BIOGRAPHICAL SKETCH

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NAME	POSITION TITLE
Michael Springer	Associate Professor of Systems Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Stanford University, Stanford, California	BS	1992-1996	Biological Sciences
Stanford University, Stanford, California	BS	1992-1996	Chemistry
UCSF, San Francisco, California	PhD	1997-2003	Cell Biology with Erin O'Shea
Harvard Medical School, Boston, Massachusetts	Post Doctoral Fellow	2004-2009	Systems Biology with Marc Kirschner

A. Personal Statement

Research: Recent advances in technology have greatly improved the quality and quantity of genomic, transcriptomic, and proteomic data. While this has the promise to lead to personalized medicine, most of this data is not actionable. The fundamental problem limiting our ability to use this data is that we still do not understand how genotype is converted to phenotype. My lab focuses on understanding a facet of this large problem: how cells quantitatively process and appropriately respond to their environment, including how mutations and evolution alter response. We use yeast as a model system for signal integration, as this high throughput system provides a nearly unparalleled ability to attack this problem from many angles and interpret the results in the context of a well understood system.
Education: With the maturation of multiple high-throughput methods, biology is now awash in data. Unfortunately most graduate students are not trained in how to handle and analyze this data. In many cases this problem is either ignored, or students are sent to learn programming in the computer science department or statistics in a statistics department. This is often impractical as the courses cover many topics that are not needed in biology and are not motivated from biology making it harder for students to translate the skills. To meet this need I, with the help of Rick Born, developed a five full-day intensive bootcamp (I developed the material for 4 of the 5 days). This bootcamp has been highly successful; over the past several years, over 400 students have taken the course.

1. Escalante-Chong R, Savir Y, Carroll SM, Ingraham JB, Wang J, Marx CJ, Springer M. Galactose metabolic genes in yeast respond to a ratio of galactose and glucose. PNAS 2015; published ahead of print January 20, 2015, doi:10.1073/pnas.1418058112
2. Wang J, Atolia E, Hua B, Savir Y, Escalante-Chong R, Springer M. Natural Variation in Preparation for Nutrient Depletion Reveals a Cost-Benefit Tradeoff . PLoS Biol 13(1) 2015: e1002041. doi:10.1371/journal.pbio.1002041
3. Springer M, Weissman J, and Kirschner MW. (2010). A general lack of compensation for gene dosage in yeast. Molecular Systems Biology. 6:368. PMCID: PMC2890323.
4. Stefan M, Gutlerner J, Born R, Springer M. The Quantitative Methods Boot Camp: Teaching quantitative thinking and computing skills to graduate students in the life sciences. PLoS Computational Biology, 2015, in press.

B. Positions and Honors

1991–1992	Research Technician, IXSYS (now AME) San Diego, CA
1993–1996	Undergraduate Research with Dr. Richard Zare Dept of Chemistry, Stanford University
1996–1997	Research Technician, IXSYS (now AME)

	San Diego, CA
1997–2003	Graduate Research with Erin O'Shea and Andrew Murray Dept of Biochemistry and Biophysics, University of California, San Francisco, CA
2004-2009	Postdoctoral Fellowship with Marc Kirschner, Harvard Medical School, Boston, MA
2005–2009	Lecturer, Systems Biology Department, Harvard Medical School, Boston, MA
2009–2016	Assistant Professor Systems Biology Department, Harvard Medical School, Boston, MA
2016–Present	Associate Professor Systems Biology Department, Harvard Medical School, Boston, MA

Honors

1993	Center for Material Sciences Fellowship Stanford University, Stanford, California
1995	Bing Fellowship Stanford University, Stanford, California
1998-2001	National Science Foundation Graduate Fellowship University of California, San Francisco, San Francisco, CA
2002-2004	Burroughs Welcome Graduate Fellowship University of California, San Francisco, San Francisco, CA
2005	Burroughs Welcome Graduate Fellowship University of California, San Francisco, San Francisco, CA
2005	Derek Bok Center Certificate of Distinction in Teaching Harvard Medical School, Boston, MA
2005-2008	Helen Hay Whitney Fellowship Harvard Medical School, Boston, MA

C. Contribution to Science

1. My early research addressed how a signaling pathway can process environmental information to achieve an appropriate biological response. I used the response of yeast to phosphate starvation as a model system. At the time it was clear that a phosphate responsive kinase regulated a transcription factor by phosphorylation on four critical sites. Phosphorylation of these sites promoted nuclear export, blocked nuclear import, and interfered with binding to a transcriptional activator. Through a series of *in vitro* and *in vivo* studies, combined with modeling, I found that different concentrations of extracellular phosphate lead to multiple transcriptional responses even though there is only one regulated transcription factor. We demonstrated that this behavior is achieved based on the specific phosphorylation kinetics by the kinase on the transcription factor and leads to differential binding of the transcription factor to specific phosphate regulated promoters. This study has been echoed by many later studies in other systems that have found that multiple phosphorylations can lead to more complex regulation and that complex patterns of phosphorylation can be achieved by simple kinetic mechanisms.

a. Jeffery, DA*, Springer M*, King DS, O'Shea E. (2001). Multi-site phosphorylation of Pho4 by the cyclin-CDK Pho80-Pho85 is semi-processive with site preference. J. Mol Biol. 306(5):997-1010. PMID: 11237614.

b. Springer M*, Wykoff D*, Miller N, O'Shea E. (2003). Differential Phosphorylation of a Transcription Factor Generates Multiple Gene Expression Programs. PLoS Biology. 1(2): E28. PMCID: PMC261874.

c. Byrne M, Miller N, Springer M, O'Shea EK. (2004). A distal, high-affinity binding site on the cyclin-CDK substrate Pho4 is important for its phosphorylation and regulation. J Mol Biol. 335(1):57-70. PMID: 14659740.

