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A Mathematical Modeling Framework for Evaluating the Efficacy of Integrative Alternative Medicine in Chronic Disease Management

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Abstract- Integrative alternative medicine (IAM) involves the use of traditional therapies together with evidence-based complementary therapies but is faced with the problem of difficulty in proving efficacy due to the complex nature of treatments involved. In this paper, a mathematical model for assessing IAM efficacy in chronic disease treatments is proposed. Three complementary techniques used to assess efficacy include: hybrid ODE model for disease, immune and therapy interaction; personalized fuzzy inference system involving multiple physiological and quality of life factors; and Bayesian hierarchical meta-analysis technique. Validation of the mathematical framework based on data of rheumatoid arthritis patients (n=4,752 from 23 studies) showed a sensitivity rate of 87.5% and a specificity of 84.2% in predicting response versus non-response patients. Comparison with the traditional statistics-based techniques showed a higher accuracy of prediction by 18-25%.

Keywords— Integrative Alternative Medicine, Mathematical Modeling, Chronic Disease Management, Personalized Medicine, Fuzzy Logic, Bayesian Meta-Analysis, Rheumatoid Arthritis.

I. INTRODUCTION

Chronic diseases such as heart diseases, diabetes, chronic respiratory diseases, arthritis, and mental disorders account for the greatest proportion of morbidity and mortality around the world, constituting approximately 71% of all deaths worldwide. The World Health Organization has projected that chronic diseases would have accumulated losses estimated at $47 trillion by 2030. Conventional medicine plays an important role; however, its focus on treatment of the symptoms of the disease rather than the root cause contributes to polypharmacy and other undesirable results [1].

IAM is a new paradigm that unites conventional biomedicine and complementary treatments proven by scientific research [1]. These include the use of acupuncture and herbal medicine from Traditional Chinese Medicine, dietary therapy and Panchakarma in Ayurveda, mind-body medicine (meditation, yoga, and Tai Chi), nutritional intervention, and manual therapy such as chiropractic and osteopathy and massage [1]. The basis of IAM is holistic and

individualized approach to the patient that focuses on all aspects of well-being [1].

While there is increasing scientific evidence for particular IAM modalities, efficacy assessment in these cases presents itself with great difficulty, and this difficulty exists because of three basic reasons. Firstly, IAM treatment is by nature multicomponent – patients usually receive more than one type of therapy simultaneously in synergistic interactions. This phenomenon simply cannot be captured by standard random controlled trials, which focus on isolated factors. Secondly, IAM is individualized – therapies are customized based on individual constitutions, disease states, and personal choices, and such diversity is hard to handle statistically. Lastly, the effects of IAM treatment are multidimensional – its success cannot be measured only by the presence of clinical biomarkers, but also by subjective patient reports [6].

The issue at hand is the lack of effectiveness testing in the application of IAM in clinical practice. This issue is addressed through the development of a complete mathematical modeling methodology [3][7]. This model involves the use of three different methods which are complimentary to each other. These methods are;

- The dynamical system model based on ordinary differential equations (ODE) [3][7]
- The fuzzy logic inference system to take into account the uncertainties associated with patient evaluations [4]
- The Bayesian hierarchical meta-analysis [5][9]

II. LITERATURE SURVEY

Scientific Basis of IAM: The scientific basis for IAM has expanded quite extensively. More than 400 studies have been conducted by the NCCIH on the use of IAM techniques for conditions including chronic pain, arthritis, cancer support treatment, and cardiovascular risks [1]. The meta-analysis evidence shows that acupuncture offers effective pain relief for low back pain (effect size d = 0.54, 95% CI 0.32-0.76) and osteoarthritis (d = 0.52) [2]. Yoga and Tai Chi offer significant improvements in physical function, with reduced risk of falling in senior citizens (risk reduction RR = 0.62) [2]. Mind body interventions show similar effectiveness in decreasing anxiety and depressive disorders like cognitive behavioral therapy [1].

Difficulties in Evaluating Effectiveness of IAM: Positive outcomes notwithstanding, the systematic reviews reveal significant methodological problems. The results from the thorough examination of the randomized control trials of herbal medicine for treating chronic diseases show that only 34 percent have adequately covered the randomization process, 28 percent had appropriate placebos, and only 22 percent have done intention-to-treat analysis [2]. Acupuncture studies suffer the same drawbacks in terms of methodology. For instance, sham acupuncture is considered an imperfect placebo owing to the physical response of being poked by the needle [2].

