

PATENT APPLICATION

CLOSED-LOOP ISOTHERMAL-RESONANT CONTROL ALGORITHMS FOR PROTEIN FOLDING MODULATION

PROVISIONAL PATENT APPLICATION

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Control algorithms for maintaining isothermal conditions while maximizing resonant protein folding modulation, including multi-input multi-output (MIMO) feedback control, multi-objective optimization, adaptive gain scheduling, model predictive control, and real-time constraint satisfaction.

CONFIDENTIAL — PATENT PENDING

Contents

ABSTRACT OF THE DISCLOSURE	3
1 BACKGROUND OF THE INVENTION	4
1.1 Field of the Invention	4
1.2 Description of Related Art	4
1.2.1 Open-Loop Operation Limitations	4
1.2.2 Limitations of Separate Temperature and Irradiation Control	4
1.2.3 Prior Art in Laboratory Temperature Control	5
1.2.4 The Need for Integrated Control	5
1.3 Objects of the Invention	5
2 SUMMARY OF THE INVENTION	7
2.1 General Statement of the Invention	7
2.2 Control System Architecture	7
2.3 Multi-Objective Cost Function	8
2.4 Operating Modes	8
3 BRIEF DESCRIPTION OF DRAWINGS	9
4 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS	10
4.1 Algorithm 1: MIMO Feedback Control	10
4.1.1 State-Space Formulation	10
4.1.2 Controller Design	10
4.1.3 Gain Matrix Design	10
4.2 Algorithm 2: Multi-Objective Optimization	11
4.2.1 Pareto Optimization	11
4.2.2 Weighted Sum Approach	11
4.2.3 Epsilon-Constraint Method	12

4.3	Algorithm 3: Adaptive Gain Scheduling	12
4.3.1	Motivation	12
4.3.2	Scheduling Variables	13
4.3.3	Interpolation	13
4.4	Algorithm 4: Model Predictive Control (MPC)	13
4.4.1	MPC Formulation	13
4.4.2	Thermal-Optical Model	14
4.4.3	Real-Time Implementation	14
4.5	Algorithm 5: Constraint Satisfaction	15
4.5.1	Constraint Types	15
4.5.2	Hard vs. Soft Constraints	15
4.5.3	Safety Interlocks	15
4.6	Algorithm 6: Resonance Tracking	16
4.6.1	Motivation	16
4.6.2	Extremum Seeking Control	16
4.6.3	Resonance Tracking Loop	17
4.7	Algorithm 7: Isotope-Mode Automatic Reconfiguration	17
4.7.1	Mode Detection	17
4.7.2	Reconfiguration Actions	17
4.8	Implementation Considerations	18
4.8.1	Computation Platforms	18
4.8.2	Recommended Architecture	18
4.8.3	Communication	18
4.9	Performance Specifications	18
5	CLAIMS	19
5.1	MIMO Feedback Control Claims	19
5.2	Multi-Objective Optimization Claims	19

5.3	Adaptive Control Claims	20
5.4	Model Predictive Control Claims	20
5.5	Constraint Satisfaction Claims	21
5.6	Resonance Tracking Claims	21
5.7	Isotope Mode Claims	22
5.8	System Claims	22
ABSTRACT		24
INVENTOR DECLARATION		25

ABSTRACT OF THE DISCLOSURE

Control algorithms for closed-loop operation of protein folding modulation apparatus, enabling simultaneous isothermal maintenance and resonant modulation maximization. The algorithms comprise: (a) multi-input multi-output (MIMO) feedback control using temperature and folding signal readouts to adjust microwave power, frequency, and cooling power; (b) multi-objective optimization that minimizes temperature deviation ΔT while maximizing folding modulation M , with configurable weighting; (c) adaptive gain scheduling that adjusts control parameters based on operating conditions; (d) model predictive control (MPC) using a thermal-optical model to anticipate system response; (e) constraint satisfaction algorithms ensuring temperature bounds, power limits, and safety interlocks; (f) resonance-tracking algorithms that maintain optimal frequency despite system drift; and (g) isotope-mode switching that automatically reconfigures control parameters for D₂O operation. The algorithms enable unambiguous discrimination between resonant and thermal effects by maintaining strict temperature control ($|\Delta T| < 0.1^\circ\text{C}$) while achieving significant folding modulation ($M > 30\%$). Implementation may be on embedded controllers, FPGAs, or host computers. Applications include automated protein folding modulation for research, manufacturing, and therapeutic use.

