Development of a new approach for early Drosophila embryos BMP signaling pathway identification using Fuzzy logic based optimization and Fuzzy inference system

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Objective of the work

In this research, we are developing a fuzzy logic-based optimization algorithm for mathematical model evaluation using qualitative experimental data.

Our primary objective is to establish a comprehensive framework to integrate experimental and modeling outputs at appropriate levels of detail (LOD), and utilize as much data as possible to extract sufficient information to discriminate the most consistent mechanisms for a signaling pathway.

Significance and Innovation

Barrier for Mathematical models of development

Bone morphogenetic proteins (BMPs) are important morphogens and signalling molecules that regulate embryonic development. BMP-dependent processes during development include embryonic axial patterning, imaginal wing primordium patterning, and germline stem cell regulation. Mathematical models of development such as reaction-diffusion (RD) models provide a deeper understanding of spatial and temporal patterning of morphogen, and the BMP signaling pathway. However, uncertainty of qualitative experimental data and the complexity of the model remain a barrier for modeling in development.

Fuzzy processing for qualitative image data

To address the gap between quantification modeling in developmental patterning with qualitative or low quality data such as staining image or fluorescent intensity data, some traditional techniques including normalization and satisfaction have been used to transform data into quantification. In this research, we develop a fuzzy logic based image processing to overcome this problem for three reasons: 1). Fuzzy logic is highly flexible to transform linguistic or qualitative value into quantitative value according to membership functions. 2). Fuzzy number can naturally represent vagueness of observation without setting any boundary or pre-assumptions. 3). Fuzzy logic can handle problems with imprecise and incomplete data, and can model nonlinear functions of arbitrary complexity. 4). Fuzzy operations such as complement, union can be easily applied to fuzzy sets.

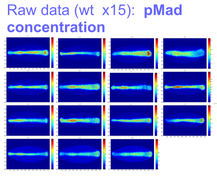
Fuzzy inference system and optimization

Fuzzy inference system(FIS) is computing framework based on fuzzy set, fuzzy if-then rules, and fuzzy reasoning and is widely applied in many research fields for knowledge representation or input-output mapping. The strength of FIS relies on the ability to condense sets of linguistic concepts into knowledge representation, and also builds the non-linear mapping between input and output. To integrate different fuzzy image datasets, to compare the datasets with mathematics modeling, and to inference the best fitting BMP signaling pathway from fuzzy if-then rules, the FIS and optimization techniques will be developd and apply.

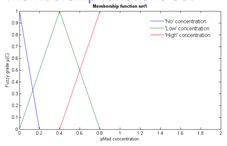
Method

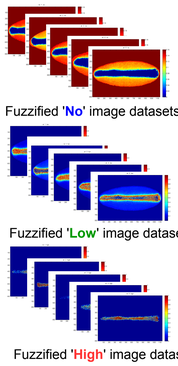
Fuzzy logic and fuzzy operations for image processing

Raw data (wt x15): **pMad concentration**



Membership functions set





Fuzzy set operations

Fuzzy set: A={(x,μA(x))|x∈ U}

Union: μA∪B(x) = max(μA(x),μB(x))

Intersection: μA∩B(x) = min(μA(x),μB(x))

Complement: μnot A(x) = 1-μA(x))

Fuzzy if-then rules

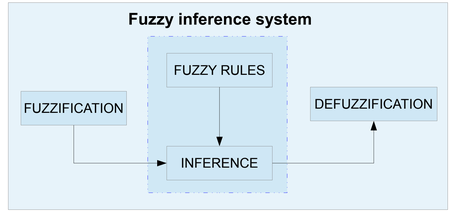
Rule:

If μ(x1) is A1 AND μ(x2) is A2

Then: y is B1

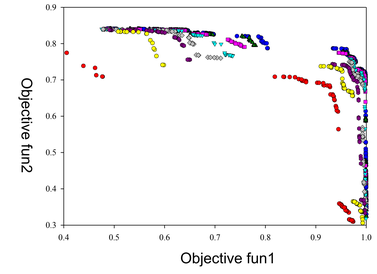
Fuzzy inference system

Fuzzy inference is a computer paradigm based on fuzzy set theory, fuzzy if-then- rules and fuzzy reasoning



Multi-objective optimization

For a problem with more than two objective functions, the variable vector X is Pareto optimal in the feasible space