2. Genetically encoded fluorescent proteins have revolutionized biology. Many of the initial studies focused on using GFP as a vital marker for protein localization. I realized that GFP could also be used to allow single-cell quantitation of protein levels, thereby vastly improving on a number of quantitative experiments that had previously relied on population level enzymatic readouts. As the repertoire of fluorescent proteins increased I was one of the first people to extend this to measuring environmental perturbations in a high-throughput, internally controlled manner and to conducting genetic screens. This has allowed me to ask a series of wide ranging question that have an impact on several fields: 1) aneuploidy: we determined that protein levels in

most cases are not directly sensed by the cells, 2) duplicated genes: we showed that under specific environmental stresses, some duplicate genes can compensate for their paralog, and 3) transcription: in collaboration with the Buratowski lab we identified a chromatin assembly complex that affects promoter directionality.

a. Springer M*, Wykoff D*, Miller N, O'Shea E. (2003). Differential Phosphorylation of a Transcription Factor Generates Multiple Gene Expression Programs. PLoS Biology. 1(2): E28. PMCID: PMC261874.
b. Springer M, Weissman J, and Kirschner MW. (2010). A general lack of compensation for gene dosage in yeast. Molecular Systems Biology. 6:368. PMCID: PMC2890323.
c. DeLuna A*, Springer M*, Kirschner MW, Kishony R. (2010). Need-based upregulation of protein levels in response to deletion of their duplicate genes. PLoS Biol. 8(3); e1000347. PMCID: PMC2846854.
d. Marquardt S, Escalante-Chong R, Pho N, Wang J, Churchman S, Springer M, and Buratowski S. (2014). A chromatin-based mechanism for limiting divergent non-coding transcription. Cell. 157(7); 1712-1723. PMCID:PMC4090027

3. Signal transduction cascades are typically thought to begin with sensors. These sensors bind to ligands and initiate signaling pathway, which have the potential to process this signal in a number of ways, ending with transcriptional or post-transcriptional changes in the cell. In contrast to this model, we found that transporters themselves can serve as signal integrating/processing molecules even if their mechanism of uptake is passive diffusion. Specifically, competitive transport of ligand leads the internal concentration of ligand to depend on the ratio of inputs. Our work suggests that a critical portion of information processing in a major metabolic decision is made upstream of the canonical signaling network and highlights the dual role transporters can play in both nutrient uptake and signal integration. Additionally, our work shows that this 'ratio sensing' may be widespread in biology. Many common biological processes such as futile cycle and certain transcription factor binding architectures can respond to the ratio of inputs.

a. Escalante-Chong R, Savir Y, Carroll SM, Ingraham JB, Wang J, Marx CJ, Springer M. Galactose metabolic genes in yeast respond to a ratio of galactose and glucose. PNAS 2015; published ahead of print January 20, 2015, doi:10.1073/pnas.1418058112

4. Mass spectrometry is currently the only tool that has the potential to quantitatively determine post-translational modifications (PTMs) on a proteome scale. While numerous PTMs have been identified, mass spectrometry is still hampered by the fact that techniques for identifying modified peptides require enrichment and techniques for quantitating PTMs require synthesis of expensive labeled peptides. To this end, in collaboration with the Steen Lab, we have developed a series of related methods for quantitating modified peptides. Specifically, 1) we developed a technique whereby full-length heavy labeled protein standards can be used to identify sites and levels of peptide modification, 2) we showed that demodifying enzymes can be used to quantitate a post-translational modification of interest without the need for a labeled standard, and 3) we have catalogued and developed an abundance based method for predicting the detectable level of all peptides from mass spectrometry, thereby highlighting the limits of current mass spectrometry methodologies.

a. Steen H, Jebanathirajah JA, Springer M, Kirschner MW. (2005). Stable isotope-free relative and absolute quantitation of protein phosphorylation stoichiometry by MS. Proc Natl Acad Sci U S A. 102(11):3948-53. PMCID: PMC552780.
b. Singh S*, Springer M*, Steen J, Kirschner MW, Steen H. (2009). FLEXIQuant: a novel tool for the absolute quantification of proteins, and the simultaneous identification and quantification of potentially modified peptides. J Proteome Res. 8(5):2201-10. PMCID: PMC2868505.
c. Muntel J, Boswell, SA, Tang S, Ahmed S, Wapinski I, Foley G, Steen H, Springer M. Abundance-based classifier for the prediction of mass spectrometric peptide detectability upon enrichment. Molecular & Cellular Proteomics (2014). 10.1074/mcp.M114.044321 PMID: 25473088.