PATENT APPLICATION

APPARATUS FOR FREQUENCY-SELECTIVE PROTEIN FOLDING MODULATION WITH TEMPERATURE COMPENSATION AND ISOTOPE-SHIFT CAPABILITY

PROVISIONAL PATENT APPLICATION

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An apparatus for precision microwave irradiation of protein samples at the resonant jamming frequency ($\sim$14.65 GHz), featuring active temperature compensation to distinguish resonant effects from thermal heating, and automatic isotope-shift frequency scaling for D_2O verification experiments.

CONFIDENTIAL — PATENT PENDING

Contents

ABSTRACT OF THE DISCLOSURE

An apparatus for modulating protein folding rates through precision microwave irradiation at resonant frequencies. The apparatus comprises: (a) a frequency-agile microwave source tunable across 8–20 GHz with resolution of 0.001 GHz; (b) a thermally-controlled sample chamber with active temperature regulation to $\pm 0.05°C$; (c) a real-time folding detection system; (d) a closed-loop feedback controller that maintains isothermal conditions during irradiation; and (e) an isotope-mode controller that automatically scales the operating frequency by factor $1/\sqrt{2}$ for D_2O experiments. The apparatus enables unambiguous discrimination between resonant and thermal effects on protein folding by maintaining constant sample temperature while varying irradiation frequency. Key innovations include: temperature-compensated power modulation to eliminate thermal artifacts; dual-frequency operation for simultaneous H_2O/D_2O comparison; pulsed irradiation modes for intermediate trapping; and integration with spectroscopic detection systems. The apparatus implements the resonant protein folding modulation method derived from Recognition Science, targeting the molecular gate timescale $\tau_{19} \approx 68$ ps corresponding to a jamming frequency of approximately 14.65 GHz.

Keywords: microwave apparatus, protein folding, temperature compensation, isotope shift, frequency-selective irradiation, molecular gate, resonant modulation

1 BACKGROUND OF THE INVENTION

1.1 Field of the Invention

The present invention relates generally to apparatus for studying and controlling protein folding, and more specifically to precision microwave irradiation systems with temperature compensation and isotope-shift capability for resonant modulation of protein conformational dynamics.

1.2 Description of Related Art

1.2.1 Existing Microwave Irradiation Systems

Prior art microwave systems used in biochemistry include:

(a) **Domestic/industrial microwave ovens:** Operating at 2.45 GHz (ISM band), these devices provide bulk heating with no frequency selectivity. Temperature control is typically $\pm 5^{\circ}$C at best, far too imprecise for distinguishing resonant from thermal effects.

(b) **Microwave synthesizers:** Laboratory microwave reactors for chemical synthesis (e.g., CEM Discover, Biotage Initiator) operate at 2.45 GHz with improved temperature monitoring but still rely on thermal mechanisms. Frequency is fixed.

(c) **Dielectric spectroscopy systems:** Broadband systems for measuring dielectric properties can sweep from MHz to THz but are designed for measurement, not controlled irradiation. Power levels are typically too low for biological effects.

(d) **NMR/MRI systems:** While highly precise, these operate at much lower frequencies (100–900 MHz for NMR, 60–400 MHz for MRI) and are designed for spectroscopy/imaging, not protein folding modulation.

(e) **Terahertz sources:** THz systems (0.1–10 THz) probe higher-frequency molecular vibrations but are outside the molecular gate frequency range relevant to protein folding.

Limitation	Description
Wrong frequency range	Prior systems operate at 2.45 GHz or in THz range; none target 12–17 GHz
Poor temperature control	±1–5°C typical; insufficient to distinguish resonant from thermal effects
No isotope mode	No systems provide automatic frequency scaling for D_2O experiments
No feedback control	Open-loop operation leads to uncontrolled sample heating
No folding detection	Separate apparatus required for monitoring; no integrated real-time detection
No pulsed operation	Continuous-wave only; cannot trap folding intermediates

Table 1: Limitations of prior art microwave apparatus

1.2.2 Limitations of Prior Art Apparatus

1.2.3 The Need for Precision Apparatus

The method of resonant protein folding modulation (described in related Patent Application 001) requires apparatus with specific capabilities not available in any prior art system:

(1) **Frequency precision:** The jamming frequency at 14.65 GHz must be set with precision of at least 0.01 GHz to ensure resonance.

(2) **Temperature stability:** To distinguish resonant from thermal effects, sample temperature must be maintained within ±0.1°C despite microwave absorption.

(3) **Isotope-shift capability:** For verification experiments, the frequency must be scalable by exactly $1/\sqrt{2}$ for D_2O operation.

(4) **Real-time monitoring:** Protein folding state must be monitored during irradiation to detect resonant effects.