Keywords: closed-loop control, isothermal, resonant modulation, MIMO, multi-objective optimization, model predictive control, adaptive control, feedback, protein folding

1 BACKGROUND OF THE INVENTION

1.1 Field of the Invention

The present invention relates generally to control systems for scientific instrumentation, and more specifically to closed-loop control algorithms that simultaneously maintain isothermal conditions and maximize resonant modulation of protein folding.

1.2 Description of Related Art

1.2.1 Open-Loop Operation Limitations

Prior protein folding modulation systems operate in open-loop mode:

- (a) **Fixed power operation:** Microwave power is set manually without feedback. Temperature drifts during operation.
- (b) **Manual frequency selection:** Frequency is set once without real-time optimization. Resonance may drift due to temperature or sample changes.
- (c) **Separate temperature control:** Temperature is controlled independently of irradiation, leading to oscillations and overshoot.
- (d) **No folding feedback:** The folding signal is measured for data collection but not used to optimize irradiation parameters.

1.2.2 Limitations of Separate Temperature and Irradiation Control

When temperature control and irradiation are operated independently:

- (1) **Control loop interference:** Microwave heating is treated as a disturbance by the temperature controller, leading to oscillatory behavior.
- (2) **Slow response:** Temperature controllers designed for steady-state operation cannot track rapid heating from pulsed irradiation.
- (3) **No optimization:** There is no mechanism to trade off temperature stability against modulation effectiveness.

- (4) **Thermal-resonant ambiguity:** Without tight temperature control, observed effects may be thermal rather than resonant.

1.2.3 Prior Art in Laboratory Temperature Control

Standard laboratory temperature controllers:

Controller Type	Typical Accuracy	Limitations
On-off (bang-bang)	$\pm 2\text{--}5^\circ\text{C}$	Large oscillations
PID	$\pm 0.1\text{--}1^\circ\text{C}$	Slow response to disturbances
Cascade PID	$\pm 0.05\text{--}0.5^\circ\text{C}$	Complex tuning
Water bath	$\pm 0.01\text{--}0.1^\circ\text{C}$	Slow thermal mass

Table 1: Standard laboratory temperature controllers

None of these controllers are designed for the specific challenge of maintaining isothermal conditions during resonant microwave irradiation.

1.2.4 The Need for Integrated Control

What is needed is an integrated control system that:

- (1) Treats microwave irradiation and temperature control as a **unified** system;
- (2) Uses **multiple feedback signals** (temperature, folding, power);
- (3) Implements **multi-objective optimization** balancing thermal stability and modulation;
- (4) Provides **model-based prediction** to anticipate heating effects;
- (5) Ensures **constraint satisfaction** for safety and isothermal compliance.

1.3 Objects of the Invention

It is an object of the present invention to provide control algorithms that:

- (1) Maintain isothermal conditions ($|\Delta T| < 0.1^\circ\text{C}$) during microwave irradiation;
- (2) Maximize folding modulation subject to isothermal constraints;

- (3) Adapt to varying operating conditions and sample properties;
- (4) Predict and compensate for heating effects before they occur;
- (5) Ensure safe operation through constraint satisfaction;
- (6) Support both H₂O and D₂O operation with automatic reconfiguration.

2 SUMMARY OF THE INVENTION

2.1 General Statement of the Invention

The present invention provides a family of closed-loop control algorithms for protein folding modulation apparatus, comprising:

- (a) MIMO feedback control architecture;
- (b) Multi-objective cost function optimization;
- (c) Adaptive gain scheduling;
- (d) Model predictive control (MPC);
- (e) Constraint satisfaction and safety algorithms;
- (f) Resonance tracking;
- (g) Isotope-mode automatic reconfiguration.