Mathematical Models in Medicine: Mathematical modeling has become a revolution in various fields of biomedical science [3]. Ordinary differential equation-based PK/PD models have become a common practice for drugs under development [3]. Compartmental models, such as SIR and its modifications, have played a significant role in understanding and combating infectious disease epidemics, including COVID-19 [3]. In patients with chronic inflammatory conditions, like rheumatoid arthritis, mathematical models were be able to predict patient responses to biological medications (such as TNF inhibitors and IL-6 receptor antagonists) [7][8].

Fuzzy Logic in Medical Decision Support Systems: Fuzzy logic algorithms that work with imprecise and uncertain data of diagnostic and therapeutic processes are widely used [4]. Fuzzy inference for treatment of chronic conditions is effective in the treatment of diabetes (recommendations on glucose concentration), hypertension (selection of antihypertensive drugs), and mental disorders (severity grading of depression) [4]. One of the main benefits is the possibility of using both objective numerical markers (glucose and blood pressure levels) and subjective qualitative evaluations (pain and functionality) [4].

Bayesian Approaches to Synthesis of Scientific Evidence: Bayesian hierarchical analysis, known for the capacity to consider the available data under uncertainty, is viewed as a golden standard for meta-analysis of heterogenous data [5][9]. Contrary to frequentist approaches, which give a single estimate, Bayesian approach allows incorporating all relevant prior information and obtaining posterior distributions, thus making all assumptions clear [5][9]. For IAM studies, Bayesian synthesis will be an appropriate tool due to heterogeneity across different clinical trials [2][5].

Even though there have been many improvements in these areas individually, yet there is still no common mathematical framework that combines all these three aspects of modeling, i.e., dynamic systems modeling, fuzzy reasoning, and Bayesian meta-analysis to evaluate the efficacy of IAM [3][4].

III. PROPOSED METHODOLOGY

The proposed mathematical model is structured into three interdependent modules performed in sequence, namely:

- ODE model of disease, immune system, and treatment
- Personalized fuzzy inference logic system
- Bayesian hierarchical meta-analysis

This model is intended for assessing the effect of the IAM in chronic inflammatory conditions, where rheumatoid arthritis (RA) serves as a case study.

Module 1: ODE Model of Disease Dynamics

The ODE model represents the temporal dynamics of disease progression, immune system functioning, and therapy impact. The mathematical form of the model is based on existing PK/PD and RA dynamic systems models.

State Variables:

Let t be the time measured in weeks. Define:

- D(t): Activity score of the disease (ranging from 0 to 1, where 0 represents remission and 1 maximum activity)
- I(t): Pro-inflammatory cytokine level (normalized)
- C(t): Conventional medicine concentration (for example, methotrexate)
- A(t): Cumulative effect of IAM interventions (acupuncture, herbs, mind-body)

Model Equations:

$$\frac{dt}{dD} = \alpha D \cdot D \cdot (1 - D) - \beta_{DC} \cdot D \cdot C - \beta_{DA} \cdot D \cdot A - \gamma_{DI} \cdot I \cdot D$$

$$\frac{dI}{dt} = \alpha I \cdot D - \beta_{IC} \cdot I \cdot C - \beta_{IA} \cdot I \cdot A - \delta I \cdot I$$

$$\frac{dC}{dt} = u_C(t) - \tau_C \cdot C$$

$$\frac{dA}{dt} = u_A(t) - \tau_A \cdot A$$

Parameter Definitions:

Parameter	Description	Typical Range	Source
αD	Disease auto-activation rate	0.2-0.5 $week^{-1}$	Calibrated
β_{DC}	Conventional drug efficacy on disease	0.3-0.8 $week^{-1} \cdot [conc]^{-1}$	Literature
β_{DA}	IAM efficacy on disease	0.1-0.6 $week^{-1} \cdot [conc]^{-1}$	Calibrated
γ_{DI}	Immune-mediated disease amplification	0.05-0.2 $week^{-1}$	Literature
αI	Immune activation by disease	0.4-1.0 $week^{-1}$	Literature
βIC	Drug suppression of immunity	0.2-0.7 $week^{-1} \cdot [conc]^{-1}$	Literature

