The joint structure–function dynamics of glaucoma progression

Lyne Racette

Eugene and Marilyn Glick Eye Institute, Indiana University, Indianapolis, IN, USA

Jonathan E Helm

Department of Operations and Decision Technologies, Indiana University Kelley School of Business, Bloomington, IN, USA

Mitchell Dul

Department of Biological & Visual Sciences and Graduate Center for Vision Research, State University of New York College of Optometry, New York, NY, USA

Iván Marín-Franch

Departamento de Optica Facultad de Fisica, Universitat de Valencia, Burjassot, Spain

Abstract

While the presence and rate of glaucoma progression influence treatment decisions, the methods currently available to detect and monitor progression are imprecise and do not allow clinicians to make accurate assessments of the status of their patients. Models that focus on combining structural and functional parameters may improve our ability to detect and monitor glaucoma progression. Several of these models, however, are limited by their reliance on population statistics and on the static assumptions they make about the nature of glaucoma progression. Dynamic modeling of glaucoma progression may lead to a better understanding of glaucoma progression that could eventually translate into making individualized treatment decisions.

Keywords: glaucoma, progression, structure–function relationship

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The key to monitoring glaucoma patients and determining how aggressive therapy should be is based, in part, on identifying how rapidly the disease is progressing. Many glaucoma patients get worse with time, but if they are doing so very slowly their vision loss may not reach functional significance during their lifetime and treatment may not be necessary. On the other hand, when there is evidence of more rapid progression, clinical intervention is required and is guided, in part, by the rate of progression. In spite of significant advancements in imaging technology and diagnostic tests, determining whether glaucoma is progressing remains a challenge.

Recent efforts have focused on combining structural and functional data to monitor glaucoma progression. The rationale for doing so is that these two types of data may provide complementary information. For example, studies have shown that structural changes can be detected prior to, after, or at the same time as functional changes [1,2]. Therefore, simultaneously making use of the structural and functional data that are routinely obtained in glaucoma clinics has the potential to improve our ability to detect change.

Determining how structural and functional data should be combined, however, is complicated by the fact that the relationship between structure and function is not well understood in glaucoma [3]. For example, while some studies suggested that structure and function were best defined by a curvilinear relationship [4–6], recent studies have demonstrated that the structure–function relationship may be linear when both measurements are expressed in linear units [7–11]. Furthermore, apparent structure–function associations are influenced by sample composition, measurement variability, and statistical methods [10].

Given that the underlying relationship between structure and function is not well characterized, approaches based on joint dynamic modeling of structural and functional progression offer a promising avenue to describe observed changes in glaucoma. Dynamic models have been developed for other chronic diseases [12,13] and this approach could be applied to glaucoma progression. Recent efforts in

this direction have been made and deserve attention. Schell et al. [14] proposed a dynamic model to personalize the frequency of clinic visits for glaucoma patients based on each patient's historical intra-ocular pressure levels and their performance on visual field tests. After each set of visual field and intra-ocular pressure assessments, the model calls for more or less frequent testing based on the predicted probability of progression in the near future, which is a function of all of the patient's previous test results. Initially, this approach relies on a series of three readings taken on the patient and on trajectory information gathered from large clinical trials to model expected progression. As information accumulates on a person, these data are recursively incorporated into the model to make adjustments to the underlying population model based on each patient's personal history of tests, driving further projections on progression.

This work, however, only considered visual field and intra-ocular pressure and did not include key structural measures that can provide additional useful information regarding progression. Furthermore, general progression dynamics were modeled using population data and these dynamics did not change over time. Hence, the only dynamic component was the incorporation of new test results over time, while the general path of progression was assumed to be the same for all patients, leading to only partial personalization of testing schedules.

In comparison, the dynamic structure–function model [15] has been developed to capture changes in the rate and pattern of progression over time from both structural and functional measures jointly. The model summarizes joint progression with two vectors, a vector for the state of disease and a vector for the velocity of progression, and provides an intuitive graphical representation of the status of the disease that can be used as a tool to promote effective communication between clinicians and their patients. The dynamic structure–function model is flexible in that it can be readily implemented for more than two structural and functional indices. For instance, the model can describe joint progression of mean deviation, rim area, and retinal nerve fiber layer thickness, three indices commonly used in clinical practice to assess progression. This model does not rely on population statistics and gives equal weight to

both structural and functional data. This is in contrast to many other models that have been developed to combine structural and functional data in a clinically meaningful way, including machine learning classifiers [16] and Bayesian models [17,18]. Some of these models based on population statistics are motivated by the idea that if no information is available, the best prior estimation is that a patient progresses at the same rate as other patients with similar characteristics (e.g., stage of disease). Other models make a prior estimation of the rate of progression from structural measures and refine the estimation with functional measures.

Even though approaches based on population statistics are well founded, large errors can occur for individual subjects that depart from mean normal behavior. Given the very large between-subjects differences in structural and functional measures, the usefulness of these models is limited by the fact that they can provide misleading results for many individual patients. Hood et al. [19], for example, have shown that between-subject differences account for up to 87% of the total variance in retinal nerve fiber layer thickness and up to 71% of the variance in visual field measurements. In the same vein, Marín-Franch et al. have shown that between-subject differences account for more dissociation between rim area and visual sensitivity than test–retest variability (Marín-Franch et al. IOVS 2013;54:ARVO E-Abstract 2247). These large between-subject differences severely limit the performance of any method that uses population statistics to assess glaucoma progression.

Efforts to develop predictive models of glaucomatous progression occur in a setting where no specific glaucoma test or combination of tests is regarded as a reference standard for the detection of glaucomatous progression. In addition, statistically significant change may not be clinically relevant. Information derived from these models might be most useful when considered in conjunction with the myriad of factors that are taken into account in the clinical decision making process. These factors include the stage of glaucoma at initial presentation, life expectancy, and quality of life of the patient.

In summary, accurate detection of glaucoma progression will result in more efficient management of the disease. Teasing out true progression from between-subjects differences is both important and

challenging. Individualized dynamic models offer several advantages and show promise in improving our ability to detect progression more accurately in each patient. In the future, these models could be used to tailor treatment approaches for each patient and efforts in this direction have begun [14]. They could also improve our ability to identify those patients who are at risk of progressing rapidly. This could translate to a more efficient use of healthcare resources, by allowing more frequent monitoring of high-risk patients while increasing time between clinical appointments for low-risk patients.

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