"Spatiotemporal mathematical modeling of myocardin-related transcription factor-A signaling"

Benjamin Spar

Opening Comments

These abstracts detail an independent research project that I have been working on for the past year and a half. I began in the summer before my sophomore year, and I am now continuing the project as part of my independent work for Computer Science. The first abstract was submitted to the 2014 annual meeting of the American Society of Cell Biology (ASCB), a large academic biology conference focusing on the biology of the cell (hence the name of the organization). I have also included a mock abstract for a computer science conference with a biological focus. This second (unpublished) abstract describes the same results at the first, but I changed its focus for a much more quantitative audience. The language in both abstracts is highly technical because of my audience. Unfortunately, this convention renders the details almost unintelligible to anyone other than a biologist, so I have also included a more readable explanation to start things off.

Abstract Explanation

Consider a mammalian cell as a small fluid-filled balloon. Inside the cell is another balloon, the nucleus, in which DNA (among other things) is kept. The fluid outside of the nucleus is called the cytoplasm. Various proteins move between the cytoplasm and the nucleus in a process called nucleocytoplasmic translocation or nucleocytoplasmic shuttling. Many cellular processes are controlled by the amount of certain proteins in the nucleus, so understanding the mechanisms that control how much of a given protein is in the nucleus at any given time is of great importance. MRTF-A is one such protein, and the amount of MRTF-A in the nucleus relative to the total amount of MRTF-A (a ratio called the nuclear localization) is controlled by another protein called actin. We increased the total amount of MRTF-A in the cell and observed that the MRTF-A nuclear localization also changes. We then wrote out the system as a series of mathematical equations and found that the mathematics did not explain the results we saw.

Biology Abstract

Spatiotemporal mathematical modeling of myocardin-related transcription factor-A signaling

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Myocardin-related transcription factor-A (MRTF-A; also known as Mkl1, MAL, BSAC) is involved in many cellular processes including migration, organogenesis, and tumor metastasis. MRTF-A is activated by nuclear translocation, which is regulated by the nucleocytoplasmic distribution of monomeric and filamentous actin. The currently accepted conceptual model is that MRTF-A is only exported from the nucleus when bound to G-actin, and only imported when unbound. To test the robustness of this conceptual model, we transfected MRTF-A under a strong constitutive promoter into NIH-3T3 fibroblasts. MRTF-A nuclear localization was quantified using immunostaining.

Surprisingly, we found that the nuclear localization of MRTF-A was altered in cells expressing ectopic protein compared to endogenous. Specifically, treatment with cytoskeletal disruptors such as jasplakinolide or cytochalasin D, or stimulation with serum, had different effects on localization of ectopic versus endogenous MRTF-A. Computational kinetic modeling of the MRTF-A/actin regulatory axis using systems of differential equations was unable to quantitatively explain these results. Stochastic kinetic modeling using the slow-scale stochastic simulation algorithm, a variant of the Gillespie algorithm, was unable to reproduce the distribution of MRTF-A localization using physiologically relevant protein copy numbers. Taken together, our results show that the currently accepted conceptual model of MRTF-A nucleocytoplasmic shuttling does not sufficiently explain MRTF-A kinetics.

Hypothetical Submission to a Computer Science Conference

Myocardin-related transcription factor-A (MRTF-A; also known as Mkl1, MAL, BSAC) is involved in many cellular processes including migration, organogenesis, and tumor metastasis. MRTF-A actively shuttles between the nucleus and cytoplasm via a mechanism controlled by actin, a component of the cytoskeleton. We have experimentally observed significant cell-to-cell variability in the localization of MRTF-A that cannot be explained by a deterministic ordinary differential equation (ODE) model. To explore the role of intrinsic noise and protein concentration on stochastic fluctuations in MRTF-A localization, we implemented the slow-scale stochastic simulation algorithm, an approximation of the statistically exact Gillespie algorithm for stiff systems. Protein copy numbers and reaction rate constants were derived from the literature, when available, or optimized using differential evolution against experimental data when unavailable. We find that the intrinsic noise from such physiologically relevant parameters generates very little stochastic variation and does not explain our experimental distribution of MRTF-A localization, even when accounting for measurement error. Extrinsic noise was modeled by variability in the input signal to the MRTF-A/actin regulatory axis, namely the activation state of the regulatory protein RhoA. This noisy input was able to generate significant stochastic variation in MRTF-A localization but did not recover the exact experimental distribution of MRTF-A localization. Taken together, these results indicate that the current conceptual model of MRTF-A regulation does not quantitatively explain stochastic variation in MRTF-A kinetics.

