Analysis of Component Selection in Cellular Dynamic Equations: Understanding the Building Blocks of Our Model

Analysis for VAD Applications

November 29, 2024

1 Introduction

Understanding why specific components and distributions were chosen for each equation in our system is crucial for appreciating how the model captures cellular behavior. Each term has been selected based on biological principles and mathematical considerations of how cells respond to mechanical and biochemical signals.

2 Cell Orientation Equation Analysis

The cell orientation equation takes the form:

$$\dot{\theta} = A \cdot h_a(a_t) \cdot h_c(c_t) \cdot h_s(s_t) \cdot \exp\big(\kappa(u_t)\cos(\theta - \mu(u_t)) + \beta(u_t)\sin^2(\theta - \mu(u_t))\big) + g(u_t) \tag{1}$$

2.1 Fisher-Bingham Distribution Selection

The core of this equation uses the Fisher-Bingham distribution for several reasons:

- Unlike simpler circular distributions, it captures asymmetric deviations from the mean direction, which is crucial in complex flow environments
- The $\cos(\theta - \mu(u_t))$ term naturally represents alignment with flow direction
- The $\sin^2(\theta - \mu(u_t))$ term allows for asymmetric responses to flow perturbations
- The exponential form ensures smooth transitions in orientation changes

2.2 Modifying Functions

The base distribution is modified by three functions representing cellular state:

2.2.1 Actin Dependence

$$h_a(a_t) = \exp\left(-\frac{(a_t - a_{opt})^2}{\sigma_a^2}\right) \tag{2}$$

This Gaussian form was chosen because:

- It captures the existence of an optimal actin concentration for reorientation
- The symmetric decay reflects how both too little and too much actin impair cell mobility
- The width parameter σ_a represents cellular tolerance to actin variation

2.2.2 Cadherin Influence

$$h_c(c_t) = \frac{1}{1 + \exp(k(c_t - c_0))} \tag{3}$$

The sigmoidal function was selected because:

- It models the sharp transition in cell behavior when cadherin levels cross a threshold
- The asymptotic behavior prevents unrealistic responses at extreme cadherin levels
- The steepness parameter k captures how quickly cells transition between states

2.2.3 Senescence Effect

$$h_s(s_t) = \exp(-\lambda s_t) \tag{4}$$

The exponential decay was chosen because:

- It represents the progressive loss of reorientation ability with increasing senescence
- The single parameter λ makes the model more tractable
- The form ensures the effect is always positive but diminishing

3 Actin Dynamics Equation Analysis

The actin dynamics equation represents the balance between polymerization and depolymerization of the cytoskeleton:

$$\frac{da}{dt} = k_1(s)[a_{max}(s) - a] \cdot \frac{|u_t|^n}{K^n + |u_t|^n} \cdot h(c) - k_2(s)a \tag{5}$$

3.1 Growth Term Structure

The term $k_1(s)[a_{max}(s) - a]$ was chosen to represent actin polymerization because:

- The linear dependence on $(a_{max}(s) - a)$ ensures bounded growth
- $a_{max}(s)$ decreasing with senescence captures reduced cellular capacity
- The form naturally prevents actin concentration from exceeding physical limits

3.2 Hill Function Selection

The mechanical response term $\frac{|u_t|^n}{K^n+|u_t|^n}$ uses a Hill function because:

- It captures the switch-like response of actin assembly to mechanical stress
- The parameter n controls the sharpness of the transition
- Saturation at high stress levels reflects biological limitations
- The form is well-established in mechanobiology literature

3.3 Cadherin Coupling

The cadherin influence term $h(c)$ takes a Michaelis-Menten form:

$$h(c) = \frac{c}{K_c + c} \tag{6}$$

This form was selected because:

- It represents how cadherin clustering promotes local actin assembly
- The saturation reflects limited nucleation sites for actin polymerization
- The single parameter K_c makes the model more tractable

4 Cadherin Dynamics Equation Analysis

The cadherin equation models adhesion molecule dynamics:

$$\frac{dc}{dt} = k_{1,base} \cdot \frac{a}{a_{ref}} \cdot \exp(-\lambda s) \cdot (1 - \frac{c}{c_{max}}) \cdot \frac{|u_t|^n}{K^n + |u_t|^n} - k_{2,base}(1 + \gamma s)c \tag{7}$$

4.1 Production Term Components

Each factor in the production term serves a specific purpose:

4.1.1 Actin Dependence

The term $\frac{a}{a_{ref}}$ was chosen because:

- It represents how actin provides necessary structural support for adhesions
- The linear relationship reflects direct proportionality at physiological concentrations
- Normalization by a_{ref} makes the parameter biologically meaningful

4.1.2 Senescence Effect

The exponential decay $\exp(-\lambda s)$ was selected because:

- It captures the progressive impairment of protein production
- The form ensures monotonic decrease with increasing senescence
- The single parameter allows for simple experimental validation

4.1.3 Concentration Limitation

The term $(1 - \frac{c}{c_{max}})$ ensures:

- Production stops at maximum concentration
- Linear decrease in production rate as concentration increases
- Natural bound on cadherin accumulation