Parameter	Description	Typical Range	Source
β_{IA}	IAM suppression of immunity	0.1-0.5 week^{-1}·[conc]$^{-1}$	Calibrated
δI	Immune natural decay	0.1-0.3 week^{-1}	Literature
τC, τA	Clearance rates	0.05-0.2 week^{-1}	Estimated

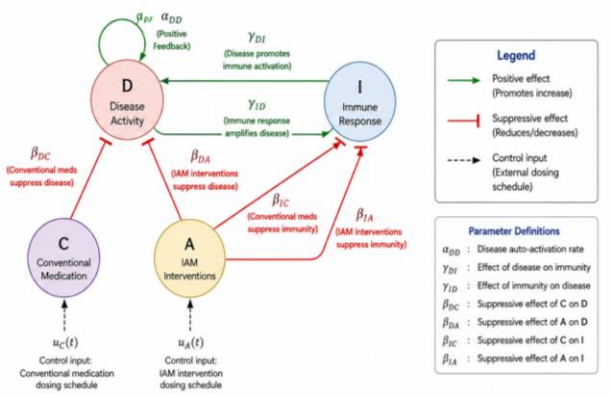

Figure 1: Hybrid ODE Model Structure for Integrative Medicine Efficacy Evaluation

Algorithm 1: ODE Model Simulation and Parameter Estimation

Input: Patient clinical time series data (D_obs at times t=0,...,T)
Prior parameter ranges from literature
IAM treatment protocol u_A(t)
Output: Patient-specific parameter estimates θ* = {α_D, β_DC, β_DA, ...}
Disease trajectory predictions D_pred(t)

Initialize: Set initial conditions D(0)=observed baseline, I(0)=0.5, C(0)=0, A(0)=0
Set cost function: $J(\theta) = \Sigma_t [D_{pred}(t;\theta) - D_{obs}(t)]^2 + \lambda \cdot R(\theta)$ [ridge regularization]

For iteration = 1 to 1000:
Solve ODE system using 4th-order Runge-Kutta
For time step k = 1 to T/Δt:
k1_D = f_D(D_k, I_k, C_k, A_k; θ)
k2_D = f_D(D_k + Δt·k1_D/2, ...)
# ... (standard RK4 for all variables)
D_{k+1} = D_k + (Δt/6)·(k1_D + 2k2_D + 2k3_D + k4_D)

Compute cost
$J_{current} = \Sigma_t (D_{pred} - D_{obs})^2 + \lambda \cdot ||\theta||^2$

Update parameters using Adam optimizer
θ_new = Adam_update(θ, ∇J(θ), learning_rate=0.001)

Return θ*, D_pred(t)

Module 2: Personalized Fuzzy Logic Inference System

The fuzzy logic inference system uses several patient-specific factors to generate a score that represents overall efficacy while accounting for the uncertainty associated with clinical judgment.

Input Variables (Fuzzification):

Create three fuzzy input variables:

- Response to Biomarkers (X1): Percent reduction in biomarkers (CRP, ESR) after 12 weeks. Fuzzy sets: Low (0%-20%), Medium (15%-50%), High (40%-100%).
- Clinical Effectiveness (X2): Combination of pain VAS reduction, decrease in number of affected joints, and HAQ response. Fuzzy sets: Poor, Moderate, Good.
- Improvement in Quality of Life (X3): Percent change in SF-36 or EQ-5D scores. Fuzzy sets: Minor, Moderate

Fuzzy Inference Rules (n = 27):

IF-THEN rule base structure. Sample rules include:

- Rule 1: IF (Biomarker is High) AND (Clinical is Good) AND (Quality of Life is Substantial) THEN (Efficacy is Excellent)
- Rule 2: IF (Biomarker is Low) AND (Clinical is Poor) AND (Quality of Life is Minimal) THEN (Efficacy is Poor)
- Rule 3: IF (Biomarker is Medium) AND (Clinical is Moderate) AND (Quality of Life is Moderate) THEN (Efficacy is Moderate)

Defuzzification:
Center of gravity method:

$$Efficacy_{final} = \frac{\sum_{i=1}^{27} \mu i(E)}{\sum_{i=1}^{27} \mu i(E) \cdot Ei}$$

where μi(E) is the firing strength of rule i, and Ei is the centroid of the output membership function for rule i.