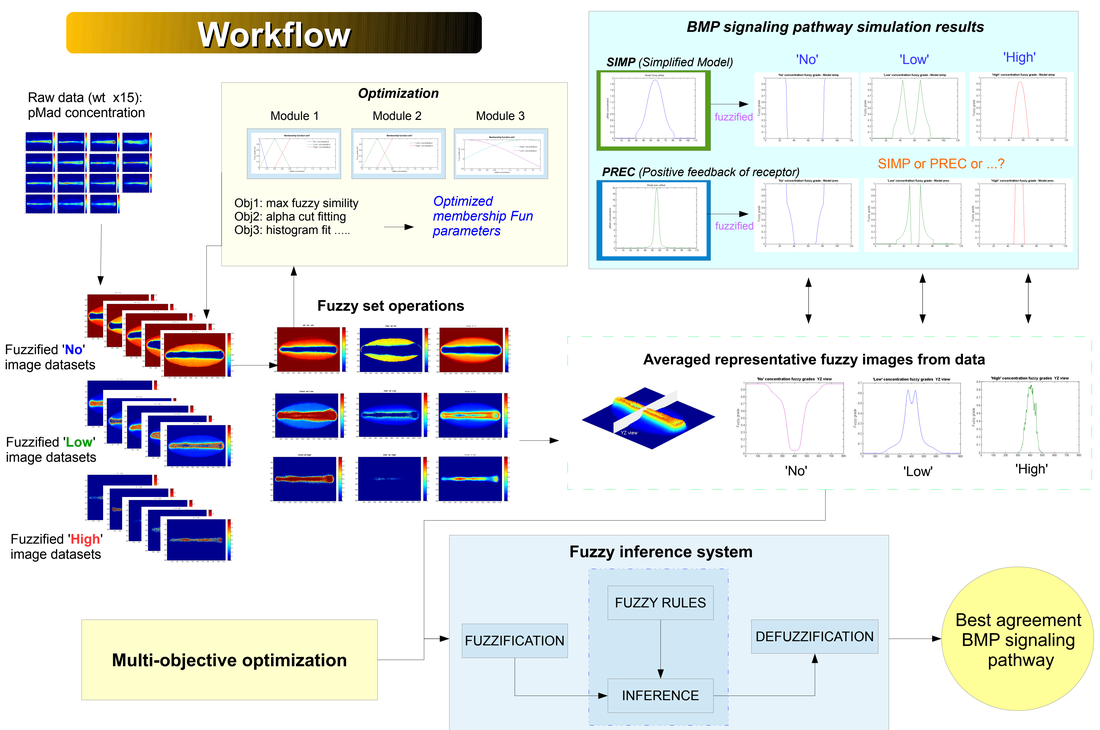


Transport-reaction model for BMP-mediated signaling

In early Drosophila embryos, two BMP members Dpp and Scw direct patterning of the dorsal ectoderm.Extracellular regulators sog and Tsg form a heterodimer inhibitor (Sog/Tsg) that binds to Dpp-Scw dynamics and contribute to the BMP signaling. The degradation of Sog by Tld enhances the gradient of inhibitor-bound.

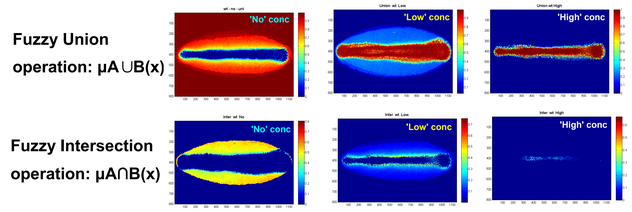
$$\frac{\partial B}{\partial t} = D_B \nabla^2 B + \phi_B(x) - k_3 I \cdot B + k_{-3} IB + \lambda\, Tld \cdot IB - k_5 B \cdot R + k_{-5} BR$$
$$\frac{\partial S}{\partial t} = D_S \nabla^2 S + \phi_S(x) - k_2 S \cdot T + k_{-2} I$$
$$\frac{\partial T}{\partial t} = D_T \nabla^2 T + \phi_T(x) - k_2 S \cdot T + k_{-2} I + \lambda\, Tld \cdot IB - \delta_T T$$
$$\frac{\partial I}{\partial t} = D_I \nabla^2 I + k_2 S \cdot T - k_{-2} I - k_3 I \cdot B + k_{-3} IB$$
$$\frac{\partial IB}{\partial t} = D_{IB} \nabla^2 IB + k_3 I \cdot B - k_{-3} IB - k_3 I \cdot B + \lambda\, Tld \cdot IB$$
$$\frac{\partial BR}{\partial t} = k_5 B \cdot R - k_{-5} BR - \delta_E BR$$
$$R_{tot} = R + BR$$

Workflow

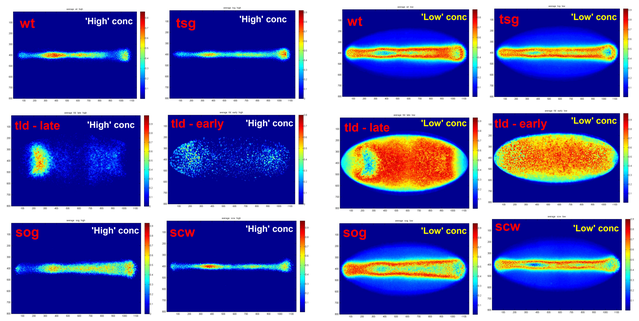


Preliminary results

Fuzzy set operation results of wild-type Drosophila embryos images



Averaged representative fuzzy images of wild- type and mutant Drosophila embryos



Future Work

Experimental results have explained the patterning and BMP signaling pathway for Drosophila wing disc development, and two morphoses Dpp and Wg, and Hh are most important factors affect the patterning of the wing disc. We will apply the framework integrated the optimization techniques and fuzzy inference system which we built and validated in this research to elucidate the Drosophila wing disc patterning and BMP signaling pathway.