Multiple Gene Regulatory Strategies Enable Decoding of Transcription Factor Dynamics

YIJIA CHEN[1,3], Xiaolu Guo[2,3], and Alexander Hoffmann[2,3]

[1] Bruins-in-Genomics Summer Undergraduate Research Program, [2] Institute for Quantitative and Computational Biosciences, and [3] Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, USA

Introduction

- **Dynamic Regulation of Prominent Stimulus Response Transcription Factors (TFs)**
  - The dynamics of TFs contribute to the elicitation of diverse end responses, highlighting the versatility of cellular responses (Givré et al., 2023, Scientific Reports).
  - TFs like NFκB, p53, and ISGF3 display intricate regulation through feedback and feedforward loops (Sen et al., 2020, Cell Systems).
- **Significance of "Signaling Codons" in TF Dynamics**
  - 6 identified "signaling codons" as key elements capturing stimulus-specific information within TF dynamics (Adelaja et al., 2021, Immunity)
  - Can unravel the intricate interplay between external stimuli and gene expression.
  - Can shed light on how cells interpret and respond to diverse environmental cues.
- **Open Question**
  - Understanding the precise gene regulatory strategies required to differentiate distinct signaling codon deployments remains an open question.

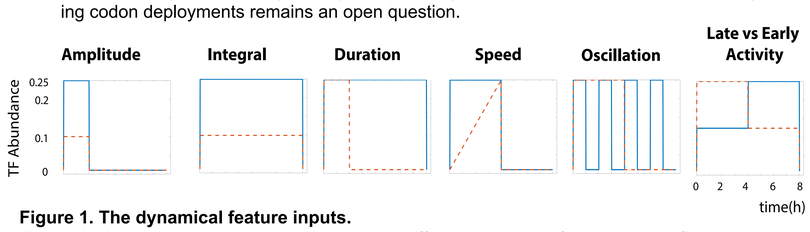
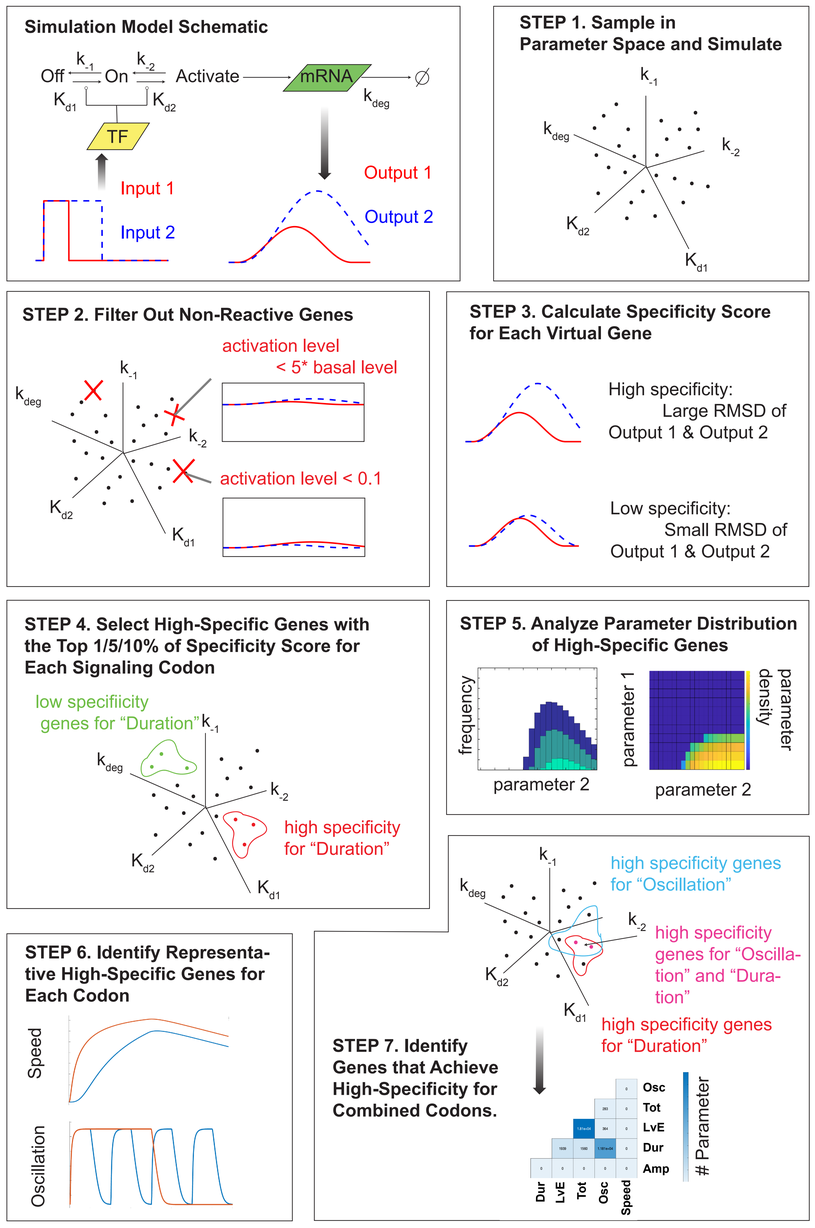


Figure 1. The dynamical feature inputs.
For each signaling codons, 2 inputs that convey different dynamical features are defined.

