*A Manuscript Microscope 'Sentence Audit' of:*

# Biophysical basis of cellular multi-specificity encoded in a model molecular switch

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**Manuscript Source:** https://www.biorxiv.org/content/10.1101/2020.01.04.893909v2

**Manuscript Authors:** Tina Perica, Christopher J. P. Mathy, Jiewei Xu, Gwendolyn M. Jang, Yang Zhang, Robyn Kaake, Noah Ollikainen, Hannes Braberg, Danielle L. Swaney, David G. Lambright, Mark J. S. Kelly, Nevan J. Krogan & Tanja Kortemme

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The sections of the research paper input text parsed in this audit.

| Section No. | Headings | Sentences |
|---|---|---|
| Section: 1 | Targeted perturbations to GTPase interaction interfaces | 1 |
| N/A | --- --- --- --- --- --- --- | 0 |
| N/A | --- --- --- --- --- --- --- | 0 |
| N/A | --- --- --- --- --- --- --- | 0 |
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## The Sentence Audit Of The Research Paper

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**Title**

# Biophysical basis of cellular multi-specificity encoded in a model molecular switch

**S0 [001]** Abstract

Abstract

**S0 [002]** Molecular switches are central to signal transduction in protein interaction networks.

Molecular switches are central ...

... to signal transduction ...

... in protein interaction networks.

**S0 [003]** One switch protein can independently regulate distinct cellular processes, but the molecular mechanisms enabling this functional multi-specificity remain unclear.

One switch protein can independently regulate distinct cellular processes, ...

... but the molecular mechanisms enabling this functional multi-specificity remain unclear.

**S0 [004]** Here we integrate system-scale cellular and biophysical measurements to study how a paradigm switch, the small GTPase Ran/Gsp1, achieves its functional multi-specificity.

Here we integrate system-scale cellular ...

... and biophysical measurements ...

... to study how a paradigm switch, ...

... the small GTPase Ran/Gsp1, ...

... achieves its functional multi-specificity.

**S0 [005]** We make 55 targeted point mutations to individual interactions of Ran/Gsp1 and show through quantitative, systematic genetic and physical interaction mapping that Ran/Gsp1 interface perturbations have widespread cellular consequences that cluster by biological processes but, unexpectedly, not by the targeted interactions.

We make 55 targeted point mutations ...

... to individual interactions ...

... of Ran/Gsp1 ...

... and show ...

... through quantitative, ...

... systematic genetic ...

... and physical interaction mapping ...

... that Ran/Gsp1 interface perturbations have widespread cellular consequences ...

... that cluster ...

... by biological processes but, ...

... unexpectedly, ...

... not ...

... by the targeted interactions.

**S0 [006]** Instead, the cellular consequences of the interface mutations group by their biophysical effects on kinetic parameters of the GTPase switch cycle, and cycle kinetics are allosterically tuned by distal interface mutations.

Instead, ...
... the cellular consequences ...
... of the interface mutations group ...
... by their biophysical effects ...
... on kinetic parameters ...
... of the GTPase switch cycle, ...
... and cycle kinetics are allosterically tuned ...
... by distal interface mutations.

**S0 [007]** We propose that the functional multi-specificity of Ran/Gsp1 is encoded by a differential sensitivity of biological processes to different kinetic parameters of the Gsp1 switch cycle, and that Gsp1 partners binding to the sites of distal mutations act as allosteric regulators of the switch.

We propose ...
... that the functional multi-specificity ...
... of Ran/Gsp1 is encoded ...
... by a differential sensitivity ...
... of biological processes ...
... to different kinetic parameters ...
... of the Gsp1 switch cycle, ...
... and that Gsp1 partners binding ...
... to the sites ...
... of distal mutations act ...
... as allosteric regulators ...
... of the switch.

**S0 [008]** Similar mechanisms may underlie biological regulation by other GTPases and biological switches.

Similar mechanisms ...
... may underlie biological regulation ...
... by other GTPases ...
... and biological switches.