(5) **Feedback control:** Closed-loop control is required to maintain isothermal conditions while varying frequency.

1.3 Objects of the Invention

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

(1) Generates precision microwave radiation at frequencies in the 8–20 GHz range with resolution of 0.001 GHz;

(2) Maintains sample temperature to within $\pm 0.1^{\circ}\mathrm{C}$ during irradiation;

(3) Provides automatic frequency scaling for isotope-shift experiments;

(4) Integrates real-time protein folding detection;

(5) Implements closed-loop feedback for isothermal operation;

(6) Supports pulsed irradiation for intermediate trapping experiments.

2 SUMMARY OF THE INVENTION

2.1 General Statement of the Invention

The present invention provides an integrated apparatus for resonant protein folding modulation comprising:

(a) A frequency-agile microwave source with continuous tunability from 8 to 20 GHz;

(b) A precision sample chamber with microwave-transparent windows and integrated temperature control;

(c) A multi-modal folding detection system;

(d) A closed-loop feedback controller for isothermal operation;

(e) An isotope-mode controller for automatic frequency scaling;

(f) A pulsed irradiation controller for intermediate trapping.

2.2 Key Technical Innovations

2.2.1 Temperature-Compensated Power Modulation

The apparatus implements a novel temperature-compensated power modulation (TCPM) algorithm:

$$P(t) = P_{\text{target}} \times \left[1 - k_p(T(t) - T_{\text{set}}) - k_i \int_0^t (T(s) - T_{\text{set}})\, ds\right] \tag{1}$$

where $P(t)$ is the instantaneous power, $T(t)$ is the measured temperature, T_{set} is the target temperature, and k_p, k_i are proportional and integral gain constants. This algorithm adjusts microwave power in real-time to maintain constant sample temperature despite varying absorption.

2.2.2 Isotope-Shift Frequency Scaling

The apparatus includes a dedicated isotope-mode controller that implements:

$$f_{\mathrm{D_2O}} = \frac{f_{\mathrm{H_2O}}}{\sqrt{2}} \approx 0.7071 \times f_{\mathrm{H_2O}} \tag{2}$$

When isotope mode is activated, the controller automatically:

(i) Scales the operating frequency by factor $1/\sqrt{2}$;

(ii) Adjusts power levels to account for different D_2O dielectric properties;

(iii) Modifies temperature control parameters for D_2O thermal characteristics.

2.2.3 Dual-Chamber Configuration

An optional dual-chamber configuration allows simultaneous irradiation of H_2O and D_2O samples at their respective resonant frequencies, enabling real-time comparison under identical conditions.

2.3 Functional Block Diagram

The apparatus comprises the following functional blocks:

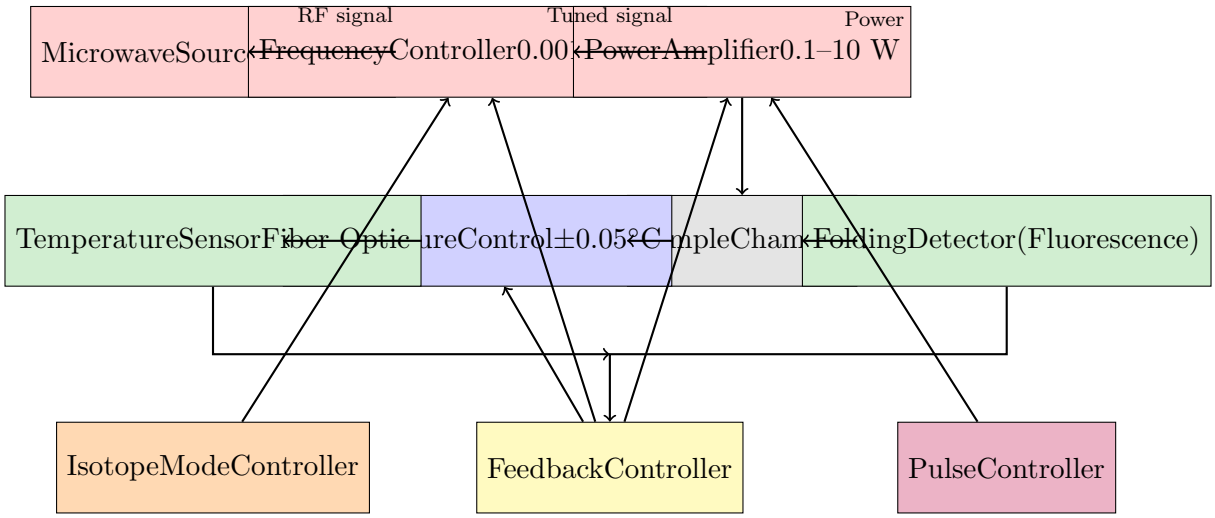

Figure 1: Functional block diagram of the apparatus

3 BRIEF DESCRIPTION OF DRAWINGS

Figure 1: Functional Block Diagram

A block diagram showing the interconnection of the major functional components: microwave source, frequency controller, power amplifier, sample chamber, temperature control system, folding detector, feedback controller, isotope mode controller, and pulse controller.

