Integrated design of RNA-based regulatory systems for cellular control and information processing.

RNA implementation of strand displacement cascades in bacteria.

Engineer unnatural, computational strand displacement architectures using stranded displacement in bacteria.

Engineer computational RNA strand displacement devices to autonomously process the transcription.

Engineer RNA neural networks that dynamically synopmize cell state.

DNA synthesis in vivo.

Whole-tissue or whole-cell, nucleotide-resolution simulations encompassing several layers of modeling (predictive, regulatory, metabolic, and systems biology).

Computational design of protein-RNA and RNA-RNA interfaces suitable for engineering protein-based or RNA-based sensors.

Design of protein-ligand and RNA-ligand binding sites and/or aptamers for orthogonal and high-performing, durable and high-mutation-rate RNA-based sensors.

Expand RNA modification apparatus and technology that can modify non-natural RNA

protein-ligand and RNA-ligand interactions, and protein and RNA-based sensors.

400 base pairs.

in vivo.

in A-T-G-C base pairs.

100's-fold change in gene expression.

10-fold change in gene expression.

50% success rate.

500-amino acid proteins.

300-amino acid proteins.

and carbohydrates.

in vivo.

mammalian cell state.

Simultaneous, tunable, timed expression of many transcription factors controlling mammalian cell state.

Durable and high-mutation-rate DNA-RNA-protein condensates that can engage and manipulate the chromatin state of living systems.

Routine prediction of structures for 3,000-amino acid proteins, including those conferred by: A) single-cell sequence control, or B) genes conferring drug resistance.

Modeling and design of dynamic: DNA-RNA-protein condensates that can expand beyond the functionality of natural complexes. Design of chromatin states that can be manipulated to change function.

Routine prediction of protein structures.

Biological design of large, complex genetic systems (genomes) with targeted expression levels and with at least four distinct unnatural amino acid building blocks.

Ability to select for any function, including those conferred by: A) small molecules, toxins, or carbohydrates, and; B) proteins or nucleic acids.

Durable and high-mutation-rate in vivo continuous DNA-malfunctions and evolution systems in model organisms.

Direct sequencing of proteins and carbohydrates.

De novo RNA synthesis in vivo with single-stranded RNA leading strand control.

Full control over statistical properties of RNA diversification in vivo.

De novo design and/or prediction of macromolecular dynamics and dynamic macromolecular structures.

Design of dynamic regulatory circuits and pathways.

Routine design of large proteins, beta topologies, membrane proteins, and loops.

Modeling and design of dynamic: RNA-RNA nanomachines that can engage and manipulate the chromatin state of living systems.

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BIOMOLECULE, PATHWAY, AND CIRCUIT ENGINEERING

Goal

Breakthrough Capability

Milestone

On-demand design, generation, and evolution of macromolecules for desired functions.

De novo prediction of RNA structure, protein structure, and complexes of DNA/RNA and proteins from primary sequence and the ability to make predictions of macutability and effect of mutations from structure.

Routine prediction of structures for 500-amino acid proteins and 200-nucleotide-RNA domains that fold correctly 50% of the time and RNA-protein complexes that form correctly 20% of the time.

Design proteins that fold correctly 50% of the time and RNA-protein complexes that form correctly 20% of the time.

Routine design of protein-RNA interactions, and protein and RNA-protein complexes.

De novo design and/or prediction of macromolecular dynamics and dynamic macromolecular structures.

Design of chromatin regulatory circuits and pathways.

Modeling and design of dynamic: RNA-RNA nanomachines that can engage and manipulate the chromatin state of living systems. Modeling and design of dynamic: RNA-RNA nanomachines that can engage and manipulate the chromatin state of living systems. Modeling and design of dynamic: RNA-RNA nanomachines that can engage and manipulate the chromatin state of living systems.

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