Author Commentary

Benjamin Spar

Motive and Audience in Abstracts

Writing a scientific abstract very closely mirrors the process of scientific inquiry itself. A system is introduced and the hypothesis is motivated and justified either as a solution to an existing gap in scientific knowledge or as a demonstration that such knowledge is incomplete. In this case, I introduce the MRTF-A signaling axis and justify its importance in relation to other cell processes.

But motive is also intrinsically linked to audience. My overall hypothesis is that our understanding of how MRTF-A moves around in a cell is incomplete. However, in the biology abstract, the motive is framed in terms of biological processes. I focus most of this abstract on explaining my cell culture experiments and their motivation, not discussing my modeling techniques. A computer science conference, on the other hand, would expect a different motive, such as using well-known simulation methods on a novel biological system. In my mock computer science abstract, I focus on the role of random fluctuations (called stochastic noise or stochastic variability) in MRTF-A localization. My hypothesis is the same as that in the biology abstract, but I go into much more detail about the exact modeling techniques instead of the biochemical experiments. In other words, I used my expected audience as the primary determinant of my project explanation and motivation.

Abstracts for Different Settings

An abstract for a scientific conference is essentially a very short version of the steps above. Biology conference abstracts are actually intended to be incomplete research—they include a question but likely not an answer. In this case, I have identified that our understanding of MRTF-A nucleocytoplasmic shuttling is incomplete. I have not presented and validated an alternate hypothesis that explains my data. In other words, my conference abstract asks a scientific question (like motive) but does not answer it. Once biological research includes both the ask and the answer (motive and thesis), the results are publishable in journals. As I have only asked a question (Why does our conceptual model of MRTF-A localization not quantitatively explain my experimental data?), my results are not yet publishable, but they are ready for a conference. Unsurprisingly, abstracts for conferences tend to be in various stages of completion, but they all have in common that there is clearly more work to be done before the proposed hypothesis can be confirmed or denied.

Computer science conferences actually function more like journals; submissions take the form of a 1000-1500–word paper that, like biology journals, contains a complete hypothesis and supporting results. The mock computer science abstract I wrote is therefore not appropriate for a real computer science conference. It was written to illustrate how abstracts change when targeted to different audiences.

Fellow Commentary

Abigail M. Kelly

Writing an abstract is essentially distilling all of our research and an entire paper into one or two paragraphs. What will help us determine which details actually end up in the abstract is our audience. Benjamin's abstracts do an excellent job of showcasing how the same research can be reframed when writing for different audiences. Not only can we see that Ben's word choices and orienting changed between the biology and computer science abstracts, we can also see that he reworked his motive so that his research would appeal to his intended audience. Ben's commentary also gives us a glimpse into the importance of knowing our discipline. Abstracts are often what researchers submit to conferences or journals for publication, and in order to be accepted, the abstract must not only speak to that audience but also follow their guidelines. Ben gives us the useful example of the difference between a biology conference and a biology journal. At biology conferences, it is expected that research is still in process. Thus, these abstracts should focus on motive and do not need to include a thesis or argument. For biology journals, however, having an argument is a must. This differentiation is something that we should keep in mind when crafting our abstracts: knowing our audience means knowing what format they will expect. When writing an abstract, check with professors or others in the field, read papers or abstracts that have been submitted to the conference or publication in the past, and make sure your abstract follows these conventions and speaks the language of the audience.