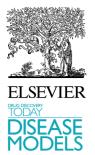
### **Drug Discovery Today: Disease Models**



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Computational Models of Neurological Disorder

# Computer modeling for pharmacological treatments for dystonia

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Dystonia is a movement disorder that produces involuntary muscle contractions. Current pharmacological treatments are of limited efficacy. Dystonia, like epilepsy is a disorder involving excessive activity of motor areas including motor cortex and several causal gene mutations have been identified. In order to evaluate potential novel agents for multitarget therapy for dystonia, we have developed a computer model of cortex that includes some of the complex array of molecular interactions that, along with membrane ion channels, control cell excitability.

#### Introduction

A number of movement disorders, as well as epilepsy, are associated with increased activity, and likely with hyperexcitability, in cortex. Dystonia is a movement disorder which produces involuntary muscle contractions. It involves pathology in multiple brain areas including basal ganglia, thalamus, cerebellum, and sensory and motor cortices. Although much of the research in dystonia has looked at the role of the basal ganglia, pharmacological treatment is often provided directly to the muscle through injection of botulinum toxin,

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anticholinergic agents and benzodiazepines. Motor cortex is another possible target for drug therapy, with manifestations that include augmented beta oscillations. Using a mechanistic multiscale model of primary motor cortex, we have assessed parameter combinations that produce dystonia to suggest potential drug combinations that might interfere with these pathological dynamics.

#### Schematized and mechanistic models for dystonia

Dystonia is a movement disorder that produces intermittent prolonged involuntary muscle activation that results in twisting, turning or posturing of a limb or other body part and repetitive prolonged movements. As with other movement disorders, the difficulty in modeling dystonia stems from the complexity of the motor system itself: the large set of specialized nuclei in brain and spinal cord that are interacting to produce movement in continuous concert with sensory areas in the sensorimotor loop. These areas include basal ganglia,

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thalamus, cerebellum, red nucleus, anterior horn, etc. Even when a primary pathology can be localized to a particular area, plastic responses in other motor and sensory areas will alter the expression of the disease in a way that can either ameliorate or exacerbate disability, and treatments may target areas other than the area of primary pathology. For example, although task-specific focal dystonia such as writers cramp is thought to occur due to overlearning in sensory and motor cortical areas, some of the treatments used are targeting basal ganglia.

The large number of areas involved in motor activity would be best served by simulations that encompass all of these areas. Such an approach requires working out plausible input and output signal patterns for each nucleus or area, and then requires working with highly *schematized models*. Schematized models typically use mean-field approximations, where brain areas are approximated by scalar signals representing overall activity. Some schematized models may include more detailed integrate-and-fire or scalar (perceptron) neural network models [1–3]. However, this intermediate modeling level also lacks the cell and molecular details useful for comparison with pharmacological intervention.

Sanger and Merzenich [4] used a schematized model to identify likely patterns of positive feedback between sensory and motor cortical areas that would lead to runaway excitation. Their cortical control-theory model was able to identify particular dynamical patterns that could potentially be interrupted to prevent the recurrence of these pathological patterns. Interestingly, this provided some suggestion as to the mechanism of self-treatment using 'sensory tricks', where the patient relaxes the dystonia by touching a particular spot – for example, often on the side of the chin to reduce the headturning of torticollis. However, the limitation of this model, as for other schematized models, was that it could not suggest drugs or drug targets for treatment.

Mechanistic multiscale modeling is an alternative to schematized models that does afford the opportunity to reach down to the molecular scale of pharmacology and thereby assist in the development of novel treatments. These models will include more levels or scales than are included in the schematized model, and for purposes of drug discovery should include some molecular detail.

#### A mechanistic model of cortical hyperexcitability

Dystonia is a *dynamical disorder* that can be defined by its particular patterns of muscle activation. The excessive muscle activity of dystonia is a consequence of dynamical disorder in brain and spinal cord, associated with higher than normal activity patterns. To the extent that the disease is caused by cortical dysfunction, as assumed by control theory models [4], we identify *hyper-activity* as a manifestation of *hyperexcitability*.

The major disorder of cortical hyperexcitability is epilepsy, manifested by seizures. In both epilepsy and dystonia, underlying causes will include changes or anomalies in ion channel and receptor densities, as well as in cortical wiring [5], which produce excitation/inhibition imbalances and with excessive cortical firing and excessive synchrony [6– 10]. The intensity, pattern, and spread of hypersynchrony differ between epilepsy and dystonia. Electroencephalographic signatures of the two disorders also differ, with seizures characterized by powerful discharges that may be time locked to the movement while dystonia shows an increase in beta (12–25 Hz) oscillations [11–13]. In addition to there being various patterns of hyperexcitability in cortex, there are various ways to produce hyperexcitability *in silico*.

We developed a mechanistic multiscale model of cortex (Fig. 1) in which we could identify patterns of activity for: (1) normal; (2) dystonia; (3) epileptiform (seizure) [14]. Model scales ranged from molecular to network so as to permit us to associate potential pharmacological manipulations with alterations in network dynamics. These models therefore combine the domain of computational systems biology – molecular interactions, with the traditional approach to computational neuroscience – models of cells as electrically interacting units with only ion channels represented at the molecular level.

Varying the densities of voltage-sensitive ion channels and receptor densities on pyramidal neurons and interneurons within reasonably ranges resulted in families of models that could be classified as having normal, dystonia-like, or epileptiform activity patterns (Fig. 2). Dystonia models were characterized by synchronous population discharges at beta frequency (~20 Hz). In each case, there were multiple parameter sets that produced similar dynamics [15–18]. This phenomenon is well known in biology where the combinatorics of multiple alleles for every feature, for every ion channel, enzyme and receptor, means that no two people are entirely alike. Despite not being alike, all people show similar dynamics, a phenomenon referred to as parameter degeneracy [19].

We locate particular models that produce dystonia in highdimensional parameter space. A three-dimensional slice of the eleven-dimensional parameter space (Fig. 3), shown in a normalized space relative to a baseline value, demonstrated that dystonia cases tend to have higher levels of voltage-gated  $Ca^{2+}$  channels (L-, N-, T-types; labeled Ca), lower levels of BK K<sup>+</sup> channels in the plasma membrane, and higher levels of ryanodine (RYR) channels in endoplasmic reticulum. In a particular case, we can indicate a direction in parameter space (Fig. 3, arrow) going from a dystonia parameter-set to a normal parameter-set. For any dystonic case in our set, we can identify a simple path, involving one or two parameter changes, which leads to a normal set, indicating alterations to be effected in our simulated 'patient' that would treat the Download English Version:

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