PATENT APPLICATION

PULSE PROTOCOL METHODS FOR RESONANT PROTEIN FOLDING MODULATION AND INTERMEDIATE TRAPPING

PROVISIONAL PATENT APPLICATION

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Methods for applying pulsed microwave irradiation at the jamming frequency to modulate protein folding, including synchronized pulse timing relative to folding initiation, duty cycle optimization, pulse trains for kinetic studies, frequency-chirped pulses, phase-locked detection schemes, intermediate trapping protocols, and isothermal pulsing control rules.

CONFIDENTIAL — PATENT PENDING

Contents

ABSTRACT OF THE DISCLOSURE

Methods for applying pulsed electromagnetic radiation at a resonant jamming frequency (approximately 14.65 GHz for H_2O, 10.4 GHz for D_2O) to modulate protein folding dynamics. The methods comprise: (a) synchronized pulse timing relative to folding initiation events including temperature jump, rapid mixing, and pH jump; (b) duty cycle optimization to balance folding modulation against thermal load; (c) pulse train protocols for kinetic characterization of folding pathways; (d) frequency-chirped pulses for broadband resonance excitation; (e) phase-locked detection schemes for enhanced signal-to-noise ratio; (f) intermediate trapping protocols using precisely timed pulses to arrest folding at specific stages; and (g) isothermal pulsing control rules that maintain constant sample temperature despite pulsed irradiation. The methods enable precise temporal control of protein folding modulation, allow characterization of folding intermediates not accessible by continuous-wave irradiation, and provide enhanced discrimination between resonant and thermal effects. Pulse timing parameters are derived from the molecular gate timescale ($\tau_{19} \approx 68$ ps) and the Recognition Science framework. Applications include structural biology research, drug discovery, biopharmaceutical manufacturing quality control, and therapeutic intervention in protein misfolding diseases.

Keywords: pulsed irradiation, protein folding, intermediate trapping, duty cycle, pulse train, chirp, phase-locked detection, isothermal pulsing, folding kinetics

1 BACKGROUND OF THE INVENTION

1.1 Field of the Invention

The present invention relates generally to methods for controlling protein folding using electromagnetic radiation, and more specifically to pulsed irradiation protocols that enable temporal control of folding modulation, intermediate trapping, and enhanced discrimination between resonant and thermal effects.

1.2 Description of Related Art

1.2.1 Continuous-Wave Irradiation Limitations

Prior methods for electromagnetic modulation of protein folding (including those described in related Patent Application 001) primarily employ continuous-wave (CW) irradiation. While effective, CW irradiation has several limitations:

(a) **Thermal accumulation:** Continuous power delivery leads to progressive sample heating, making it difficult to distinguish resonant from thermal effects.

(b) **No temporal resolution:** CW irradiation modulates the entire folding process uniformly; it cannot selectively affect specific folding stages.

(c) **No intermediate access:** CW irradiation either slows or does not slow folding; it cannot "freeze" the protein at intermediate states.

(d) **Limited kinetic information:** CW provides only endpoint or steady-state measurements; transient kinetics are obscured.

1.2.2 Prior Pulsed Microwave Methods

Pulsed microwave techniques have been used in other contexts:

(1) **Pulsed electron paramagnetic resonance (EPR):** Uses microwave pulses to manipulate electron spins. Frequencies are typically 9–95 GHz but pulses are designed for spin manipulation, not protein folding modulation.

(2) **Pulsed NMR:** Uses radiofrequency pulses (100–900 MHz) for nuclear spin manipulation. Different frequency range and different physical mechanism.

(3) **Pulsed microwave heating:** Industrial and laboratory microwave systems with pulsed operation to control average power. Pulses are designed for thermal management, not resonant coupling.

(4) **Terahertz time-domain spectroscopy:** Uses sub-picosecond pulses at THz frequencies. Different frequency range and primarily a spectroscopic technique.

None of these prior art methods address pulsed irradiation at the molecular gate frequency (∼14.65 GHz) synchronized with protein folding initiation.

