

# 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**

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## 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  $\Delta T$  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 D<sub>2</sub>O 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 H<sub>2</sub>O and D<sub>2</sub>O 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

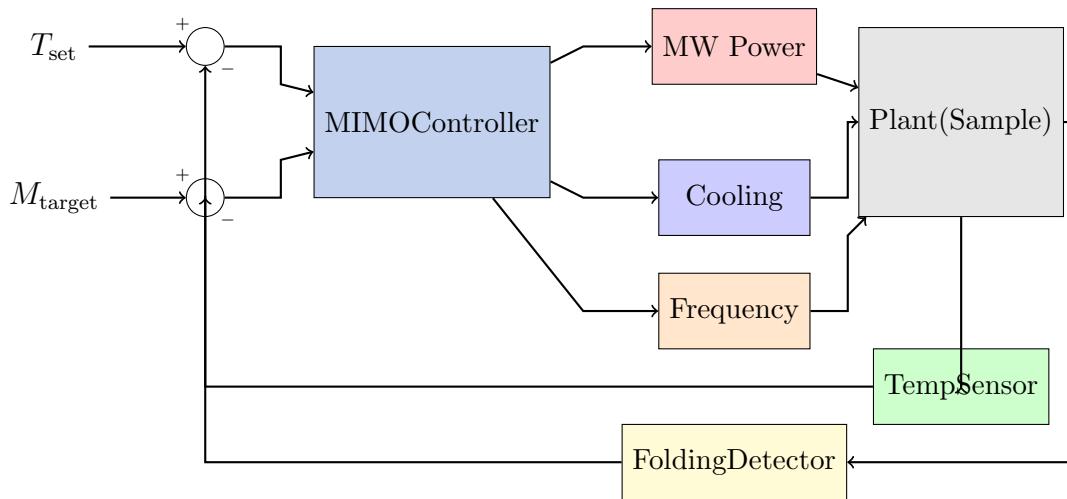


Figure 1: MIMO control system architecture

### 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	$\Delta T$ 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 H<sub>2</sub>O/D<sub>2</sub>O 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)
- $\mathbf{x}_{\text{ref}}$  is the reference state
- $\mathbf{u}_{\text{ff}}$  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:

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

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

subject to constraints (see Section 4.5).

### 4.2.2 Weighted Sum Approach

The simplest approach combines objectives with weights:

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

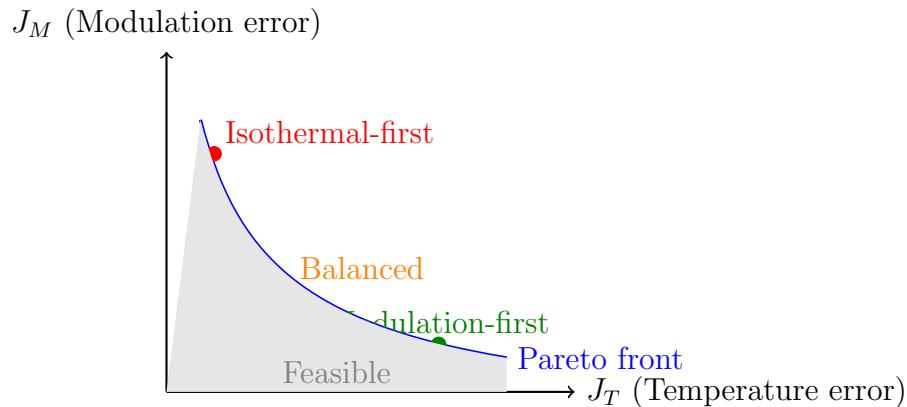


Figure 2: Pareto front showing trade-off between temperature control and modulation

#### 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 ( $H_2O$  vs.  $D_2O$ ) 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  $\sigma$  is the scheduling variable vector and  $\alpha_i$  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.

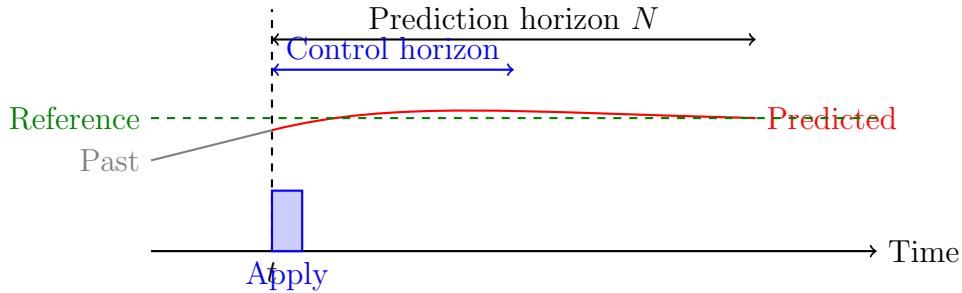


Figure 3: Model Predictive Control: prediction horizon and receding horizon implementation

#### 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
- $\alpha$  = microwave absorption coefficient
- $k_{\text{cool}}$  = passive cooling rate
- $\beta$  = resonant coupling strength
- $f_{\text{res}}$  = resonance frequency
- $\gamma$  = 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°C (hard), < 0.1°C (soft)
Microwave power	$P_{\text{MW}}$	$0 \leq P \leq P_{\max}$
Cooling power	$P_{\text{cool}}$	$0 \leq P \leq P_{\text{cool,max}}$
Frequency range	$f$	$f_{\min} \leq f \leq f_{\max}$
Power rate of change	$ \dot{P} $	$< \dot{P}_{\max}$
Temperature rate	$ \dot{T} $	< 1°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  $T > T_{\max}$
- (2) Power cutoff if cooling fails
- (3) Frequency limits enforced in hardware

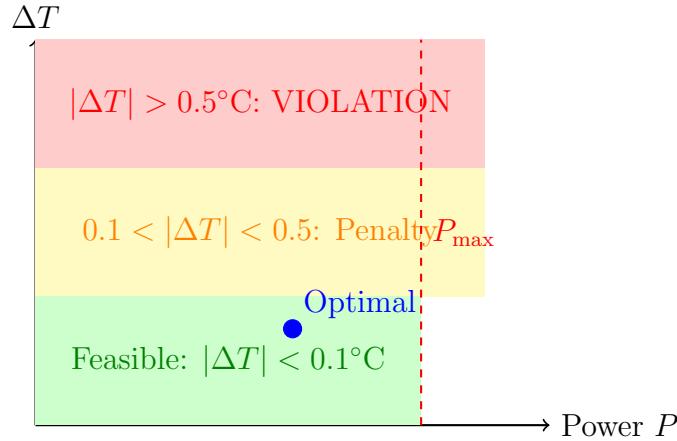


Figure 4: Constraint satisfaction regions in power–temperature space

## 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  $\omega_p$  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 H<sub>2</sub>O or D<sub>2</sub>O
- (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 H<sub>2</sub>O to D<sub>2</sub>O mode:

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

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	$> 100 \text{ Hz}$	For pulsed operation
Frequency tracking	$\pm 0.05 \text{ GHz}$	Resonance lock
Mode switch time	$< 1 \text{ s}$	$\text{H}_2\text{O} \leftrightarrow \text{D}_2\text{O}$
Computation latency	$< 1 \text{ ms}$	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  $\pm 0.05$  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 H<sub>2</sub>O or D<sub>2</sub>O;
  - (b) reconfiguring the operating frequency to approximately 14.65 GHz for H<sub>2</sub>O or 10.4 GHz for D<sub>2</sub>O;
  - (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<sub>2</sub>O (14.65 GHz) and D<sub>2</sub>O (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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