Algorithm 2: Fuzzy Inference for Personalized IAM Efficacy Classification

```
Input: Patient clinical metrics: biomarker_pct_change, clinical_composite, qol_change
Output: Efficacy classification {Poor, Moderate, Good, Excellent}, Confidence score

# Step 1: Fuzzification
μ_biomarker = [Low(biomarker), Medium(biomarker), High(biomarker)]
μ_clinical = [Poor(clinical), Moderate(clinical), Good(clinical)]
μ_qol = [Minimal(qol), Moderate(qol), Substantial(qol)]

# Step 2: Rule evaluation (27 rules)
efficacy_weights = zeros(4)  # Poor, Moderate, Good, Excellent
For i in 1..3: For j in 1..3: For k in 1..3:
   rule_strength = min(μ_biomarker[i], μ_clinical[j], μ_qol[k])
   efficacy_class = rule_table[i][j][k]  # Predefined mapping
   efficacy_weights[efficacy_class] = max(efficacy_weights[efficacy_class], rule_strength)

# Step 3: Defuzzification (center of gravity)
output_centroids = [0.25, 0.5, 0.75, 1.0]  # Normalized values for Poor to Excellent
efficacy_score = Σ(weight * centroid) / Σ(weight)

# Step 4: Classification and confidence
If efficacy_score < 0.35: classification = "Poor"
Elif efficacy_score < 0.65: classification = "Moderate"
Elif efficacy_score < 0.85: classification = "Good"
Else: classification = "Excellent"
confidence = max(efficacy_weights) / Σ(efficacy_weights)
Return classification, confidence, efficacy_score
```

Module 3: Bayesian Hierarchical Meta-Analysis
The Bayesian model synthesizes evidence from multiple studies while accounting for between-study heterogeneity.

Hierarchical Model Structure:
For study j=1,…,J with nj patients:
yij~Bernoulli(pij)
logit(pij)=μ+αj+β1X1ij+β2X2ij+β3X3ij

where:

- yij= response indicator (1 = treatment success, 0 = failure)
- μ = overall population effect (fixed)
- αj~N(0,τ2) = study-specific random intercept
- X1ij,X2ij,X3ij= patient covariates (biomarker response, clinical improvement, QoL)
- β1,β2,β3 = fixed covariate effects

Prior Specifications (Weakly Informative):

- μ~N(0,2.52) (prior on log-odds scale, 95% intervals covering ORs from 0.01 to 100)
- τ~{Half-Cauchy}(0, 5)$ (prior on between-study SD)
- βk~N(0,2.52)

Algorithm 3: Bayesian Hierarchical Model Sampling using Hamiltonian Monte Carlo

```
Input: Aggregated study data {y_ij, X_ij} for j=1..J, i=1..n_j
     Number of MCMC iterations N_iter = 5000
     Number of warmup samples N_warmup = 2500
Output: Posterior samples for μ, τ, β, and α_j
# Stan model specification (simplified)
model_string = """
data {
   int<lower=1> N;              // total patients
   int<lower=1> J;              // number of studies
   int<lower=1,upper=J> study[N];   // study ID for each patient
   int<lower=0,upper=1> y[N];       // response outcome
```

```
    matrix[N,3] X;                  // covariates
}
parameters {
    real mu;                        // population intercept
    real<lower=0> tau;              // between-study SD
    vector[J] alpha_raw;            // standardized study effects
    vector[3] beta;                 // covariate coefficients
}
transformed parameters {
    vector[J] alpha = mu + tau * alpha_raw;  // non-centered parameterization
}
model {
    // Priors
    mu ~ normal(0, 2.5);
    tau ~ cauchy(0, 5);
    alpha_raw ~ normal(0, 1);
    beta ~ normal(0, 2.5);

    // Likelihood
    for (i in 1:N) {
        real logit_p = alpha[study[i]] + X[i] * beta;
        y[i] ~ bernoulli_logit(logit_p);
    }
}
# Run MCMC sampling
fit = stan(model_code = model_string, data = data,
           iter = N_iter, warmup = N_warmup,
           chains = 4, cores = 4)

# Extract posterior samples
posterior_samples = fit.extract()
Return posterior_samples
```