1.2.3 Folding Initiation Methods

Protein folding can be initiated by several methods:

Method	**Timescale**	**Mechanism**
Temperature jump (T-jump)	∼1–10 ns	Laser-induced heating
Rapid mixing	∼100 μs – 1 ms	Dilution from denaturant
pH jump	∼10 μs – 1 ms	Protonation state change
Photolysis	$<$ 1 ns	Photocleavage of protecting group
Pressure jump	∼1 μs	Hydrostatic pressure release

Table 1: Protein folding initiation methods and timescales

1.2.4 The Need for Synchronized Pulsing

What is needed is a pulsed irradiation method that:

(1) Is **synchronized** with folding initiation to enable stage-selective modulation;

(2) Uses **optimized duty cycles** to minimize thermal load while maximizing resonant effect;

(3) Employs **pulse trains** to extract kinetic information;

(4) Provides **intermediate trapping** capability;

(5) Maintains **isothermal conditions** through intelligent power control.

1.3 Objects of the Invention

It is an object of the present invention to provide pulsed irradiation methods that:

(1) Synchronize microwave pulses with protein folding initiation;

(2) Optimize duty cycles for maximum effect with minimum heating;

(3) Enable trapping and characterization of folding intermediates;

(4) Provide kinetic information through pulse train protocols;

(5) Enhance signal-to-noise ratio through phase-locked detection;

(6) Maintain isothermal conditions during pulsed irradiation.

2 SUMMARY OF THE INVENTION

2.1 General Statement of the Invention

The present invention provides a family of pulsed irradiation methods for resonant protein folding modulation, comprising:

(a) Synchronized pulse timing relative to folding initiation;

(b) Duty cycle optimization protocols;

(c) Pulse train methods for kinetic characterization;

(d) Frequency-chirped pulse protocols;

(e) Phase-locked detection schemes;

(f) Intermediate trapping methods;

(g) Isothermal pulsing control rules.

2.2 Pulse Timing Fundamentals

2.2.1 Characteristic Timescales

The pulse protocols of the present invention are designed around the following characteristic timescales:

Timescale	**Value**	**Significance**
Molecular gate period	$\tau_{19} \approx 68$ ps	Minimum pulse width for resonance
Dihedral transition time	$\sim$1–10 ns	Elementary folding step
Secondary structure formation	$\sim$100 ns – 1 μs	Helix/sheet nucleation
Hydrophobic collapse	$\sim$1–10 μs	Chain compaction
Complete folding	$\sim$1 ms – 1 s	Native state achievement

Table 2: Characteristic timescales for pulse protocol design

2.2.2 Pulse Width Requirements

For effective resonant coupling, the pulse width T_{pulse} should satisfy:

$$T_{\text{pulse}} \geq N_{\text{cycles}} \times \tau_{19} \tag{1}$$

where $N_{\text{cycles}} \geq 10$ for coherent interaction. This gives a minimum pulse width of approximately 680 ps (∼1 ns practical minimum).

2.3 Protocol Categories

The methods of the present invention fall into seven categories:

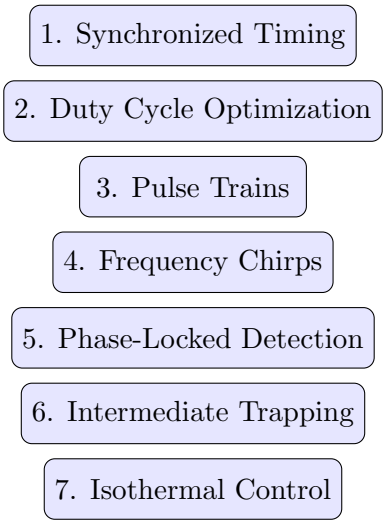

Figure 1: Seven categories of pulse protocols

3 BRIEF DESCRIPTION OF DRAWINGS

Figure 1: Seven Categories of Pulse Protocols

A diagram showing the seven categories of pulse protocols covered by the present invention.

Figure 2: Synchronized Pulse Timing

Timing diagrams showing pulse synchronization with T-jump, rapid mixing, and pH-jump folding initiation.

Figure 3: Duty Cycle Optimization

Diagrams illustrating different duty cycles and their effects on thermal load and resonant modulation.