2.2 Control System Architecture

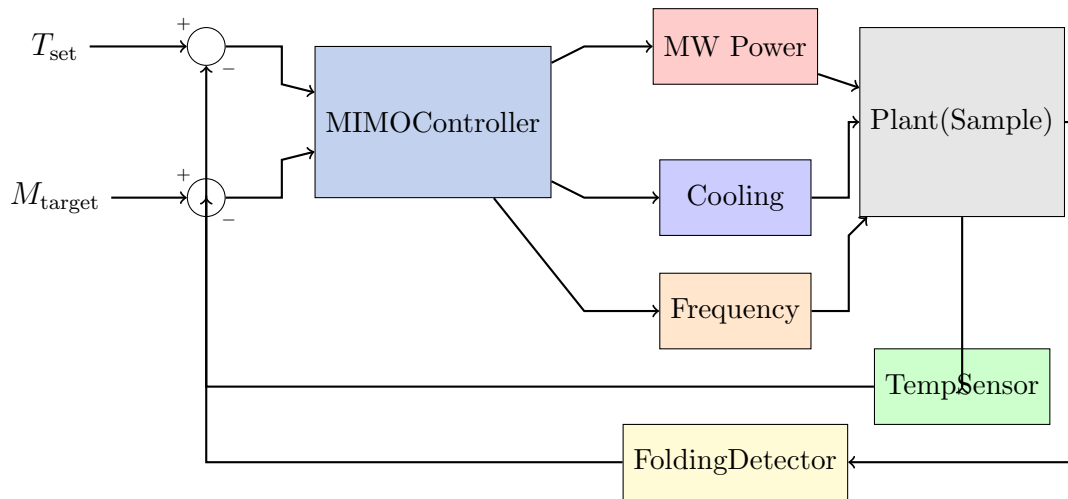


Figure 1: MIMO control system architecture

2.3 Multi-Objective Cost Function

The controller minimizes a cost function that balances isothermal maintenance and modulation maximization:

$$J = w_T \cdot (\Delta T)^2 + w_M \cdot (M_{\text{target}} - M)^2 + w_P \cdot P^2 + w_{\dot{P}} \cdot (\dot{P})^2 \quad (1)$$

where:

- $\Delta T = T - T_{\text{set}}$ is the temperature deviation
- M is the measured folding modulation
- P is the microwave power
- \dot{P} is the rate of power change (for smoothness)
- $w_T, w_M, w_P, w_{\dot{P}}$ are configurable weights

2.4 Operating Modes

Mode	Priority	Weights	Use Case
Isothermal-first	ΔT minimization	$w_T \gg w_M$	Mechanism verification
Modulation-first	M maximization	$w_M \gg w_T$	Maximum effect
Balanced	Equal priority	$w_T \approx w_M$	Normal operation
Power-limited	Minimize power	w_P large	Low-power applications

Table 2: Control operating modes

3 BRIEF DESCRIPTION OF DRAWINGS

Figure 1: MIMO Control System Architecture

A block diagram showing the multi-input multi-output control architecture with temperature and folding feedback.

Figure 2: Multi-Objective Optimization Surface

A 3D surface showing the trade-off between temperature deviation and folding modulation.

Figure 3: Adaptive Gain Scheduling

A diagram showing how control gains adapt based on operating conditions.

Figure 4: Model Predictive Control Horizon

A time-series diagram showing the MPC prediction and control horizons.

Figure 5: Constraint Satisfaction Regions

A diagram showing feasible operating regions defined by temperature and power constraints.

Figure 6: Resonance Tracking Algorithm

A flowchart showing the frequency optimization loop.

Figure 7: Isotope Mode Switching

A state diagram showing automatic reconfiguration for H₂O/D₂O operation.

4 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

4.1 Algorithm 1: MIMO Feedback Control

4.1.1 State-Space Formulation

The system is modeled in state-space form:

$$\dot{\mathbf{x}} = \mathbf{Ax} + \mathbf{Bu} \quad (2)$$

$$\mathbf{y} = \mathbf{Cx} + \mathbf{Du} \quad (3)$$

where:

- State vector: $\mathbf{x} = [T, \dot{T}, M, \dot{M}]^T$
- Input vector: $\mathbf{u} = [P_{\text{MW}}, P_{\text{cool}}, f]^T$
- Output vector: $\mathbf{y} = [T, M]^T$

4.1.2 Controller Design

The MIMO controller uses a state-feedback formulation:

$$\mathbf{u} = -\mathbf{K}(\mathbf{x} - \mathbf{x}_{\text{ref}}) + \mathbf{u}_{\text{ff}} \quad (4)$$

where:

- \mathbf{K} is the feedback gain matrix (designed by LQR or pole placement)
- \mathbf{x}_{ref} is the reference state
- \mathbf{u}_{ff} is a feedforward term based on known disturbances