Figure 2: Sample Chamber Cross-Section

A cross-sectional view of the sample chamber showing: microwave waveguide, quartz sample holder, Peltier cooling elements, fiber-optic temperature sensor, fluorescence excitation/detection optics, and thermal insulation.

Figure 3: Temperature Control Loop

A control system diagram showing the feedback loop for maintaining isothermal conditions during microwave irradiation.

Figure 4: Isotope Mode Operation

A diagram illustrating the frequency scaling for H_2O vs. D_2O operation.

Figure 5: Pulse Timing Diagrams

Timing diagrams showing various pulse modes for intermediate trapping experiments.

Figure 6: Dual-Chamber Configuration

A diagram of the optional dual-chamber system for simultaneous H_2O/D_2O comparison.

4 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

4.1 Microwave Source Subsystem

4.1.1 Frequency-Agile Source

The microwave source subsystem comprises a frequency-agile signal generator with the following specifications:

Parameter	Specification
Frequency range	8–20 GHz (continuous)
Frequency resolution	0.001 GHz (1 MHz)
Frequency accuracy	±0.0001 GHz (±100 kHz)
Frequency stability	±1 ppm over operating temperature
Phase noise	< –100 dBc/Hz at 10 kHz offset
Switching time	< 1 ms
Output power (pre-amp)	0 to +10 dBm

Table 2: Microwave source specifications

The source is based on a phase-locked loop (PLL) synthesizer architecture with a low-noise reference oscillator. Preferred implementations include:

(i) Yttrium iron garnet (YIG) oscillator with PLL control;

(ii) Direct digital synthesis (DDS) with frequency multiplication;

(iii) Voltage-controlled oscillator (VCO) bank with PLL.

4.1.2 Power Amplifier

The power amplifier provides the following characteristics:

Preferred implementations use traveling-wave tube (TWT) amplifiers or solid-state GaN power amplifiers.

4.1.3 Frequency Controller

The frequency controller implements the following functions:

Parameter	Specification
Frequency range	8–20 GHz
Output power	0.1 to 10 W (continuously adjustable)
Power resolution	0.01 W
Power accuracy	± 0.1 W or $\pm 5\%$, whichever is greater
Harmonic suppression	> 30 dB
Modulation bandwidth	DC to 10 MHz (for pulsed operation)

Table 3: Power amplifier specifications

(1) **Manual frequency setting:** Direct entry of target frequency via digital interface.

(2) **Frequency sweep:** Programmable frequency sweeps for resonance mapping:

$$f(t) = f_{\text{start}} + \frac{f_{\text{stop}} - f_{\text{start}}}{t_{\text{sweep}}} \times t \tag{3}$$

(3) **Isotope scaling:** Automatic application of $1/\sqrt{2}$ factor when isotope mode is active.

(4) **Feedback adjustment:** Fine frequency adjustment based on feedback controller input.

4.2 Sample Chamber Subsystem

4.2.1 Chamber Design

The sample chamber is designed to:

(a) Efficiently couple microwave energy into the sample;

(b) Provide optical access for fluorescence detection;

(c) Enable precise temperature control;

(d) Accommodate both H_2O and D_2O samples;

(e) Minimize sample volume while maintaining uniform irradiation.

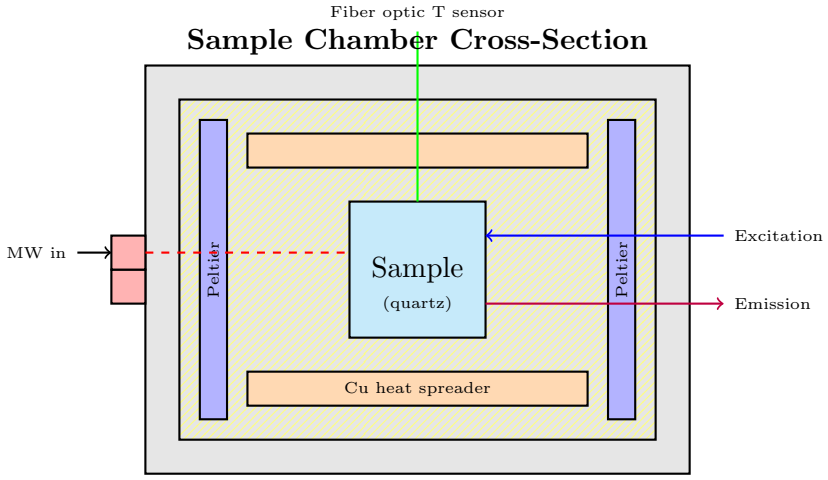

Figure 2: Cross-sectional view of the sample chamber showing thermal management and optical access