Figure 4: Pulse Train Protocol

Timing diagram for pulse train kinetic measurements.

Figure 5: Frequency-Chirped Pulse

Time-frequency diagram of a chirped pulse sweeping through the resonance.

Figure 6: Phase-Locked Detection Scheme

Block diagram of the phase-locked detection system.

Figure 7: Intermediate Trapping Protocol

Timing diagram showing pulse application for trapping folding intermediates.

Figure 8: Isothermal Pulsing Control Loop

Control system diagram for maintaining constant temperature during pulsed irradiation.

4 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

4.1 Protocol 1: Synchronized Pulse Timing

4.1.1 Principle

Protein folding is a multi-stage process. By synchronizing microwave pulses with the folding initiation event, specific stages of folding can be selectively modulated.

4.1.2 Synchronization with Temperature Jump (T-Jump)

T-jump folding initiation uses a laser pulse to rapidly heat the sample, causing cold-denatured or temperature-sensitive proteins to begin folding.

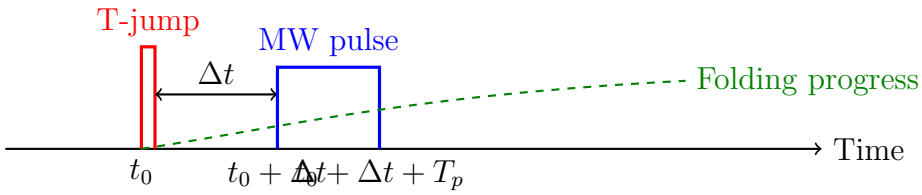

Figure 2: Synchronized pulse timing with T-jump initiation

Protocol Parameters:

- T-jump pulse: 5–20 ns duration, $\Delta T = 5$–$20°C$
- Synchronization delay Δt: Programmable, 0 – 100 ms
- MW pulse frequency: 14.65 GHz (H_2O) or 10.4 GHz (D_2O)
- MW pulse width T_p: 1 ns – 10 ms
- Trigger: Electrical sync from T-jump laser

4.1.3 Synchronization with Rapid Mixing

Rapid mixing uses stopped-flow or continuous-flow mixers to dilute a protein from denaturing conditions into folding-permissive buffer.

Protocol Parameters:

- Mixing dead time: 100 μs – 1 ms (instrument-dependent)
- Synchronization delay Δt: Programmable, 0 – 10 s
- Trigger: Electrical sync from mixer stop/flow sensor

4.1.4 Synchronization with pH Jump

pH jump uses rapid addition of acid or base to change the protonation state of a protein, triggering folding.

Protocol Parameters:

- pH change: Typically 2–3 units
- Equilibration time: 10 μs – 1 ms
- Synchronization delay Δt: Programmable, 0 – 10 s
- Trigger: Electrical sync from injection valve

4.1.5 Delay Scanning

By varying the synchronization delay Δt across multiple experiments, the effect of irradiation on different folding stages can be mapped:

$$M(\Delta t) = \text{Modulation as function of pulse delay} \tag{2}$$

This creates a "folding modulation kinetic trace" revealing which stages are most sensitive to resonant irradiation.

4.2 Protocol 2: Duty Cycle Optimization

4.2.1 Definition

The duty cycle D is the fraction of time the microwave source is active:

$$D = \frac{T_{\text{on}}}{T_{\text{on}} + T_{\text{off}}} = \frac{T_{\text{on}}}{T_{\text{period}}} \tag{3}$$

4.2.2 Trade-offs

Duty Cycle	Resonant Effect	Thermal Load
$D = 100\%$ (CW)	Maximum	Maximum
$D = 50\%$	Moderate	50% of CW
$D = 10\%$	Reduced	10% of CW
$D = 1\%$	Minimal	1% of CW

Table 3: Duty cycle trade-offs

4.2.3 Optimal Duty Cycle Determination

The optimal duty cycle balances resonant modulation against thermal effects:

$$D_{\text{opt}} = \arg\max_{D} \left[\frac{M(D)}{\Delta T(D)} \right] \tag{4}$$

where $M(D)$ is the modulation magnitude and $\Delta T(D)$ is the temperature rise.

