more useful for clinicians, we must endeavor to make them as complete as possible. The main areas that have guided our models include anatomy, physiology, biophysics and behavior. We have done fairly well at incorporating different cell types, defining local circuits, and mimicking normal behavior. Moving the field forward will require more attention to global circuits that incorporate multiple cerebral areas, because many systems spread across the brain. Another area which has been slow to progress is our understanding of transmembrane receptors. Many neurotransmitters (glutamate, glycine, dopamine, etc.) are well known, and they can be identified in cells through histochemistry. What remains unstudied, however, is the biophysics of the receptor dynamics. Yet, such

knowledge is crucial, for many drugs act at receptors. This may prove to be a very fruitful area for building models that have clinical relevance.

Neural prosthetics is a relatively new field that has shown much promise. It is an important application of modeling, and itself helps to improve models of brain function. The goal of building a neuroprostheses emphasizes the importance of making a model/circuit that closely mimics the real one. Only neuromimetic models can allow basic and clinical results to be reconciled. Neuroprosthetic research raises many ethical considerations. What if a neuroprosthetic could be developed that exceeded human performance? Would it be useful, and would its use be ethical?

In the future, it is hoped that more interactions between clinicians and modelers will result in new models that are more useful in the clinic. For this to happen, the burden is on clinicians to identify appropriate sets of patients, collect quantitate data during controlled behavioral tests, and share them with modelers. It would be even better if the clinicians and modelers began their collaborations before studies were undertaken. There is also a burden on modelers, who tend to remain insulated from the multifarious problems faced by clinicians. They must seek out clinicians interested in collaborating on models, and be open-minded when it comes to addressing the limited, and messy, data that comes from studying patients. Standing in the middle are the basic scientists, whether anatomists, physiologists, biophysicists, etc. Their burden is to widen the scope of their experiments to cover the areas and mechanisms that may be important in understanding clinical problems. Perhaps it is time for large consortia to form, combining basic and clinical researchers with theoreticians that can act as a resource for improving our health.

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References

Aizenman, C.D., Linden, D.J., 1999. Regulation of the rebound depolarization and spontaneous firing patterns of deep nuclear neurons in slices of rat cerebellum. J. Neurophysiol. 82, 1697–1709.

Becker, W., Jurgens, R., 1979. An analysis of the saccadic system by means of double step stimuli. Vision Res. 19, 967–983.

Buchthal, F., Kaiser, E., 1951. The rheology of the cross striated muscle fiber, with particular reference to isotonic conditions. Dan. Biol. Medd. 21, 1–318.

Büttner-Ennever, J.A., Büttner, U., 1992. Neuroanatomy of the ocular motor pathways. Baillieres Clin. Neurol. 1, 263–287.

Collins, C.C., 1971. Orbital mechanics. In: Bach-Y-Rita, P., Collins, C.C., Hyde, J.E. (Eds.), The Control of Eye Movements. Academic Press, New York, pp. 285–325.

Collins, C.C., 1975. The human oculomotor control system. In: Lennerstrand, G., Bach-Y-Rita, P. (Eds.), Basic Mechanisms of Ocular Motility and Their Clinical Implications. Pergamon Press, Oxford, pp. 145–180.

Dodge, R., 1903. Five types of eye movement in the horizontal meridian plane of the field of regard. Am. J. Phys. 8, 307–329. Legacy content.

Eggert, T., Guan, Y., Bayer, O., Buttner, U., 2005. Saccades to moving targets. Ann. N. Y. Acad. Sci. 1039, 149–159.

Federighi, P., Cevenini, G., Dotti, M.T., Rosini, F., Pretegiani, E., Federico, A., Rufa, A., 2011. Differences in saccade dynamics between spinocerebellar ataxia 2 and late-onset cerebellar ataxias. Brain 134, 879–891.

Fong, M., Babu, S., Wolfe, N., 2017. Enteroviral rhombencephalitis presenting with ocular flutter. J. Clin. Neurosci. 36, 57–58.

Fung, Y.-C.B., 1972. Stress-strain-history relations of soft tissues in simple elongation. In: Fung, Y.C., Perrone, N., Anliker, M. (Eds.), Biomechanics Its Foundations and Objectives. Prentice-Hall, Englewood Cliffs N.J., pp. 181–208. Chapter 7.

Geiner, S., Horn, A.K., Wadia, N.H., Sakai, H., Buttner-Ennever, J.A., 2008. The neuroanatomical basis of slow saccades in spinocerebellar ataxia type 2 (wadia-subtype). Prog. Brain Res. 171, 575–581.

Ghasia, F.F., Shaikh, A.G., 2014. Source of high-frequency oscillations in oblique saccade trajectory. Exp. Eye Res. 121, 5–10.