4.2.2 Sample Holder

The sample holder is constructed from high-purity fused quartz (SiO_2) with the following properties:

Property	**Value**
Material	Fused quartz (Suprasil or equivalent)
Dielectric constant (10–20 GHz)	$\sim$3.8
Loss tangent (10–20 GHz)	< 0.0001
Optical transmission	$> 90\%$ (250–700 nm)
Thermal conductivity	$\sim$1.4 W/(m·K)
Sample volume	50–500 μL (configurable)
Wall thickness	0.5–1.0 mm

Table 4: Sample holder specifications

Alternative materials include:

(i) Sapphire (Al_2O_3): Higher thermal conductivity but higher cost;

(ii) Borosilicate glass: Lower cost but higher microwave losses;

(iii) PTFE (Teflon): Low dielectric loss but poor optical properties.

4.2.3 Microwave Coupling

Microwave energy is coupled into the sample chamber via:

(1) **Rectangular waveguide:** WR-62 (12.4–18 GHz) or WR-42 (18–26.5 GHz) with tapered transition for broadband operation.

(2) **Coaxial-to-waveguide adapter:** For connecting to the power amplifier output.

(3) **Impedance matching:** Tunable iris or stub matching network to optimize power transfer to the sample.

(4) **Field uniformity:** Cavity design or mode stirrer to ensure uniform field distribution across the sample volume.

4.3 Temperature Control Subsystem

4.3.1 Design Requirements

Temperature control is critical for distinguishing resonant from thermal effects. The subsystem must:

(a) Maintain sample temperature to ±0.05°C (goal) or ±0.1°C (minimum);

(b) Respond to power absorption within 100 ms;

(c) Operate over temperature range of 4–50°C;

(d) Function with both H_2O and D_2O samples.

4.3.2 Temperature Sensor

The preferred temperature sensor is a fiber-optic fluorescence-based thermometer:

Parameter	**Specification**
Type	Fluorescence decay (GaAs or similar)
Resolution	0.01°C
Accuracy	±0.05°C
Response time	< 50 ms
Immunity to RF/microwave	Complete (no metallic components)
Operating range	–40 to +200°C
Probe diameter	< 1 mm

Table 5: Temperature sensor specifications

The fiber-optic sensor is immune to electromagnetic interference from the microwave field, unlike thermocouples or RTDs.

4.3.3 Thermal Management

Active temperature control is provided by:

(1) **Peltier (thermoelectric) modules:** Bi_2Te_3-based modules provide heating and cooling capacity of 10–50 W.

(2) **Heat spreaders:** Copper plates with high thermal conductivity (∼400 W/(m·K)) distribute heat evenly.

(3) **Heat sink/fan:** External heat rejection for Peltier hot side.

(4) **Thermal insulation:** Aerogel or vacuum insulation to minimize heat exchange with environment.

4.3.4 Control Algorithm

The temperature control implements a PID (proportional-integral-derivative) controller with feedforward compensation:

$$Q(t) = K_p e(t) + K_i \int_0^t e(\tau)\, d\tau + K_d \frac{de(t)}{dt} - K_{ff} P_{\mathrm{MW}}(t) \tag{4}$$

where:

- $Q(t)$ = Peltier heating/cooling power
- $e(t) = T_{\mathrm{set}} - T(t)$ = temperature error
- K_p, K_i, K_d = PID gains
- K_{ff} = feedforward gain
- $P_{\mathrm{MW}}(t)$ = microwave power

The feedforward term ($K_{ff} P_{\mathrm{MW}}$) anticipates sample heating due to microwave absorption and preemptively activates cooling, reducing temperature excursions.