Methods



Results

1D parameter distributions locate the high specificity genes.

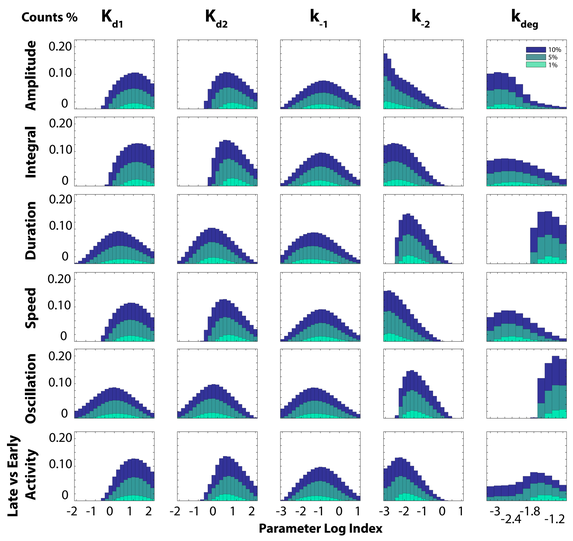


Figure 2. 1D parameter distributions distinguish each dynamical feature.

Rows correspond to each signaling codon, and columns correspond to each of the 5 parameters.

X-axis is the log_{10} index of parameter value, and Y-axis is the counts percentage of high specificity genes.

High specificity genes are defined by genes with the top 1%, 5%, and 10% of RMSD values.

2D parameter plots reveal correlations within the 5D space.

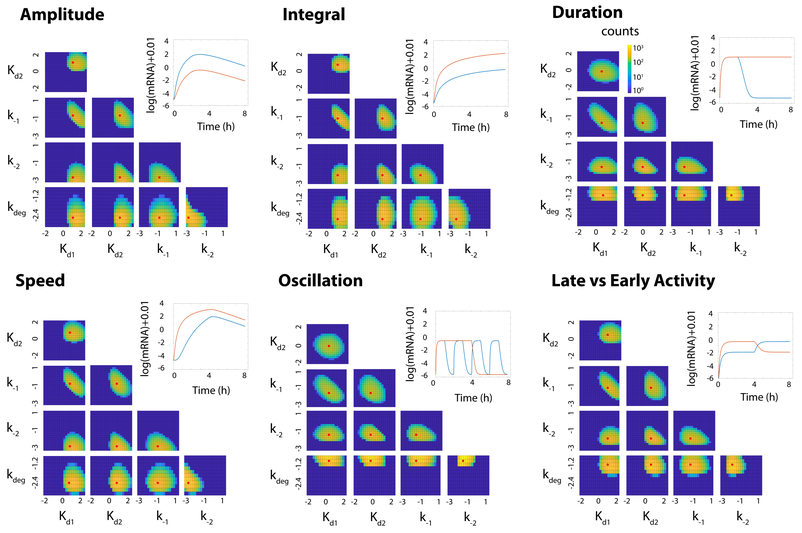


Figure 3. Heatmap of 2D parameter distribution for high specificity genes
Axis label specifies the log_{10} index of the corresponding parameter. The color represents the frequencies of virtual genes. The lighter the color is, the more virtual genes are distributed in the grid. The mRNA trajectories of representative high specificity gene are displayed and the corresponding parameter values are marked by the red dots in the heatmap.

The Pearson linear correlation coefficient between the log_{10} index of K_{d1} and k_{-1} for all codons are in the range of 0.6 - 0.7, indicating the linear relationship between them in log scale.

The combined TF dynamic features are associated with overlapping parameter sets.

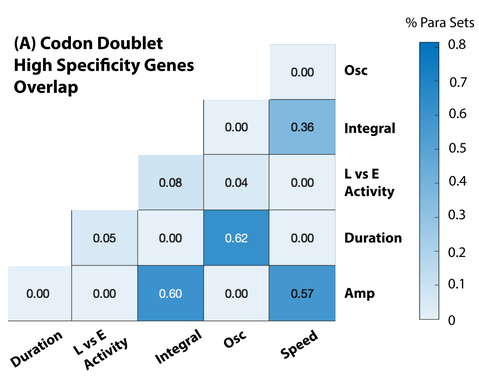
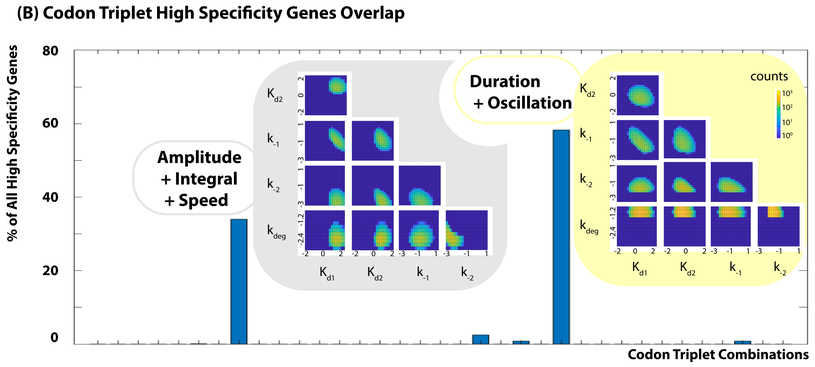