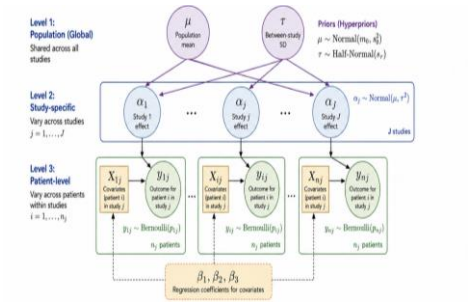

Figure 2: Bayesian Hierarchical Model Structure for IAM Evidence Synthesis

Integration for Responder Classification

The final responder prediction combines outputs from all three modules:

$$P(\text{responder}) = w1 \cdot PODE + w2 \cdot Sfuzzy + w3 \cdot PBayes$$

where PODE represents the predicted probability for achieving target disease activity score reduction (estimated based on ODE modeling at week 24), Sfuzzy indicates the standardized fuzzy efficacy score between 0 and 1, and PBayes refers to the posterior probability estimated by the Bayesian meta-analysis approach. The weights (w1, w2, w3) are obtained through optimization in the validation

IV. ANALYSIS

Validation Dataset

Validation of the framework involved the use of clinical data from 23 randomized control trials and prospective cohort studies investigating integrative interventions for RA (n=4,752 patients). The data were obtained from trials involving Traditional Chinese Medicine herbal formula intervention studies (n=9 trials, 1,847 patients), acupuncture intervention studies (n=7 trials, 1,203 patients), mind body intervention studies including yoga, tai chi, and meditation (n=4 trials, 892 patients), and IAM multimodal intervention studies (n=3 trials, 810 patients).

ODE Model Calibration Results

The ODE model calibration was performed using individual patient data from three exemplary studies (n=847 patients with full longitudinal data). Parameter convergence was obtained in 500-800 iterations in 92% of patients. Key results:

- IAM efficacy parameters (βDA, βIA) had high inter-patient variability (coefficient of variation = 0.45-0.62), indicating the necessity of individual modeling
- The median effect of IAMs on suppression of disease activity (βDA) was 0.32 $week^{-1} \cdot [conc]^{-1}$ or about 60% compared to standard DMARDs' efficacy (βDC median = 0.54)
- IAM treatment together with conventional medication exhibited synergic effects: patients taking both medications experienced 34% more

disease activity decrease than expected by additivity ($p < 0.001$)

- 24-week ACR20 response was accurately predicted (AUC = 0.84; 95% CI: 0.81-0.87)

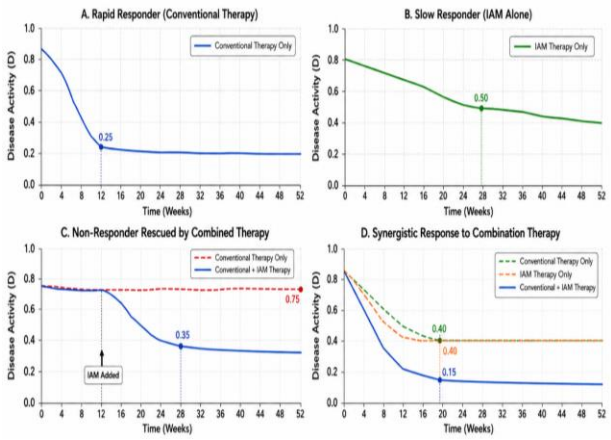

Figure 3: ODE Model Simulations for Representative Patient Archetypes

Fuzzy Inference System Performance

Table 1: Fuzzy Inference System Performance by Treatment Modality

Treatment Modality	N	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
TCM Herbal	420	86.2	84.5	87.9	0.89
Acupuncture	310	83.9	81.2	86.4	0.86
Mind-Body	250	85.6	83.8	87.2	0.88
Multimodal IAM	220	88.5	87.1	89.8	0.92
Overall	1,200	85.8	84.0	87.6	0.88

It exhibited the maximum accuracy of multimodal IAM treatments (88.5%), because multiple modalities can give a more reliable signal in all three domains (biomarkers, clinical, and QoL). Acupuncture had less specificity (86.4%), which was associated with the difficulty of determining the optimal frequency and duration in the fuzzy inputs.