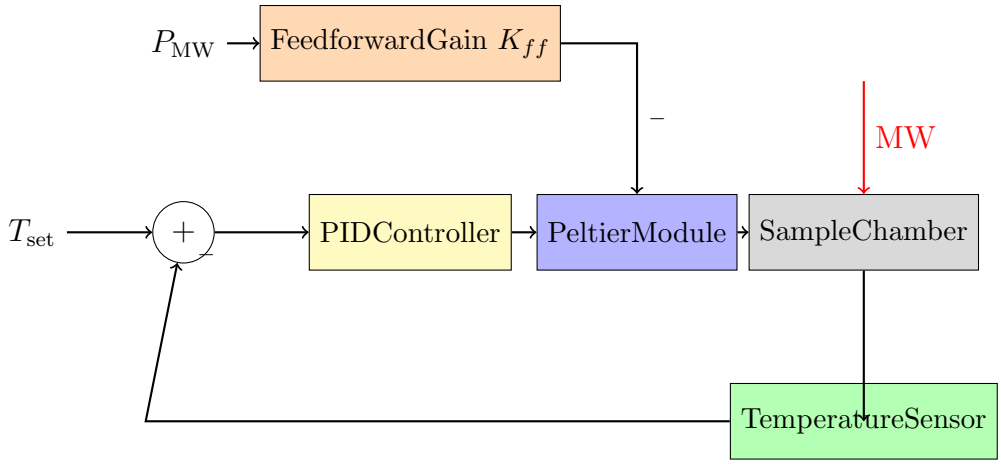

Figure 3: Temperature control loop with feedforward compensation for microwave heating

4.4 Folding Detection Subsystem

4.4.1 Detection Modalities

The apparatus supports multiple detection modalities:

(1) **Intrinsic tryptophan fluorescence:**

- Excitation: 280–295 nm (UV LED or laser)
- Emission: 320–360 nm
- Sensitivity: Detects tertiary structure changes

(2) **FRET (Förster Resonance Energy Transfer):**

- Requires labeled protein (donor/acceptor pair)
- Measures intramolecular distances
- High sensitivity to folding state

(3) **Circular dichroism (CD):**

- Far-UV (190–250 nm) for secondary structure
- Near-UV (250–320 nm) for tertiary structure
- Requires external CD spectrometer integration

(4) **Dynamic light scattering (DLS):**

- Measures hydrodynamic radius
- Detects aggregation
- Requires external DLS module

4.4.2 Preferred Implementation: Fluorescence Detection

The preferred embodiment uses intrinsic tryptophan fluorescence with:

Component	Specification
Excitation source	280 nm LED or 266 nm laser
Excitation bandwidth	10 nm (bandpass filter)
Excitation power	1–10 mW
Emission filter	340 ± 20 nm bandpass
Detector	Photomultiplier tube (PMT) or Si APD
Sampling rate	10–1000 Hz
Dynamic range	4 decades

Table 6: Fluorescence detection specifications

4.5 Feedback Controller Subsystem

4.5.1 Controller Architecture

The feedback controller is a digital signal processor (DSP) or field-programmable gate array (FPGA) implementing:

(1) Temperature feedback loop (Equation 4);

(2) Power modulation for isothermal operation (Equation 1);

(3) Frequency optimization based on folding signal;

(4) Safety interlocks (over-temperature, over-power).

4.5.2 Isothermal Operation Mode

In isothermal mode, the controller maintains constant sample temperature while irradiating at different frequencies. This is achieved by:

(a) Setting target temperature T_{set};

(b) Monitoring temperature continuously (> 10 Hz);

(c) Adjusting Peltier power via PID + feedforward;

(d) If temperature deviates $> 0.2°$C, reducing microwave power;

(e) Logging all parameters for post-experiment analysis.

4.5.3 Resonance Search Mode

In resonance search mode, the controller:

(a) Sweeps frequency across a programmed range (e.g., 12–17 GHz);

(b) Monitors folding signal at each frequency;

(c) Identifies frequency of minimum folding rate (resonance);

(d) Optionally performs fine sweep around identified minimum;

(e) Reports resonance frequency and width.

4.6 Isotope Mode Controller

4.6.1 Frequency Scaling

When operating with D_2O samples, the isotope mode controller:

(1) Receives notification of D_2O sample loading (manual or automatic detection);

(2) Computes scaled frequency: $f_{D_2O} = f_{H_2O}/\sqrt{2}$;

(3) Commands frequency controller to apply scaled frequency;

(4) Adjusts power calibration for D_2O dielectric properties;

(5) Modifies temperature control parameters for D_2O thermal properties.

4.6.2 Automatic Solvent Detection (Optional)

An optional dielectric sensor can automatically detect the solvent:

- H_2O: $\varepsilon' \approx 80$ at low frequency, $\varepsilon' \approx 30$ at 15 GHz
- D_2O: $\varepsilon' \approx 78$ at low frequency, slightly different dispersion

By measuring the dielectric constant at a reference frequency, the controller can automatically select the appropriate operating mode.