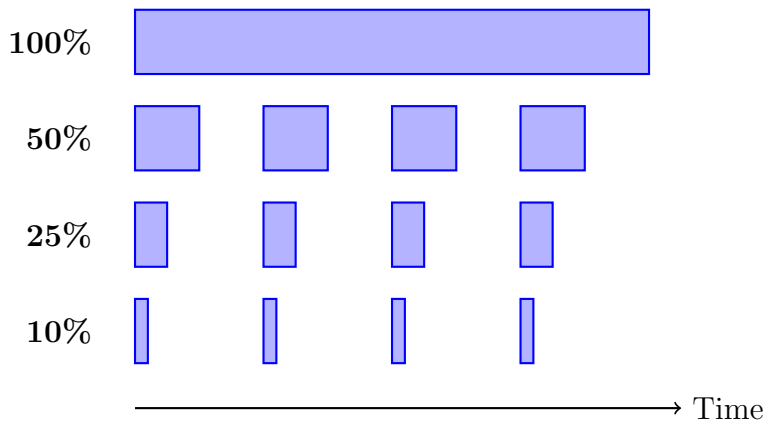

Figure 3: Different duty cycles: 100%, 50%, 25%, and 10%

4.2.4 Adaptive Duty Cycle Control

The duty cycle can be dynamically adjusted based on temperature feedback:

$$D(t) = D_{\max} \times \left[1 - \frac{T(t) - T_{\text{set}}}{\Delta T_{\max}}\right] \tag{5}$$

where $\Delta T_{\max}$ is the maximum allowed temperature rise.

4.3 Protocol 3: Pulse Train Methods

4.3.1 Single-Frequency Pulse Train

A train of N identical pulses at fixed spacing:

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

where Π is the rectangular function, T_{rep} is the repetition period, and T_{pulse} is the pulse width.

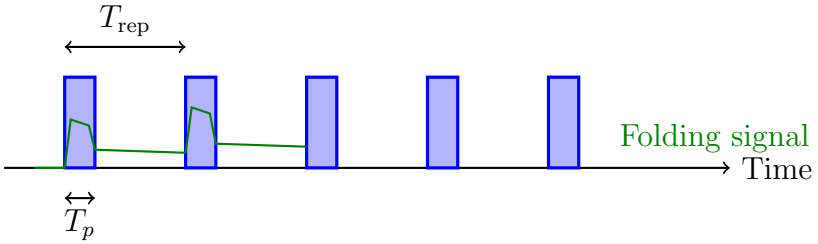

Figure 4: Pulse train with folding signal response

4.3.2 Applications of Pulse Trains

(1) **Kinetic rate determination:** Varying T_{rep} reveals characteristic folding timescales.

(2) **Signal averaging:** Multiple pulses improve signal-to-noise ratio.

(3) **Dose-response characterization:** Varying N determines cumulative effect.

(4) **Recovery time measurement:** Time between pulses when effect "wears off."

4.3.3 Logarithmic Spacing

For characterizing processes spanning many decades in time:

$$t_n = t_0 \times 10^{n/k} \tag{7}$$

where k determines the number of points per decade.

4.4 Protocol 4: Frequency-Chirped Pulses

4.4.1 Linear Chirp

A frequency-chirped pulse sweeps through a range of frequencies during the pulse:

$$f(t) = f_0 + \frac{\Delta f}{T_{\text{pulse}}} \times t \tag{8}$$

where f_0 is the starting frequency and Δf is the total frequency sweep.