Figure 4. (A) Codon doublets high specificity genes overlap. (B) Codon triplets high specificity genes overlap.

Each grid in the heatmap corresponds to one doublet of codons. The number represents the ratio of overlapping high specificity genes to the total number of high specificity genes.

"Speed", "Amplitude", and "Integral" codons, as well as "Duration" and "Oscillation" codons have their high specificity genes overlapped, indicating that they share similar gene regulatory strategies.



Deployment of activation "Speed", "Amplitude", and "Integral" shared similar regulatory strategies including long mRNA half-life, slow rate to deactivate the poised state, and high TF-responsivity to open or activate the gene promoter. "Duration", and "Oscillatory" are also decoded by similar gene regulatory strategies characterized by short mRNA half-life.

Parameters sets for virtual genes are identified that can provide optimal distinction for the deployment of each codon.

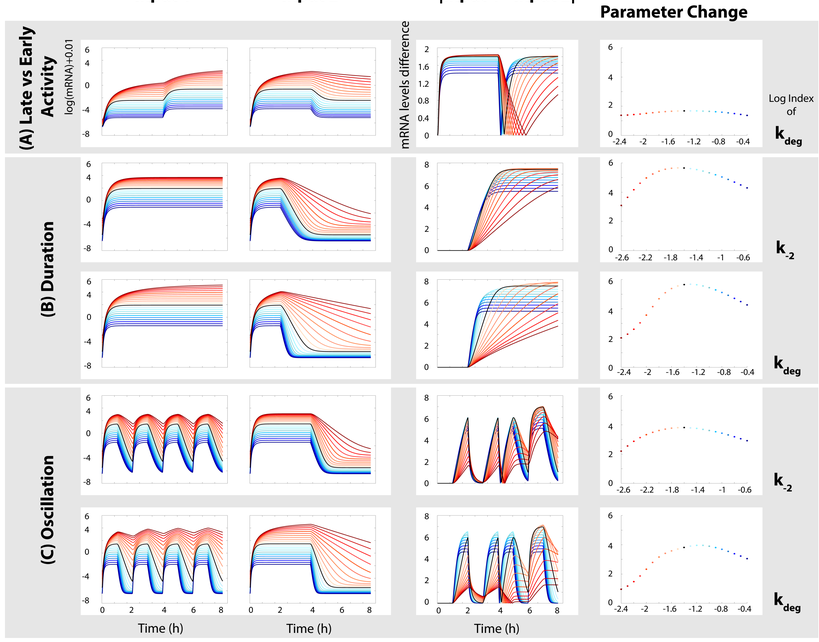


Figure 5. Representative parameter sensitivity test result examples.

Curves and dots of the same color correspond to a single parameter set. Black lines and dots depict representative mRNA trajectories for each codon. By keeping 4 parameters fixed and adjusting 1 parameter (noted on the right) in increments of $\pm 10^{0.1}$ up to 10^{1}, we simulate 20 mRNA trajectories for sensitivity testing.

The initial 2 columns show mRNA trajectories for Input 1 and Input 2. The 3rd column displays the absolute difference between these trajectories. The 4th column presents RMSD values along the change of parameter values.

(A) Non-sensitive Example: Sensitivity test for mRNA half-life (k_{deg}) for "Late vs Early Activity" codon. The change of RMSD values are minimal compared the sensitive cases, indicating that the deployment of this codon is not sensitive to the change of mRNA half-life.

(B)(C) Sensitive Examples: Sensitivity test for rate to deactivate the poised state (k_{-2}) and mRNA half-life (k_{deg}) for "Duration" and "Oscillation" codons. The change of RMSD values are noticeable for all 20 tests, indicating that the deployment of these two codons are sensitive to the chromatin deactivating rate and mRNA half-life.

As the mRNA half-life increases or the chromating deactivating rate decreases (darker red), the mRNA production loses the ability to promptly respond to the change in TF dynamics. If the parameter changes in the opposite direction (darker blue), the mRNA production level becomes smaller. Both cases lead to lower specificity.

Acknowledgement

Special thanks to all members in the Signaling Systems Lab, Dr. Xiaolu Guo, Dr. Alexander Hoffmann. Thanks to Bruins-in-Genomics Summer Undergraduate Research Program for funding the project.