**S0 [009]** Finally, our integrative platform to determine the quantitative consequences of cellular perturbations may help explain the effects of disease mutations targeting central switches.

Finally, ...
... our integrative platform ...
... to determine the quantitative consequences ...
... of cellular perturbations ...
... may help explain the effects ...
... of disease mutations targeting central switches.

**S0 [010]** Proteins perform their cellular functions within networks of interactions with many partners (1, 2).

Proteins perform their cellular functions ...
... within networks ...
... of interactions ...
... with many partners ...
... (1, 2)...
... .

**S0 [011]** This complexity raises the fundamental question of functional specificity: How can different functions be controlled individually with the required precision and accuracy, when distinct cellular processes are interconnected and often even share common regulators?

This complexity raises the fundamental question ...
... of functional specificity: ...
... How can different functions be controlled individually ...
... with the required precision ...
... and accuracy, ...
... when distinct cellular processes are interconnected ...
... and often even share common regulators?

**S0 [012]** Moreover, in highly interconnected networks even a small perturbation targeting individual interactions, introduced by posttranslational modifications, point mutations, or drug binding, could be magnified through the network and have widespread cellular consequences.

Moreover, ...
... in highly interconnected networks even a small perturbation targeting individual interactions, ...
... introduced ...
... by posttranslational modifications, ...
... point mutations, ...
... or drug binding, ...
... could be magnified ...
... through the network ...
... and have widespread cellular consequences.

**S0 [013]** Protein mutations in disease are enriched in protein-protein interfaces (3, 4), but it is unclear whether the consequences of these mutations can be explained primarily by their effects on individual interactions.

Protein mutations ...
... in disease are enriched ...
... in protein-protein interfaces ...
... (3, 4)...
... , ...
... but it is unclear ...
... whether the consequences ...
... of these mutations can be explained primarily ...
... by their effects ...
... on individual interactions.

**S0 [014]** Similarly, drug compounds are typically designed against specific targets but could affect cellular functions more broadly.

Similarly, ...
... drug compounds are typically designed ...
... against specific targets ...
... but could affect cellular functions more broadly.

**S0 [015]** Determining the extent and mechanism by which molecular perturbations affect interconnected biological processes requires an approach that quantifies effects on both the cellular network and on the molecular functions of the targeted protein (Fig. 1a).

Determining the extent ...

... and mechanism ...

... by which molecular perturbations affect interconnected biological processes requires an approach ...

... that quantifies effects ...

... on both the cellular network ...

... and on the molecular functions ...

... of the targeted protein ...

... (Fig. 1a).

**S0 [016]** To develop such an approach, we targeted a central molecular switch, a GTPase.

To develop ...

... such an approach, ...

... we targeted a central molecular switch, ...

... a GTPase.

**S0 [017]** GTPases belong to a class of common biological motifs, where a two-state switch is controlled by regulators with opposing functions (6, 7) (Fig. 1a).

GTPases belong ...

... to a class ...

... of common biological motifs, ...

... where a two-state switch is controlled ...

... by regulators ...

... with opposing functions ...

... (6, 7)...

... ...

... (Fig. 1a).

**S0 [018]** For GTPases, the two states of the switch are defined by the conformation of the GTPase in either the GTP-or GDP-bound forms, and the interconversion between the two states is catalyzed by guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs) (Fig. 1b).

For GTPases, ...

... the two states ...

... of the switch are defined ...

... by the conformation ...

... of the GTPase ...

... in either the GTP-or GDP-bound forms, ...

... and the interconversion ...

... between the two states is catalyzed ...

... by guanine nucleotide exchange factors ...

... (GEFs) ...

... and GTPase-activating proteins ...

... (GAPs) ...

... (Fig. 1b).

**S0 [019]** Other, similar biological switch motifs involve covalent modifications controlled by opposing kinase/phosphatase or acetylase/deacetylase regulators.

Other, ...

... similar biological switch motifs involve covalent modifications controlled ...

... by opposing kinase/phosphatase ...

**End of Sample Audit**

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