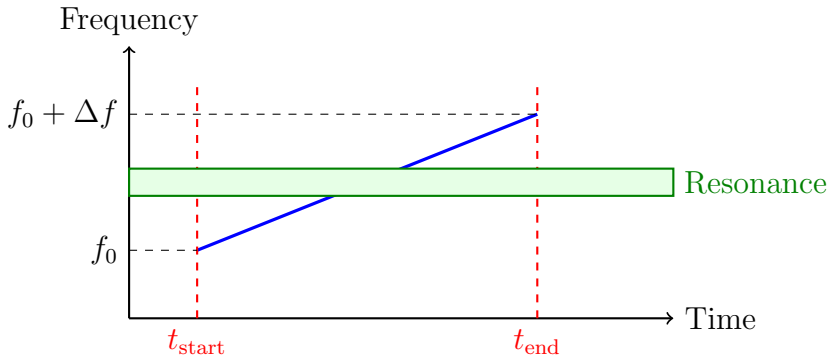

Figure 5: Linear frequency chirp sweeping through resonance

4.4.2 Applications of Chirped Pulses

(1) **Broadband excitation:** Ensures resonance is hit even if exact frequency is uncertain.

(2) **Adiabatic passage:** Slow chirp through resonance can achieve complete population inversion.

(3) **Resonance mapping:** Time-resolved detection during chirp reveals resonance position.

(4) **Isotope-blind operation:** Chirp covering both H_2O and D_2O frequencies works with mixed solvents.

4.4.3 Chirp Parameters

Parameter	Typical Value	Range
Start frequency f_0	12 GHz	8–14 GHz
Frequency sweep Δf	5 GHz	2–10 GHz
Chirp duration	1–100 μs	100 ns – 1 ms
Chirp rate	0.05–5 GHz/μs	—

Table 4: Typical chirp parameters

4.5 Protocol 5: Phase-Locked Detection

4.5.1 Principle

Phase-locked detection (also called lock-in detection) improves signal-to-noise ratio by modulating the microwave source and detecting only the component of the folding signal at the modulation frequency.

4.5.2 Implementation

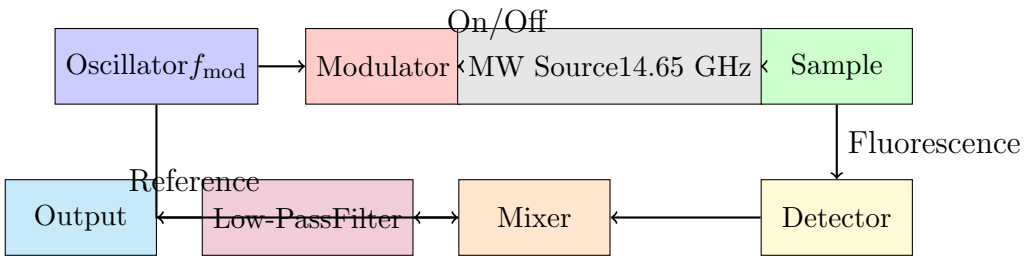

Figure 6: Phase-locked detection scheme

Protocol Parameters:

- Modulation frequency f_{mod}: 100 Hz – 100 kHz
- Lock-in time constant: $\tau = 1/(2\pi f_{\text{mod}})$ to $10/f_{\text{mod}}$
- Phase: 0° (in-phase) and 90° (quadrature) detection

4.5.3 Advantages

(1) **Noise rejection:** Rejects noise at frequencies other than f_{mod}.

(2) **Baseline elimination:** Removes static background signals.

(3) **Small signal detection:** Can detect modulation amplitudes <1% of baseline.

(4) **Thermal discrimination:** Slow thermal effects are filtered out.

4.6 Protocol 6: Intermediate Trapping

4.6.1 Principle

By applying a microwave pulse at a precisely timed moment during folding, the protein can be "frozen" in an intermediate state. The resonant coupling disrupts the molecular gate, preventing further conformational transitions.

4.6.2 Trapping Protocol

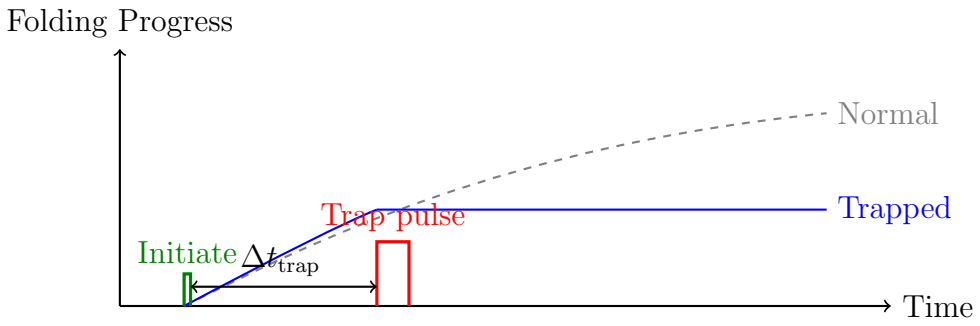

Figure 7: Intermediate trapping protocol

Protocol Steps:

(1) Initiate folding (T-jump, mixing, pH-jump, etc.).