4.1.3 Gain Matrix Design

The gain matrix \mathbf{K} is designed using Linear Quadratic Regulator (LQR) theory:

$$\mathbf{K} = \mathbf{R}^{-1}\mathbf{B}^T\mathbf{P} \quad (5)$$

where \mathbf{P} is the solution to the algebraic Riccati equation:

$$\mathbf{A}^T\mathbf{P} + \mathbf{P}\mathbf{A} - \mathbf{P}\mathbf{B}\mathbf{R}^{-1}\mathbf{B}^T\mathbf{P} + \mathbf{Q} = 0 \quad (6)$$

The weighting matrices \mathbf{Q} and \mathbf{R} are configured based on the desired operating mode:

Mode	\mathbf{Q} (state weights)	\mathbf{R} (input weights)
Isothermal-first	diag(1000, 1, 1, 0.1)	diag(0.1, 0.1, 1)
Modulation-first	diag(1, 0.1, 1000, 1)	diag(0.1, 0.1, 1)
Balanced	diag(100, 1, 100, 1)	diag(1, 1, 1)

Table 3: LQR weight matrices for different operating modes

4.2 Algorithm 2: Multi-Objective Optimization

4.2.1 Pareto Optimization

The multi-objective optimization problem is:

$$\min_{\mathbf{u}} J_T(\mathbf{u}) = \int_0^T (\Delta T(t))^2 dt \quad (7)$$

$$\min_{\mathbf{u}} J_M(\mathbf{u}) = \int_0^T (M_{\text{target}} - M(t))^2 dt \quad (8)$$

subject to constraints (see Section 4.5).

4.2.2 Weighted Sum Approach

The simplest approach combines objectives with weights:

$$J = \lambda J_T + (1 - \lambda) J_M, \quad \lambda \in [0, 1] \quad (9)$$

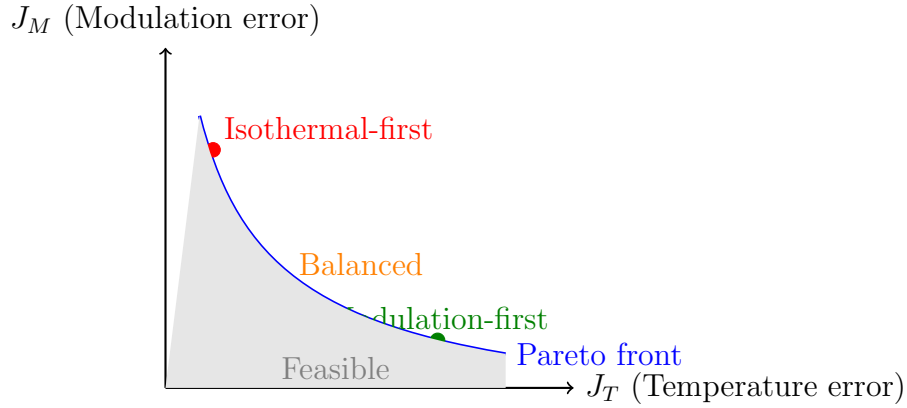


Figure 2: Pareto front showing trade-off between temperature control and modulation

4.2.3 Epsilon-Constraint Method

An alternative formulation constrains one objective:

$$\min_{\mathbf{u}} J_M(\mathbf{u}) \quad (10)$$

$$\text{s.t. } J_T(\mathbf{u}) \leq \epsilon_T \quad (11)$$

This ensures isothermal compliance ($J_T \leq \epsilon_T$) while maximizing modulation.

4.3 Algorithm 3: Adaptive Gain Scheduling

4.3.1 Motivation

System dynamics vary with operating conditions:

- Sample volume affects thermal mass
- Temperature affects dielectric properties
- Protein concentration affects folding signal
- Solvent (H₂O vs. D₂O) affects heating rate

Fixed gains cannot optimally handle this variation.

4.3.2 Scheduling Variables

Gains are scheduled based on:

Variable	Symbol	Effect on Gains
Temperature	T	Higher $T \rightarrow$ higher cooling gain
Power level	P	Higher $P \rightarrow$ higher temperature feedback gain
Solvent	$\text{H}_2\text{O}/\text{D}_2\text{O}$	$\text{D}_2\text{O} \rightarrow$ modified thermal gains
Sample volume	V	Larger $V \rightarrow$ slower gains (thermal inertia)

Table 4: Gain scheduling variables

4.3.3 Interpolation

Gains are interpolated between pre-computed values:

$$\mathbf{K}(\sigma) = \sum_{i=1}^N \alpha_i(\sigma) \mathbf{K}_i \quad (12)$$

where σ is the scheduling variable vector and α_i are interpolation weights (e.g., from lookup table or polynomial).