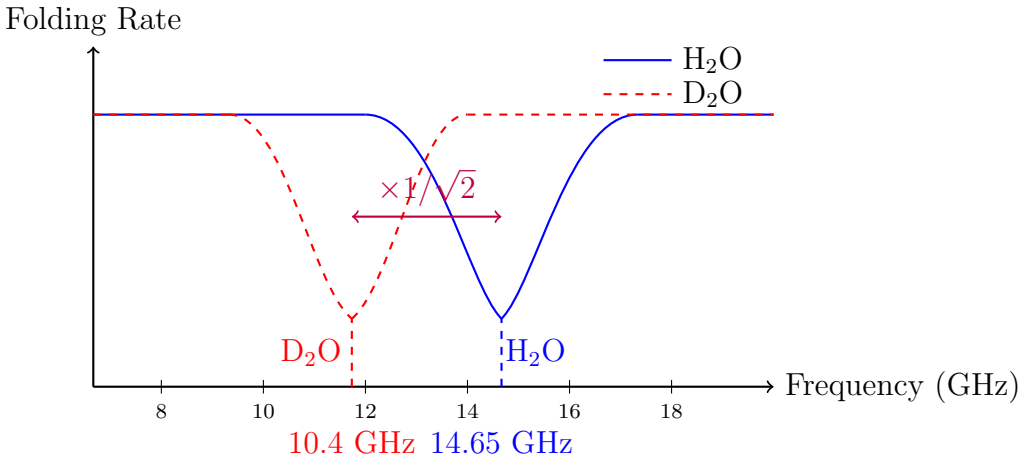

Figure 4: Isotope mode frequency scaling: The resonance frequency shifts by factor $1/\sqrt{2}$ when H_2O is replaced by D_2O

4.7 Pulse Controller Subsystem

4.7.1 Pulse Modes

The apparatus supports several pulse modes for different applications:

(1) **Continuous wave (CW):** Constant power at fixed frequency.

(2) **Gated CW:** Fixed frequency with programmable on/off duty cycle:

$$P(t) = \begin{cases} P_0 & \text{if } (t \mod T) < T_{\text{on}} \\ 0 & \text{otherwise} \end{cases} \tag{5}$$

(3) **Single pulse:** One-shot pulse with programmable duration (1 ns – 1 s).

(4) **Pulse train:** Multiple pulses with programmable spacing:

$$P(t) = P_0 \sum_{n=0}^{N-1} \Pi\left(\frac{t - nT_{\text{rep}} - T_{\text{pulse}}/2}{T_{\text{pulse}}}\right) \tag{6}$$

(5) **Chirped pulse:** Frequency swept during pulse for broadband excitation.

4.7.2 Timing Specifications

Parameter	Specification
Minimum pulse width	1 ns
Maximum pulse width	Unlimited (CW)
Pulse width resolution	1 ns
Rise/fall time	< 5 ns
Repetition rate	DC to 10 MHz
Timing jitter	< 100 ps RMS
Trigger delay	Programmable, 0–10 s
External trigger input	TTL/LVTTL, 50 Ω

Table 7: Pulse controller timing specifications

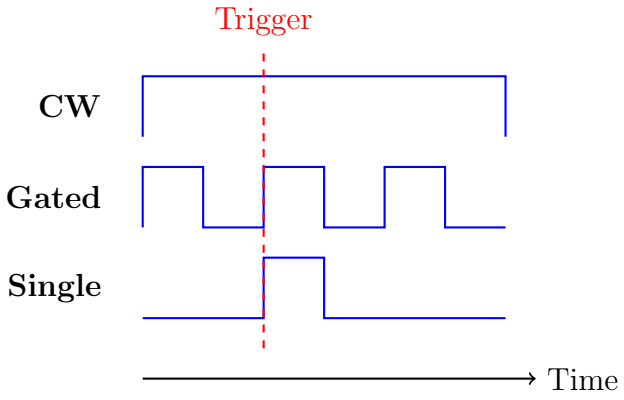

Figure 5: Pulse timing diagrams: CW, gated, and single-pulse modes

4.8 Dual-Chamber Configuration (Optional)

4.8.1 Design Concept

The optional dual-chamber configuration enables simultaneous irradiation of H_2O and D_2O samples under identical conditions:

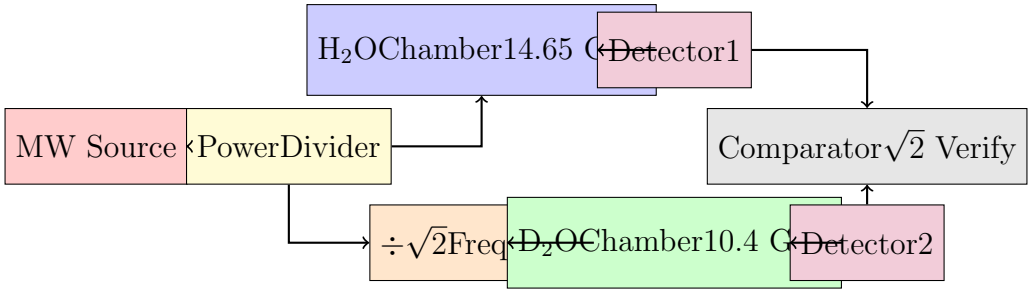

Figure 6: Dual-chamber configuration for simultaneous H_2O/D_2O comparison

4.8.2 Advantages

The dual-chamber configuration provides:

(a) Simultaneous measurement eliminates temporal drift;

(b) Same microwave source ensures correlated frequency;

(c) Direct comparison validates $\sqrt{2}$ isotope shift;

(d) Rigorous control experiment in every run.