(2) Wait for delay time Δt_{trap} corresponding to desired intermediate.

(3) Apply trapping pulse at jamming frequency.

(4) Maintain continuous irradiation to prevent escape from trapped state.

(5) Characterize intermediate using spectroscopic methods.

(6) Optionally, turn off irradiation to allow completion of folding.

4.6.3 Trap Pulse Parameters

Parameter	Typical Value	Notes
Trap pulse onset Δt_{trap}	1 μs – 100 ms	Stage-dependent
Trap pulse width	10 ns – 10 ms	Must exceed τ_{19}
Trap pulse power	1–10 W	Sample-dependent
Maintenance power	0.1–1 W	Lower than trap
Frequency	14.65 GHz (H_2O)	Or 10.4 GHz (D_2O)

Table 5: Intermediate trapping pulse parameters

4.6.4 Applications

(1) **Structural biology:** Trap and characterize normally transient intermediates.

(2) **Drug discovery:** Identify druggable intermediate states.

(3) **Misfolding studies:** Trap misfolding intermediates for aggregation studies.

(4) **Mechanism elucidation:** Map folding pathway by trapping at different times.

4.7 Protocol 7: Isothermal Pulsing Control

4.7.1 Challenge

Pulsed irradiation deposits energy in the sample, causing temperature fluctuations. For rigorous comparison of resonant vs. thermal effects, the sample temperature must remain constant.

4.7.2 Control Algorithm

(1) **Predictive cooling:** Before each pulse, apply pre-cooling to bring sample below T_{set}.

(2) **Real-time feedback:** During pulse, monitor temperature and adjust pulse width/power.

(3) **Inter-pulse equilibration:** Ensure temperature returns to baseline between pulses.

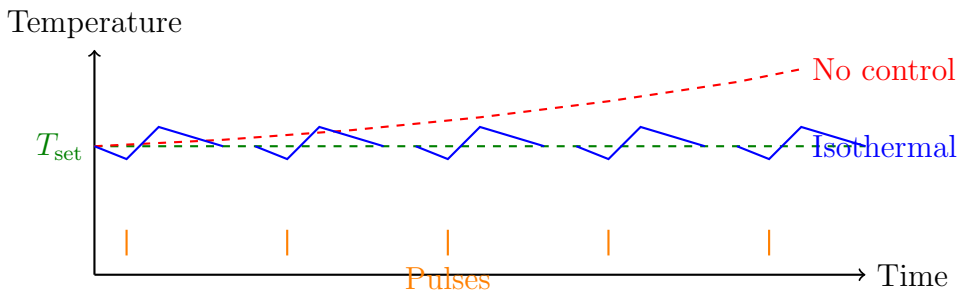

Figure 8: Isothermal pulsing control: Temperature maintained despite pulsed irradiation

4.7.3 Control Equations

Pre-cooling setpoint:

$$T_{\text{pre}} = T_{\text{set}} - \alpha \times P_{\text{pulse}} \times T_{\text{pulse}} \tag{9}$$

where α is a calibrated heating coefficient (K/J).

Inter-pulse cooling time:

$$t_{\text{cool}} \geq \frac{C_{\text{sample}}}{k_{\text{cool}}} \times \ln\left(\frac{T_{\text{peak}} - T_{\text{set}}}{0.01°\text{C}}\right) \tag{10}$$

where C_{sample} is the sample heat capacity and k_{cool} is the cooling rate constant.