4.4 Algorithm 4: Model Predictive Control (MPC)

4.4.1 MPC Formulation

MPC solves an optimization problem at each time step:

$$\min_{\mathbf{u}_{0:N-1}} \sum_{k=0}^{N-1} [\|\mathbf{x}_k - \mathbf{x}_{\text{ref}}\|_{\mathbf{Q}}^2 + \|\mathbf{u}_k\|_{\mathbf{R}}^2] + \|\mathbf{x}_N - \mathbf{x}_{\text{ref}}\|_{\mathbf{P}}^2 \quad (13)$$

$$\text{s.t. } \mathbf{x}_{k+1} = \mathbf{A}_d \mathbf{x}_k + \mathbf{B}_d \mathbf{u}_k \quad (14)$$

$$\mathbf{x}_k \in \mathcal{X}, \quad \mathbf{u}_k \in \mathcal{U} \quad (15)$$

where N is the prediction horizon and \mathcal{X}, \mathcal{U} are constraint sets.

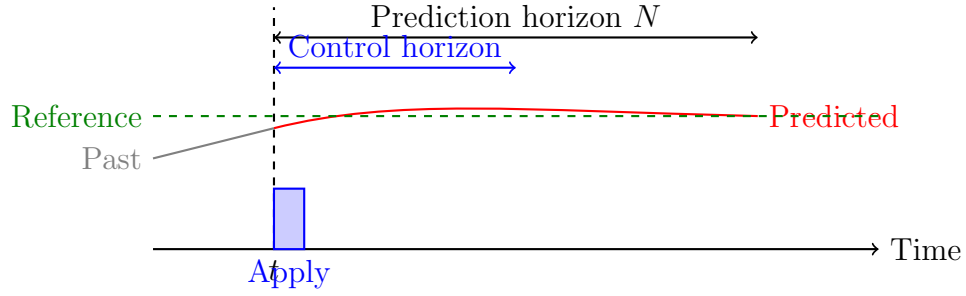


Figure 3: Model Predictive Control: prediction horizon and receding horizon implementation

4.4.2 Thermal-Optical Model

The MPC uses a simplified thermal-optical model:

$$C_s \frac{dT}{dt} = \alpha P_{\text{MW}} - k_{\text{cool}}(T - T_{\text{amb}}) - P_{\text{cool}} \quad (16)$$

$$\frac{dM}{dt} = \beta(f - f_{\text{res}})^{-2} \cdot P_{\text{MW}} - \gamma M \quad (17)$$

where:

- C_s = sample heat capacity
- α = microwave absorption coefficient
- k_{cool} = passive cooling rate
- β = resonant coupling strength
- f_{res} = resonance frequency
- γ = modulation decay rate

4.4.3 Real-Time Implementation

For real-time operation, the MPC optimization is solved using:

- (1) Quadratic programming (QP) solvers (e.g., OSQP, qpOASES)
- (2) Explicit MPC (pre-computed piecewise affine control law)

- (3) Neural network approximation of optimal policy

Typical solution time: < 1 ms for prediction horizon $N = 20$.

4.5 Algorithm 5: Constraint Satisfaction

4.5.1 Constraint Types

Constraint	Expression	Limit
Temperature deviation	$ T - T_{\text{set}} $	$< 0.5^\circ\text{C}$ (hard), $< 0.1^\circ\text{C}$ (soft)
Microwave power	P_{MW}	$0 \leq P \leq P_{\text{max}}$
Cooling power	P_{cool}	$0 \leq P \leq P_{\text{cool,max}}$
Frequency range	f	$f_{\text{min}} \leq f \leq f_{\text{max}}$
Power rate of change	$ \dot{P} $	$< \dot{P}_{\text{max}}$
Temperature rate	$ \dot{T} $	$< 1^\circ\text{C/s}$

Table 5: System constraints

4.5.2 Hard vs. Soft Constraints

- (a) **Hard constraints:** Must never be violated. Implemented as inequality constraints in optimization.
- (b) **Soft constraints:** Violation incurs penalty but is allowed. Implemented as slack variables:

$$|T - T_{\text{set}}| \leq \epsilon_T + s_T, \quad s_T \geq 0 \quad (18)$$

with penalty $w_s s_T^2$ added to cost function.