4.9 User Interface and Data Acquisition

4.9.1 Control Interface

The apparatus is controlled via:

(1) **Local control panel:** Touchscreen display for basic operations.

(2) **Computer interface:** USB, Ethernet, or GPIB connection to control computer running dedicated software.

(3) **Scripting interface:** Python or MATLAB API for automated experiments.

(4) **Remote access:** Web interface for remote monitoring and control.

4.9.2 Data Logging

All parameters are logged with timestamps:

- Frequency (0.001 GHz resolution)
- Power (0.01 W resolution)
- Temperature (0.01°C resolution)
- Folding signal (16-bit ADC)
- Pulse timing (1 ns resolution)
- Isotope mode status

Data is stored in HDF5 format for efficient post-processing.

4.10 Safety Features

4.10.1 Interlocks

The apparatus includes safety interlocks:

(1) **Over-temperature:** Microwave power shuts off if $T > T_{\max}$ (programmable, default 60°C).

(2) **Door interlock:** Power disabled when sample access door is open.

(3) **Over-power:** Hardware limiter prevents $P > P_{\max}$ (default 10 W).

(4) **Thermal runaway:** Automatic shutdown if temperature rises > 1°C/s.

(5) **Emergency stop:** Physical button immediately disables all power.

4.10.2 Shielding

The apparatus is fully shielded to prevent microwave leakage:

- Enclosure: Aluminum or steel with conductive gaskets
- Leakage specification: < 1 mW/cm^2 at 5 cm from any surface (per IEEE C95.1)
- Viewports: Conductive mesh (aperture $< \lambda/10$)

5 CLAIMS

What is claimed is:

5.1 Apparatus Claims

1. An apparatus for modulating protein folding rate by resonant microwave irradiation, comprising:

2. a microwave source capable of generating electromagnetic radiation tunable in the frequency range of 8 to 20 GHz;

3. a frequency controller configured to set the frequency of said microwave source with a resolution of at least 0.01 GHz;

4. a sample chamber configured to hold a protein sample and to receive microwave radiation from said source;

5. a temperature sensor configured to measure the temperature of said sample;

6. a temperature control system configured to maintain the sample temperature within $\pm 0.1^\circ$C of a target temperature;

7. a feedback controller configured to adjust at least one of microwave power and temperature control based on said temperature measurement; and

8. a folding detector configured to measure protein folding state in real time.

9. The apparatus of claim 1, wherein the frequency controller is configured to set the frequency to approximately 14.65 ± 0.5 GHz for H_2O samples.

10. The apparatus of claim 1, further comprising an isotope mode controller configured to automatically scale the operating frequency by a factor of $1/\sqrt{2}$ when D_2O samples are used.

11. The apparatus of claim 3, wherein the isotope mode controller is configured to operate at approximately 10.4 ± 0.5 GHz for D_2O samples.

12. The apparatus of claim 1, wherein the temperature sensor comprises a fiber-optic fluorescence-based thermometer immune to electromagnetic interference from the microwave radiation.

13. The apparatus of claim 1, wherein the temperature control system comprises:

(i) at least one Peltier thermoelectric module in thermal contact with said sample chamber;

(ii) a heat spreader configured to distribute thermal energy evenly across said sample chamber; and

(iii) a heat sink for rejecting heat from the hot side of said Peltier module.

14. The apparatus of claim 1, wherein the feedback controller implements a PID control algorithm with feedforward compensation for microwave power absorption.

15. The apparatus of claim 7, wherein the feedforward compensation preemptively adjusts cooling in proportion to applied microwave power to minimize temperature excursions.

16. The apparatus of claim 1, wherein the sample chamber comprises a microwave-transparent sample holder made of fused quartz or sapphire.

17. The apparatus of claim 1, wherein the folding detector comprises a fluorescence detection system configured to measure intrinsic tryptophan fluorescence with excitation at 280–295 nm and emission detection at 320–360 nm.

18. The apparatus of claim 1, further comprising a power amplifier capable of output power from 0.1 to 10 W with power resolution of at least 0.01 W.

19. The apparatus of claim 1, further comprising a pulse controller configured to generate pulsed microwave radiation with pulse widths from 1 nanosecond to continuous wave.

20. The apparatus of claim 12, wherein the pulse controller is configured to generate:

(i) single pulses with programmable duration;

(ii) pulse trains with programmable pulse spacing and number of pulses; and

(iii) gated continuous-wave operation with programmable duty cycle.