4.7.4 Isothermal Compliance Criteria

For a protocol to be considered "isothermal":

(1) Peak temperature excursion: $|T_{\text{peak}} - T_{\text{set}}| < 0.5°\text{C}$

(2) Time-averaged temperature: $|\langle T \rangle - T_{\text{set}}| < 0.1°\text{C}$

(3) RMS temperature fluctuation: $\sqrt{\langle (T - T_{\text{set}})^2 \rangle} < 0.2°\text{C}$

4.8 Combined Protocols

The seven protocols can be combined for advanced applications:

4.8.1 Example: Phase-Locked Intermediate Trapping

(1) Initiate folding with T-jump.

(2) Wait for delay Δt_{trap}.

(3) Apply modulated trap pulse train (Protocol 5 + 6).

(4) Use lock-in detection to confirm trapping.

(5) Characterize intermediate.

4.8.2 Example: Isothermal Chirped Pulse Scan

(1) Apply frequency-chirped pulses (Protocol 4).

(2) Use isothermal control (Protocol 7) to prevent heating.

(3) Record resonance frequency from time-resolved detection.

(4) Repeat with D_2O to confirm $\sqrt{2}$ shift.

5 CLAIMS

What is claimed is:

5.1 Synchronized Timing Claims

1. A method for modulating protein folding using synchronized pulsed irradiation, comprising:

(a) initiating protein folding by an initiation event selected from temperature jump, rapid mixing, pH jump, photolysis, and pressure jump;

(b) detecting the initiation event and generating a trigger signal;

(c) after a programmable delay Δt following the trigger signal, applying a pulse of electromagnetic radiation at a frequency in the range of 12 to 17 GHz; and

(d) measuring the effect of the pulse on protein folding.

2. The method of claim 1, wherein the frequency is approximately 14.65 GHz for H_2O samples or 10.4 GHz for D_2O samples.

3. The method of claim 1, wherein the programmable delay Δt is in the range of 0 to 10 seconds.

4. The method of claim 1, further comprising varying the delay Δt across multiple experiments to map folding stage sensitivity to irradiation.

5. The method of claim 1, wherein the initiation event is a temperature jump induced by a laser pulse.

5.2 Duty Cycle Claims

6. A method for optimizing pulsed irradiation for protein folding modulation, comprising:

(a) applying pulsed irradiation at a duty cycle D defined as the ratio of on-time to total period;

(b) measuring folding modulation magnitude $M(D)$ as a function of duty cycle;

(c) measuring temperature rise $\Delta T(D)$ as a function of duty cycle; and

(d) selecting an optimal duty cycle D_{opt} that maximizes the ratio $M(D)/\Delta T(D)$.

7. The method of claim 6, wherein the duty cycle is in the range of 1% to 100%.

8. The method of claim 6, further comprising dynamically adjusting the duty cycle based on real-time temperature feedback to maintain isothermal conditions.

5.3 Pulse Train Claims

9. A method for characterizing protein folding kinetics using pulse trains, comprising:

(a) applying a train of N pulses at the jamming frequency with pulse width T_{pulse} and repetition period T_{rep};

(b) measuring the folding response after each pulse; and

(c) analyzing the response pattern to determine folding kinetic parameters.

10. The method of claim 9, wherein the repetition period T_{rep} is varied logarithmically to span multiple decades of time.

11. The method of claim 9, wherein N is in the range of 2 to 1000 pulses.

5.4 Chirped Pulse Claims

12. A method for broadband resonant excitation of protein folding modulation, comprising:

(a) generating a frequency-chirped pulse that sweeps from a starting frequency f_0 to an ending frequency $f_0 + \Delta f$ over a pulse duration T_{chirp};

(b) applying the chirped pulse to a protein sample; and

(c) detecting the folding response during or after the pulse.

13. The method of claim 12, wherein f_0 is in the range of 8 to 14 GHz and Δf is in the range of 2 to 10 GHz.

14. The method of claim 12, wherein the chirp covers both the H_2O jamming frequency ($\sim$14.65 GHz) and the D_2O jamming frequency ($\sim$10.4 GHz).

15. The method of claim 12, further comprising time-resolved detection during the chirp to identify the resonant frequency.