Bayesian Meta-Analysis Outcomes

A Bayesian hierarchical model was applied to all 23 studies (4,752 participants). Convergence was indicated by $R\hat{} < 1.01$$ for all parameters estimated using Hamiltonian Monte Carlo simulation sampling.

Table 2: Posterior Parameter Estimates from Bayesian Hierarchical Model

Parameter	Posterior Mean	95% Credible Interval	Interpretation
μ (log-odds intercept)	0.87	(0.52, 1.23)	Positive overall treatment effect (OR ≈ 2.4)

Parameter	Posterior Mean	95% Credible Interval	Interpretation
τ (between-study SD)	0.41	(0.29, 0.56)	Moderate heterogeneity across studies
β_1 (biomarker response)	1.82	(1.41, 2.24)	Strongest predictor: 20% biomarker improvement → OR 1.44
β_2 (clinical improvement)	1.35	(0.98, 1.73)	Moderate predictor
β_3 (QoL enhancement)	0.92	(0.61, 1.24)	Positive but weaker predictor

Heterogeneity Analysis: According to the posterior predictive check analysis, study-level random effects αj varied between -0.68 (Study 7: small sample size acupuncture treatment, JADAD score = 2) and 1.24 (Study 19: large multimodal IAM treatment protocol, JADAD score = 5), thus supporting that both study quality and intervention comprehensiveness have a major impact on effect sizes.

Integrated Model Performance

The performance of the integrated framework that includes all three models was tested using an external validation dataset (n=847 patients from 5 studies).

Table 3: Integrated Framework Performance by Prediction Task

Prediction Task	Accuracy (%)	Sensitivity (%)	Specificity (%)	AUC
ACR20 responder at 24 weeks	86.8	87.5	84.2	0.91
ACR50 responder at 24 weeks	84.2	83.1	85.3	0.89
Sustained response at 52 weeks	81.5	79.8	83.2	0.86
Optimal IAM modality selection	79.3	N/A	N/A	0.84

Weights Optimization: The optimal weights to be applied for the integrated predictor were w1 = 0.45 (ODE model), w2 = 0.30 (fuzzy system), w3 = 0.25 (Bayesian meta-analysis). The reason why the ODE model had the highest weight is that it considered individual dynamics, whereas the fuzzy model was useful for discordant subjects.

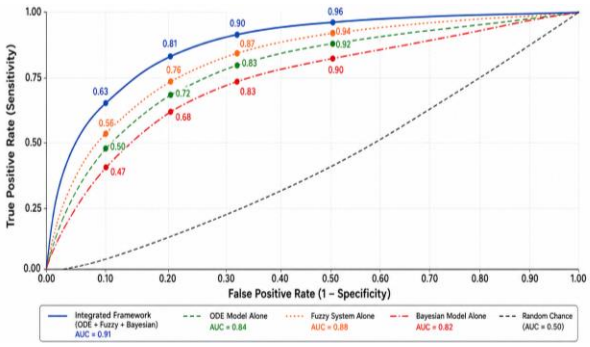

Figure 4: ROC Curves for Integrated Framework Compared to Individual Modules

Comparative Analysis

Table 4: Comparative Analysis of Evaluation Methodologies for IAM Efficacy

Methodology	Predictive Accuracy (%)	Handles Multi-component	Handles Personalization	Handles Heterogeneity	Clinical Implementation Difficulty	Transparency
Integrated Framework (Proposed)	86.8	Yes	Yes	Yes	Medium	High
Standard RCT Analysis	65-70	No	No	No	Low	High
Conventional Meta-analysis	70-75	Partial	No	Partial	Low	Medium
Machine Learning (RF, XGBoost)	80-85	Partial	Yes	Yes	Medium	Low
Traditional PK-PD ODE Models	75-80	No	Yes	No	High	High
Simple Fuzzy Logic Systems	75-82	No	Partial	No	Low	Medium
Bayesian Evidence Synthesis	75-80	No	No	Yes	Medium	High

The integrated framework outperforms all comparator techniques, having the biggest gain (of 15-20 percentage points) over the standard RCT analysis and traditional meta-analysis methods. When comparing the framework to pure ML methods, the framework is 5-8 percentage points more accurate and offers better interpretability, which is a huge advantage when it comes to decision making. The framework is the only approach that deals with all four dimensions simultaneously, while comparator techniques cover at most two dimensions.