4.5.3 Safety Interlocks

Independent of the optimization, hardware interlocks enforce:

- (1) Emergency shutdown if $T > T_{\text{max}}$
- (2) Power cutoff if cooling fails
- (3) Frequency limits enforced in hardware

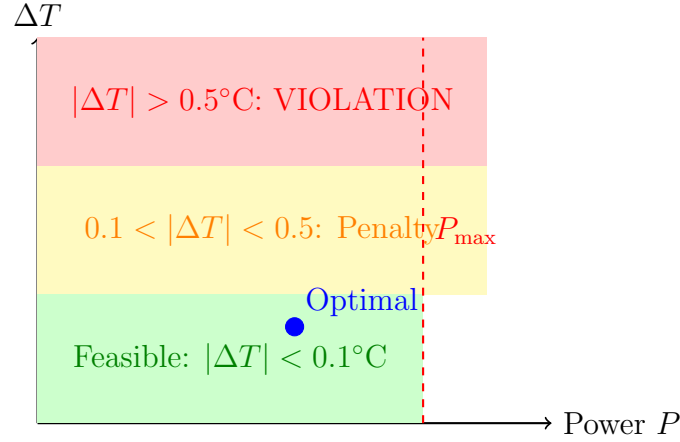


Figure 4: Constraint satisfaction regions in power–temperature space

4.6 Algorithm 6: Resonance Tracking

4.6.1 Motivation

The resonance frequency may drift due to:

- Temperature changes affecting dielectric properties
- Sample composition changes during folding
- Equipment drift

4.6.2 Extremum Seeking Control

A sinusoidal perturbation is added to the frequency:

$$f(t) = f_0 + a \sin(\omega_p t) \quad (19)$$

The folding signal is demodulated at ω_p to estimate the gradient:

$$\frac{\partial M}{\partial f} \approx \frac{2}{a} \langle M(t) \sin(\omega_p t) \rangle \quad (20)$$

The center frequency is updated:

$$\dot{f}_0 = \gamma_f \frac{\partial M}{\partial f} \quad (21)$$

4.6.3 Resonance Tracking Loop

- (1) Apply frequency perturbation (amplitude $a \sim 0.01$ GHz, frequency $\omega_p \sim 10$ Hz)
- (2) Measure folding signal $M(t)$
- (3) Demodulate to extract gradient
- (4) Update center frequency to move toward resonance peak
- (5) Repeat continuously during operation

4.7 Algorithm 7: Isotope-Mode Automatic Reconfiguration

4.7.1 Mode Detection

The controller automatically detects solvent:

- (a) **Manual selection:** Operator specifies H₂O or D₂O
- (b) **Dielectric sensing:** Measure dielectric constant at reference frequency
- (c) **Resonance scan:** Identify resonance frequency (14.65 vs. 10.4 GHz)

4.7.2 Reconfiguration Actions

When switching from H₂O to D₂O mode:

Parameter	H ₂ O Mode	D ₂ O Mode
Operating frequency	14.65 GHz	10.4 GHz
Frequency sweep range	12–17 GHz	8–13 GHz
Thermal model α	$\alpha_{\text{H}_2\text{O}}$	$\alpha_{\text{D}_2\text{O}} \approx 0.9\alpha_{\text{H}_2\text{O}}$
Cooling gain	K_{cool}	$K_{\text{cool}} \times 1.1$

Table 6: Parameter reconfiguration for isotope mode

Platform	Advantages	Disadvantages
Embedded MCU	Low cost, low power	Limited computation
FPGA	Fast, deterministic	Complex development
Host PC	Flexible, powerful	Latency, reliability
DSP	Real-time optimized	Moderate cost

Table 7: Implementation platforms

4.8 Implementation Considerations

4.8.1 Computation Platforms

4.8.2 Recommended Architecture

- (1) **Inner loop (1 kHz):** PID temperature control on embedded MCU
- (2) **Outer loop (100 Hz):** MIMO/MPC on DSP or host PC
- (3) **Supervisory (10 Hz):** Mode selection, gain scheduling on host PC

4.8.3 Communication

- Inner loop to outer loop: Low-latency link (SPI, LVDS)
- Outer loop to supervisory: Ethernet or USB
- All loops: Shared memory or message passing