5.5 Phase-Locked Detection Claims

16. A method for enhanced detection of protein folding modulation, comprising:

(a) modulating the microwave irradiation at a modulation frequency f_{mod};

(b) detecting the folding signal (e.g., fluorescence);

(c) mixing the detected signal with a reference signal at f_{mod};

(d) applying a low-pass filter to extract the component at f_{mod}; and

(e) outputting the filtered signal as the modulation amplitude.

17. The method of claim 16, wherein the modulation frequency f_{mod} is in the range of 100 Hz to 100 kHz.

18. The method of claim 16, further comprising detecting both in-phase and quadrature components.

5.6 Intermediate Trapping Claims

19. A method for trapping protein folding intermediates, comprising:

(a) initiating protein folding;

(b) waiting for a predetermined trap delay Δt_{trap} corresponding to a desired intermediate state;

(c) applying a trap pulse of electromagnetic radiation at the jamming frequency;

(d) maintaining irradiation to prevent escape from the intermediate state; and

(e) characterizing the trapped intermediate.

20. The method of claim 19, wherein the trap delay Δt_{trap} is in the range of 1 microsecond to 100 milliseconds.

21. The method of claim 19, wherein the trap pulse width is in the range of 10 nanoseconds to 10 milliseconds.

22. The method of claim 19, wherein the intermediate is characterized by one or more of: fluorescence spectroscopy, circular dichroism, NMR, mass spectrometry, and cryo-electron microscopy.

23. The method of claim 19, further comprising releasing the intermediate by turning off irradiation and observing completion of folding.

5.7 Isothermal Pulsing Claims

24. A method for maintaining isothermal conditions during pulsed irradiation of protein samples, comprising:

(a) applying predictive pre-cooling before each pulse to offset anticipated heating;

(b) monitoring sample temperature during and after each pulse;

(c) adjusting cooling power to return sample to setpoint temperature between pulses; and

(d) verifying that peak temperature excursion is less than a predetermined threshold.

25. The method of claim 24, wherein the peak temperature excursion threshold is 0.5°C.

26. The method of claim 24, wherein the time-averaged temperature is maintained within 0.1°C of the setpoint.

27. The method of claim 24, further comprising adjusting pulse power or duty cycle if temperature control is insufficient.

5.8 Combination Claims

28. A method combining synchronized timing and intermediate trapping, comprising the method of claim 1 wherein the pulse is a trap pulse according to claim 19.

29. A method combining phase-locked detection and intermediate trapping, comprising the method of claim 16 wherein the modulated irradiation is applied as a trap according to claim 19.

30. A method combining chirped pulses and isothermal control, comprising the method of claim 12 wherein isothermal conditions are maintained according to claim 24.

ABSTRACT

Methods for applying pulsed electromagnetic radiation at a resonant jamming frequency (approximately 14.65 GHz for H_2O, 10.4 GHz for D_2O) to modulate protein folding dynamics. The methods comprise seven protocol categories: (1) synchronized pulse timing relative to folding initiation events (temperature jump, rapid mixing, pH jump) with programmable delays enabling stage-selective modulation; (2) duty cycle optimization balancing folding modulation against thermal load with adaptive control; (3) pulse train protocols with variable repetition periods for kinetic characterization; (4) frequency-chirped pulses for broadband resonance excitation and resonance mapping; (5) phase-locked detection schemes for enhanced signal-to-noise ratio and thermal discrimination; (6) intermediate trapping protocols using precisely timed pulses to arrest folding at specific stages for characterization; and (7) isothermal pulsing control rules using predictive pre-cooling and real-time feedback to maintain constant sample temperature despite pulsed irradiation. The protocols may be combined for advanced applications. Pulse timing parameters are derived from the molecular gate timescale ($\tau_{19} \approx 68$ ps). Applications include structural biology research, drug discovery, biopharmaceutical manufacturing, and therapeutic intervention in protein misfolding diseases.

— END OF SPECIFICATION —

INVENTOR DECLARATION

I, Jonathan Washburn, declare that:

(1) I am the original and sole inventor of the pulse protocol methods 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: _____

Name: Jonathan Washburn

Email: washburn.jonathan@gmail.com

Date: _____

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