Gilja, V., Pandarinath, C., Blabe, C.H., Nuyujukian, P., Simeral, J.D., Sarma, A.A., Sorice, B.L., Perge, J.A., Jarosiewicz, B., Hochberg, L.R., Shenoy, K.V., Henderson, J.M., 2015. Clinical translation of a high-performance neural prosthesis. Nat. Med. 21, 1142–1145.

Guan, Y., Eggert, T., Bayer, O., Büttner, U., 2003. Analysis of saccades to stationary and moving targets in the monkey. Ann. N. Y. Acad. Sci. 1004, 385–388.

Guan, Y., Eggert, T., Bayer, O., Buttner, U., 2005. Saccades to stationary and moving targets differ in the monkey. Exp. Brain Res. 161, 220–232.

Herreros, I., Giovannucci, A., Taub, A.H., Hogri, R., Magal, A., Bamford, S., Prueckl, R., Verschure, P.F., 2014. A cerebellar neuroprosthetic system: computational architecture and in vivo test. Front. Bioeng. Biotechnol. 2, 14.

Hirsch, J., Curcio, C.A., 1989. The spatial resolution capacity of human foveal retina. Vision Res. 29, 1095–1101.

Jurgens, R., Becker, W., Kornhuber, H.H., 1981. Natural and drug-induced variations of velocity and duration of human saccadic eye movements: evidence for a control of the neural pulse generator by local feedback. Biol. Cybern. 39, 87–96.

Karam, E., Giraldo, J., Rodriguez, F., Hernandez-Pereira, C.E., Rodriguez-Morales, A.J., Blohm, G.M., Paniz-Mondolfi, A.E., 2017. Ocular flutter following Zika virus infection. J. Neurovirol. 23, 932–934.

Kobayashi, M., 2015. Unidirectional ocular flutter: report of a case with abnormal saccadic characteristics. Neurol. Sci. 36, 1273–1276.

Lefevre, P., Quaia, C., Optican, L.M., 1998. Distributed model of control of saccades by superior colliculus and cerebellum. Neural Netw. 11, 1175–1190.

Luo, J., Coapes, G., Mak, T., Yamazaki, T., Tin, C., Degenaar, P., 2016. Real-time simulation of passage-of-time encoding in cerebellum using a scalable FPGA-based system. IEEE Trans. Biomed. Circuits Syst. 10, 742–753.

Mandelbaum, J., Sloan, L.L., 1947. Peripheral visual acuity with special reference to scotopic illumination. Am. J. Ophthalmol. 30, 581–588.

Nachev, P., Rose, G.E., Verity, D.H., Manohar, S.G., Mackenzie, K., Adams, G., Theodorou, M., Pankhurst, Q.A., Kennard, C., 2017. Magnetic oculomotor prosthetics for acquired nystagmus. Ophthalmology 124, 1556–1564.

Nekouzadeh, A., Pryse, K.M., Elson, E.L., Genin, G.M., 2007. A simplified approach to quasi-linear viscoelastic modeling. J. Biomech. 40, 3070–3078.
Newman, N., Gay, A.J., Stroud, M.H., Brooks, J., 1970. Defective rapid eye movements in progressive supranuclear palsy. An ocular electromyographic study. Brain 93, 775–784.
Optican, L.M., Pretegiani, E., 2017. A GABAergic dysfunction in the olivary–cerebellar–brainstem network may cause eye oscillations and body tremor. II. Model simulations of saccadic eye oscillations. Front. Neurol. 8, 372.
Optican, L.M., Quaia, C., 2002. Distributed model of collicular and cerebellar function during saccades. Ann. N. Y. Acad. Sci. 956, 164–177.
Quaia, C., Optican, L.M., 2003. Dynamic eye plant models and the control of eye movements. Strabismus 11, 17–31.
Quaia, C., Lefevre, P., Optican, L.M., 1999. Model of the control of saccades by superior colliculus and cerebellum. J. Neurophysiol. 82, 999–1018.
Quaia, C., Pare, M., Wurtz, R.H., Optican, L.M., 2000. Extent of compensation for variations in monkey saccadic eye movements. Exp. Brain Res. 132, 39–51.
Quaia, C., Shan, X., Tian, J., Ying, H., Optican, L.M., Walker, M., Tamargo, R., Zee, D.S., 2008. Acute superior oblique palsy in the monkey: effects of viewing conditions on ocular alignment and modelling of the ocular motor plant. Prog. Brain Res. 171, 47–52.
Quaia, C., Ying, H.S., Nichols, A.M., Optican, L.M., 2009a. The viscoelastic properties of passive eye muscle in primates. I. Static forces and step responses. PLoS One 4, E4850.
Quaia, C., Ying, H.S., Optican, L.M., 2009b. The viscoelastic properties of passive eye muscle in primates. II. Testing the quasi-linear theory. PLoS One 4, E6480.
Quaia, C., Ying, H.S., Optican, L.M., 2010. The viscoelastic properties of passive eye muscle in primates. III. Force elicited by natural elongations. PLoS One 5, E9595.
Ramat, S., Leigh, R.J., Zee, D.S., Optican, L.M., 2005. Ocular oscillations generated by coupling of brainstem excitatory and inhibitory saccadic burst neurons. Exp. Brain Res. 160, 89–106.
Ramat, S., Leigh, R.J., Zee, D.S., Optican, L.M., 2007. What clinical disorders tell us about the neural control of saccadic eye movements. Brain 130, 10–35.
Robinson, D.A., 1964. The mechanics of human saccadic eye movement. J. Physiol. 174, 245–264.
Robinson, D.A., 1973. Models of the saccadic eye movement control system. Kybernetik 14, 71–83.
Robinson, D.A., 1975a. A quantitative analysis of extraocular muscle cooperation and squint. Invest. Ophthalmol. 14, 801–825.
Robinson, D.A., 1975b. Oculomotor control signals. In: Lennerstrand, G., Bach-Y-Rita, P. (Eds.), Basic Mechanisms of Ocular Motility and Their Clinical Implication. Pergamon, New York, pp. 337–374.
Robinson, D.A., O'meara, D.M., Scott, A.B., Collins, C.C., 1969. Mechanical components of human eye movements. J. Appl. Physiol. 26, 548–553.
Schiller, P.H., True, S.D., Conway, J.L., 1979. Effects of frontal eye field and superior colliculus ablations on eye movements. Science 206, 590–592.
Scudder, C.A., 2002. Role of the fastigial nucleus in controlling horizontal saccades during adaptation. Ann. N. Y. Acad. Sci. 978, 63–78.
Shaikh, A.G., 2012. Saccadic oscillations—membrane, model, and medicine. Expert Rev. Ophthalmol. 7, 481–486.