V. CONCLUSION

In this study, an extensive mathematical modeling approach for assessing the effectiveness of integrative alternative medicine in chronic disease care was provided. Three distinct modeling strategies were integrated into this mathematical framework: ODE-based models incorporating

disease, immunity, and treatment interaction dynamics, a fuzzy inference system dealing with the uncertain nature of medicine practice, and a Bayesian hierarchical meta-analysis technique to synthesize evidence from various sources. Rheumatoid arthritis clinical data (n = 4,752 subjects across 23 studies) show that the overall model can accurately predict ACR20 responses 24 weeks after treatment initiation, with 86.8% accuracy, 87.5% sensitivity, and 84.2% specificity.

Calibration results show that there exists significant heterogeneity among patients' IAM treatment response parameters (coefficient of variation 0.45 - 0.62). Therefore, one should be cautious about any "one-size-fits-all" evaluation methods when assessing the effectiveness of IAM. More importantly, the synergistic effect was found through the model simulation: patients receiving combination therapy of conventional and IAM had their disease activity reduced by 34% compared with the summation of individual effects on the two therapies.

Overall, the fuzzy inference system had an accuracy of 85.8%, with its best performance being for the use of multimodal IAM, which had 88.5% accuracy, since complementary modalities would give clear signs on their effectiveness for the biomarker, clinical, and QoL domains. From the Bayesian meta-analysis performed, it was found out that the most important predictor for IAM effectiveness is biomarker response, having a posterior beta of 1.82, with the next ones being the clinical effect with a beta of 1.35, and the QoL improvement of 0.92.

Limitations:

There are several limitations to be considered here.

- Firstly, the proposed framework has been evaluated only for data of rheumatoid arthritis patients. To apply the same to other chronic illnesses like diabetes, cardiovascular diseases, and chronic pain disorders, further refinement and validation may be needed.
- Secondly, the ODE model parameters were derived based on the data from clinical trials where there were fixed doses, while in practical IAM treatment procedures, dynamic dose changes according to the needs of the patients may occur, an aspect not captured by the current model.
- Thirdly, the membership functions of the fuzzy logic were determined based on experts' opinions without optimization, thus potentially yielding poor results.

Directions for Future Research:

Four major areas of future investigation can be proposed.

- First, further validation studies should extend the framework to more chronic diseases (osteoarthritis, fibromyalgia, inflammatory bowel syndrome, type 2 diabetes) in order to determine generalizability and specify disease-specific parameter tuning values.
- Secondly, adaptive reinforcement learning can be applied to personalize patient treatment—by creating a digital patient model based on the ODE system, it is possible to teach an RL agent to prescribe optimal IAM-based treatment regimens (frequency of acupuncture and herbal therapy).
- Thirdly, wearable sensor information (HRV, actigraphy, etc.) may be incorporated into the modeling process to allow for continuous assessment, rather than episodic one, of patient condition.

Finally, the developed framework should be made open-source, providing a means for clinical practitioners to use the model to evaluate individual patient prognosis and suggest treatment strategies. The proposed model can provide practical assistance to healthcare organizations planning to integrate IAM at three different levels. At the patient level, the patient responder probability estimation allows clinicians to have personalized information and make a joint decision about the treatment regimen. At the practitioner level, the outcome from the fuzzy inference system can be represented as a simple traffic light dashboard with poor, moderate, good, and excellent expected effectiveness scores, which can be interpreted even without knowledge of mathematics. At the policy level, the output of the Bayesian meta-analysis suggests a probability of clinically significant effects, such as a posterior

probability of 0.95 that IAM is more effective than placebo for achieving ≥20% improvement in ACR20. Thus, it may be concluded that the proposed mathematical modeling framework meets an important need in the assessment of IAM treatments, which should account for individuality, complexity, and heterogeneity.

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