5 Senescence Evolution Equation Analysis

The senescence equation describes the accumulation of aging markers:

$$\frac{ds}{dt} = k_1 \left(1 - \frac{s}{s_{max}}\right) + k_2 \frac{|u_t|}{K + |u_t|} - k_3 s \tag{8}$$

5.1 Natural Aging Term

The term $k_1(1 - \frac{s}{s_{max}})$ was chosen because:

- It represents baseline senescence progression
- The form ensures bounded growth
- Linear decrease with s reflects limited capacity for senescence markers

5.2 Mechanical Stress Response

The Michaelis-Menten term $\frac{|u_t|}{K+|u_t|}$ was selected over other options because:

- It captures how mechanical stress accelerates senescence
- Saturation reflects limited capacity for stress-induced aging
- The form is simpler than Hill function while maintaining biological relevance
- The single parameter K makes experimental validation tractable

5.3 Turnover Term

The linear decay $-k_3 s$ represents:

- Natural turnover of senescence markers
- Cellular repair mechanisms
- Background signal decay in experimental measurements

6 System Constraints

Our system faces several critical constraints that must be considered in the Model Predictive Control formulation:

6.1 Safety Constraints

Primary constraints to ensure cell viability:

$$|u_t| \leq u_{max} \quad \text{(maximum shear stress)} \tag{9}$$

$$\left|\frac{du_t}{dt}\right| \leq \Delta u_{max} \quad \text{(rate of change limitation)} \tag{10}$$

$$s \leq s_{crit} \quad \text{(senescence threshold)} \tag{11}$$

$$a \geq a_{min} \quad \text{(minimum actin required)} \tag{12}$$

6.2 Performance Constraints

Constraints needed for proper endothelialization:

$$c \geq c_{min} \quad \text{(minimum adhesion strength)} \tag{13}$$

$$|\theta - \mu(u_t)| \leq \theta_{max} \quad \text{(alignment tolerance)} \tag{14}$$

$$\left|\frac{dc}{dt}\right| \leq \epsilon_c \quad \text{(adhesion stability)} \tag{15}$$

7 Control Challenges

7.1 Multiple Time Scales

The system exhibits significant time-scale separation:

$$\tau_{orientation} \ll \tau_{actin} \ll \tau_{cadherin} \ll \tau_{senescence} \tag{16}$$

This creates challenges for:

- Controller sampling time selection
- Prediction horizon optimization
- State estimation at different time scales

7.2 State Coupling

The tight coupling between states creates complex control scenarios:

$$\begin{bmatrix} \dot{\theta} \\ \dot{a} \\ \dot{c} \\ \dot{s} \end{bmatrix} = f\left(\theta, a, c, s, u_t\right) \tag{17}$$

This coupling means:

- Actions affecting one state will influence all others
- Control moves must consider multiple competing objectives
- State predictions must account for all interactions

8 MPC Formulation

8.1 Cost Function Structure

A suitable cost function might take the form:

$$J = \sum_{k=1}^{N_p} \left\{ \begin{array}{l} w_1\|\theta_k - \theta_{ref}\|^2 + \\ w_2\|c_k - c_{ref}\|^2 + \\ w_3\|s_k\|^2 + \\ w_4\|\Delta u_k\|^2 \end{array} \right\} \tag{18}$$

8.2 Analysis of Cost Function Terms

Each term in the cost function serves a specific purpose:

- $\|\theta_k - \theta_{ref}\|^2$: Ensures cells maintain proper alignment with flow

- $\|c_k - c_{ref}\|^2$: Maintains adequate adhesion strength
- $\|s_k\|^2$: Minimizes senescence accumulation
- $\|\Delta u_k\|^2$: Penalizes aggressive control actions

The weights w_i must be carefully tuned to reflect the relative importance of each objective.

9 Implementation Challenges

9.1 Prediction Horizon Selection

The presence of multiple time scales complicates horizon selection:

$$N_p \geq \max\left\{\frac{\tau_{senescence}}{\Delta t}, \frac{\tau_{adhesion}}{\Delta t}, \frac{\tau_{orientation}}{\Delta t}\right\} \tag{19}$$

This creates a trade-off between:

- Computational tractability
- Prediction accuracy
- Control performance

9.2 State Estimation

The control system must estimate several states that are challenging to measure directly:

$$\hat{x}_k = f(\hat{x}_{k-1}, u_{k-1}) + L(y_k - \hat{y}_k) \tag{20}$$
$$\hat{y}_k = h(\hat{x}_k) \tag{21}$$

Where measurement challenges include:

- Indirect measurement of actin dynamics
- Delayed feedback on senescence levels
- Spatial variations in cell states

10 Robust Control Considerations

10.1 Model Uncertainty

The system faces several sources of uncertainty:

$$\begin{aligned} \dot{x} &= f(x, u, w) \\ y &= h(x) + v \end{aligned} \tag{22}$$

Where:

- w represents process noise (biological variability)
- v represents measurement noise
- Parameter uncertainty in reaction rates

10.2 Robustness Requirements

The controller must maintain performance despite:

$$|k_i - \hat{k}_i| \leq \Delta k_i \quad \text{(parameter uncertainty)} \tag{23}$$

$$|w| \leq w_{max} \quad \text{(bounded disturbances)} \tag{24}$$

$$|v| \leq v_{max} \quad \text{(measurement noise)} \tag{25}$$