4.9 Performance Specifications

Metric	Specification	Notes
Temperature tracking	$ \Delta T < 0.1^\circ\text{C}$ RMS	Isothermal compliance
Modulation achieved	$M > 30\%$	At resonance
Control bandwidth	> 100 Hz	For pulsed operation
Frequency tracking	± 0.05 GHz	Resonance lock
Mode switch time	< 1 s	$\text{H}_2\text{O} \leftrightarrow \text{D}_2\text{O}$
Computation latency	< 1 ms	Real-time constraint

Table 8: Control system performance specifications

5 CLAIMS

What is claimed is:

5.1 MIMO Feedback Control Claims

1. A method for closed-loop control of a protein folding modulation apparatus, comprising:
 - (a) measuring a temperature of a sample using a temperature sensor;
 - (b) measuring a folding signal of the sample using a folding detector;
 - (c) computing control outputs based on temperature error and folding error using a multi-input multi-output (MIMO) controller;
 - (d) adjusting microwave power, cooling power, and frequency based on the control outputs; and
 - (e) repeating steps (a) through (d) in a closed loop.
2. The method of claim 1, wherein the MIMO controller uses a state-space feedback formulation with a gain matrix \mathbf{K} designed using Linear Quadratic Regulator (LQR) theory.
3. The method of claim 1, wherein the control loop operates at a rate of at least 100 Hz.
4. The method of claim 1, wherein the method maintains temperature deviation $|\Delta T| < 0.1^\circ\text{C}$ while achieving folding modulation $M > 30\%$.

5.2 Multi-Objective Optimization Claims

5. A method for multi-objective control of protein folding modulation, comprising:
 - (a) defining a first objective to minimize temperature deviation from a setpoint;
 - (b) defining a second objective to maximize folding modulation;
 - (c) computing control outputs that optimize a weighted combination of the first and second objectives; and
 - (d) adjusting weights to select an operating point on a Pareto front.

6. The method of claim 5, wherein the weighted combination is $J = \lambda J_T + (1 - \lambda) J_M$ with $\lambda \in [0, 1]$.
7. The method of claim 5, further comprising an operating mode selection from:
 - (i) isothermal-first mode with temperature deviation prioritized;
 - (ii) modulation-first mode with folding modulation prioritized; and
 - (iii) balanced mode with equal priority.
8. The method of claim 5, wherein the optimization is solved using epsilon-constraint method with isothermal compliance as a hard constraint.

5.3 Adaptive Control Claims

9. A method for adaptive control of protein folding modulation, comprising:
 - (a) measuring operating conditions including temperature, power level, and sample properties;
 - (b) selecting control gains from a pre-computed set based on the operating conditions;
 - (c) interpolating between gains for smooth transitions; and
 - (d) applying the adapted gains to the control algorithm.
10. The method of claim 9, wherein the operating conditions include solvent type (H_2O or D_2O).
11. The method of claim 9, wherein gains are interpolated using polynomial or lookup table methods.

5.4 Model Predictive Control Claims

12. A method for model predictive control of protein folding modulation, comprising:
 - (a) using a thermal-optical model to predict sample temperature and folding signal over a prediction horizon;
 - (b) solving an optimization problem to find control inputs that minimize a cost function over the prediction horizon;
 - (c) applying the first control input from the optimal sequence;

- (d) advancing the prediction horizon by one step; and
 - (e) repeating steps (a) through (d) in a receding horizon manner.
13. The method of claim 12, wherein the thermal-optical model comprises:
- (i) a thermal model relating microwave power and cooling power to sample temperature; and
 - (ii) an optical model relating irradiation frequency and power to folding modulation.
14. The method of claim 12, wherein the optimization problem is solved using quadratic programming with a solution time of less than 1 millisecond.
15. The method of claim 12, wherein the prediction horizon is 10 to 50 time steps.

5.5 Constraint Satisfaction Claims

16. A method for constraint-aware control of protein folding modulation, comprising:
- (a) defining hard constraints including maximum temperature deviation and power limits;
 - (b) defining soft constraints with associated penalty functions;
 - (c) solving a constrained optimization problem that satisfies hard constraints and minimizes soft constraint violations; and
 - (d) implementing hardware safety interlocks independent of the optimization.
17. The method of claim 16, wherein the hard constraint on temperature deviation is $|\Delta T| < 0.5^{\circ}\text{C}$.
18. The method of claim 16, wherein soft constraints include a target temperature deviation of $|\Delta T| < 0.1^{\circ}\text{C}$ with a quadratic penalty for violation.