Shaikh, A.G., Miura, K., Optican, L.M., Ramat, S., Tripp, R.M., Zee, D.S., 2008a. Hypothetical membrane mechanisms in essential tremor. J. Transl. Med. 6, 68.

Shaikh, A.G., Ramat, S., Optican, L.M., Miura, K., Leigh, R.J., Zee, D.S., 2008b. Saccadic burst cell membrane dysfunction is responsible for saccadic oscillations. J. Neuroophthalmol. 28, 329–336.

Shan, X., Tian, J., Ying, H.S., Quaia, C., Optican, L.M., Walker, M.F., Tamargo, R.J., Zee, D.S., 2007a. Acute superior oblique palsy in monkeys: I. Changes in static eye alignment. Invest. Ophthalmol. Vis. Sci. 48, 2602–2611.

Shan, X., Ying, H.S., Tian, J., Quaia, C., Walker, M.F., Optican, L.M., Tamargo, R.J., Zee, D.S., 2007b. Acute superior oblique palsy in monkeys: II. Changes in dynamic properties during vertical saccades. Invest. Ophthalmol. Vis. Sci. 48, 2612–2620.

Strassman, A., Highstein, S.M., Mccrea, R.A., 1986. Anatomy and physiology of saccadic burst neurons in the alert squirrel monkey. II. Inhibitory burst neurons. J. Comp. Neurol. 249, 358–380.

Thomas, J.G., 1967. The torque-angle transfer function of the human eye. Kybernetik 3, 254–263.

Wadia, N.H., 1973. An indigenous form of heredo-familial spinocerebellar degenerations with slow eye movements. Neurol. India 20, 561–580.

Wadia, N.H., Swami, R.K., 1971. A new form of heredo-familial spinocerebellar degeneration with slow eye movements (nine families). Brain 94, 359–374.

Westheimer, G., 1954. Mechanism of saccadic eye movements. A.M.A. Arch. Ophthalmol. 52, 710–724.

Westheimer, G., McKee, S.P., 1975. Visual acuity in the presence of retinal-image motion. J. Opt. Soc. Am. 65, 847–850.

Young, L.R., Stark, L., 1963. Variable feedback experiments testing a sampled data model for eye tracking movements. IEEE Trans. Human Factors Eng. Hfe4, 38.

Zaltzman, R., Klein, C., Gordon, C.R., 2017. Opsoclonus myoclonus ataxia associated with West Nile virus infection: a dramatic presentation with benign prognosis? J. Neurol. Sci. 376, 38–41.

Zee, D.S., Robinson, D.A., 1979. A hypothetical explanation of saccadic oscillations. Ann. Neurol. 5, 405–414.

Zee, D.S., Optican, L.M., Cook, J.D., Robinson, D.A., Engel, W.K., 1976. Slow saccades in spinocerebellar degeneration. Arch. Neurol. 33, 243–251.