21. The apparatus of claim 1, wherein the frequency controller is configured to perform frequency sweeps across a programmable frequency range for resonance mapping.

22. An apparatus for simultaneous comparison of protein folding in H_2O and D_2O samples, comprising:

(a) a microwave source;

(b) a power divider configured to split the output of said microwave source into two paths;

(c) a first sample chamber for H_2O samples, irradiated at a first frequency f_1;

(d) a frequency shifter configured to shift the frequency in the second path by a factor of $1/\sqrt{2}$;

(e) a second sample chamber for D_2O samples, irradiated at a second frequency $f_2 = f_1/\sqrt{2}$;

(f) a first folding detector associated with said first sample chamber;

(g) a second folding detector associated with said second sample chamber; and

(h) a comparator configured to compare folding rates in said first and second sample chambers.

23. The apparatus of claim 15, wherein $f_1 \approx 14.65$ GHz and $f_2 \approx 10.4$ GHz.

24. The apparatus of claim 15, wherein said comparator is configured to verify that the ratio f_1/f_2 equals $\sqrt{2}$ within a tolerance of $\pm 5\%$.

5.2 Component Claims

18. A sample chamber for microwave irradiation of protein samples, comprising:

(a) a microwave-transparent sample holder configured to contain a liquid sample of 50 to 500 microliters;

(b) a waveguide coupling configured to introduce microwave radiation from 8 to 20 GHz into said sample holder;

(c) at least one Peltier thermoelectric module in thermal contact with said sample holder for temperature control;

(d) a fiber-optic temperature sensor positioned to measure sample temperature without metallic components in the microwave field; and

(e) optical access ports for fluorescence excitation and emission detection.

19. The sample chamber of claim 18, wherein the sample holder is made of fused quartz with optical transmission $> 90\%$ in the wavelength range of 250 to 700 nm.

20. The sample chamber of claim 18, wherein the waveguide coupling comprises a rectangular waveguide with an impedance matching network for optimizing power transfer to samples with different dielectric properties.

5.3 Method of Use Claims

21. A method for operating the apparatus of claim 1 to modulate protein folding, comprising:

(a) loading a protein sample into the sample chamber;

(b) setting the target temperature to a desired value;

(c) activating the temperature control system to equilibrate the sample at said target temperature;

(d) activating the microwave source at a frequency in the range of 12 to 17 GHz;

(e) monitoring the sample temperature and adjusting microwave power and/or Peltier power to maintain isothermal conditions; and

(f) measuring the protein folding rate with the folding detector.

22. The method of claim 21, further comprising performing a frequency sweep to identify the resonant frequency at which folding rate is minimized.

23. The method of claim 21, further comprising:

(a) performing a first measurement with H_2O sample at frequency f_1;

(b) performing a second measurement with D_2O sample at frequency $f_2 = f_1/\sqrt{2}$; and

(c) verifying that similar folding rate modulation is observed at both frequencies, thereby confirming a resonant mechanism.

24. A method for trapping protein folding intermediates using the apparatus of claim 12, comprising:

(a) initiating protein folding by rapid mixing, temperature jump, or pH jump;

(b) at a predetermined time after initiation, applying a pulse of microwave radiation at the jamming frequency;

(c) wherein said pulse arrests the protein in a folding intermediate state; and

(d) characterizing the folding intermediate using spectroscopic or structural methods.

25. The method of claim 24, wherein the pulse duration is between 1 nanosecond and 1 microsecond.

ABSTRACT

An apparatus for modulating protein folding rates through precision microwave irradiation at resonant frequencies derived from first principles. The apparatus comprises: a frequency-agile microwave source tunable across 8–20 GHz with 0.001 GHz resolution; a thermally-controlled sample chamber with active Peltier temperature regulation maintaining $\pm 0.05°\text{C}$ stability; a fiber-optic temperature sensor immune to electromagnetic interference; a real-time fluorescence-based folding detection system; a closed-loop PID feedback controller with feedforward compensation for isothermal operation during irradiation; an isotope-mode controller providing automatic frequency scaling by factor $1/\sqrt{2}$ for D_2O experiments; and a pulse controller for intermediate trapping. An optional dual-chamber configuration enables simultaneous H_2O/D_2O comparison. The apparatus implements the resonant protein folding modulation method targeting the molecular gate timescale $\tau_{19} \approx 68$ ps (jamming frequency $\sim$14.65 GHz), with the temperature compensation and isotope-shift capability enabling unambiguous discrimination between resonant and thermal effects.

— END OF SPECIFICATION —

INVENTOR DECLARATION

I, Jonathan Washburn, declare that:

(1) I am the original and sole inventor of the apparatus 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.

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Date: _____

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