5.6 Resonance Tracking Claims

19. A method for automatic resonance tracking during protein folding modulation, comprising:
- (a) adding a sinusoidal frequency perturbation to the operating frequency;
 - (b) measuring the folding signal response;

- (c) demodulating the response at the perturbation frequency to estimate the frequency gradient;
 - (d) adjusting the center frequency in the direction of increasing folding signal; and
 - (e) repeating steps (a) through (d) to maintain lock on the resonance peak.
20. The method of claim 19, wherein the perturbation amplitude is 0.01 to 0.1 GHz and the perturbation frequency is 1 to 100 Hz.
21. The method of claim 19, wherein the frequency is maintained within ± 0.05 GHz of the resonance peak.

5.7 Isotope Mode Claims

22. A method for automatic reconfiguration of control parameters for isotope mode operation, comprising:
- (a) detecting the solvent type as H₂O or D₂O;
 - (b) reconfiguring the operating frequency to approximately 14.65 GHz for H₂O or 10.4 GHz for D₂O;
 - (c) adjusting thermal model parameters for the detected solvent;
 - (d) adjusting control gains for the detected solvent; and
 - (e) continuing closed-loop control with the reconfigured parameters.
23. The method of claim 22, wherein solvent detection is performed by one or more of:
- (i) manual operator input;
 - (ii) dielectric constant measurement; and
 - (iii) resonance frequency identification.

5.8 System Claims

24. A control system for protein folding modulation, comprising:
- (a) a temperature sensor configured to measure sample temperature;
 - (b) a folding detector configured to measure folding signal;

- (c) a processor configured to execute a closed-loop control algorithm according to any of claims 1–23;
 - (d) a microwave power controller responsive to the processor;
 - (e) a cooling system controller responsive to the processor; and
 - (f) a frequency controller responsive to the processor.
- 25.** The system of claim 24, comprising a hierarchical architecture with:
- (i) an inner loop operating at 1 kHz for temperature control;
 - (ii) an outer loop operating at 100 Hz for MIMO/MPC control; and
 - (iii) a supervisory loop operating at 10 Hz for mode selection and adaptation.
- 26.** A non-transitory computer-readable medium storing instructions that, when executed by a processor, cause the processor to perform the method of any of claims 1–23.

ABSTRACT

Control algorithms for closed-loop operation of protein folding modulation apparatus enabling simultaneous isothermal maintenance and resonant modulation maximization. The algorithms comprise: (1) multi-input multi-output (MIMO) feedback control using temperature and folding signal readouts to adjust microwave power, frequency, and cooling power with gains designed using Linear Quadratic Regulator (LQR) theory; (2) multi-objective optimization minimizing temperature deviation while maximizing folding modulation, with configurable weighting and Pareto-optimal operating point selection; (3) adaptive gain scheduling adjusting control parameters based on temperature, power level, sample volume, and solvent type; (4) model predictive control (MPC) using a thermal-optical model to predict system response over a receding horizon; (5) constraint satisfaction ensuring temperature bounds ($|\Delta T| < 0.1^\circ\text{C}$ target, $< 0.5^\circ\text{C}$ hard limit), power limits, and safety interlocks; (6) resonance tracking using extremum seeking control with sinusoidal frequency perturbation to maintain lock on the resonance peak; and (7) isotope-mode automatic reconfiguration for H_2O (14.65 GHz) and D_2O (10.4 GHz) operation. Implementation uses hierarchical architecture with inner loop (1 kHz) for temperature, outer loop (100 Hz) for MIMO/MPC, and supervisory loop (10 Hz) for adaptation. Applications include automated protein folding modulation for research, manufacturing quality control, and therapeutic intervention.

— END OF SPECIFICATION —

INVENTOR DECLARATION

I, Jonathan Washburn, declare that:

- (1) I am the original and sole inventor of the control algorithms described and claimed in this application.
- (2) I have reviewed the above specification and claims and believe them to be accurate and complete.
- (3) I believe the claimed invention to be novel, useful, and non-obvious over the prior art.
- (4) I authorize the filing of this provisional patent application to establish a priority date.

Inventor Signature: _____

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Date: _____

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